Radiofrequency or cryoballoon ablation for index pulmonary vein isolation: What is the impact on long-term clinical outcomes after repeat ablation?

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Abstract
Aims: The current study sought to assess the impact of the utilized energy source during index ablation on long-term clinical outcomes after repeat ablation of atrial fibrillation (AF). Index ablation procedures were either performed using radiofrequency current (RFC) (RFC group) or cryoballoon (CB) ablation (CB group). Repeat ablation was performed by the use of RFC.

Methods: A total of 195 patients (138 RFC group; 57 CB group) with paroxysmal AF were included. All patients had a recurrence of AF following the index ablation procedure. Freedom from AF was estimated with the Kaplan-Meier method.

Results: After a 3 years follow-up, the estimated arrhythmia-free survival did not differ between the two groups (RFC group 48% vs CB group 47%, P = .78). During index ablation, procedure times were significantly shorter in the CB group (95 [80, 140] vs 140 [115, 164] minutes, P ≤ .001), whereas fluoroscopy times (16 [11; 22] vs 19 [14; 25] minutes, P = .003), the dose area product (1862 [1203; 2922] vs 3148 [1756; 5888] cGy cm², P ≤ .001) and the amount of contrast dye (92 ± 32 vs 123 ± 33 mL, P ≤ .001) were significantly lower in the RFC group. During repeat ablation, procedure times were significantly shorter in patients being initially treated with RFC (115 [85; 145] vs 125 [105; 150] minutes, P = .007). There was a trend towards a higher pulmonary vein reconnection rate in the RFC group without meeting statistical significance (P = .074).
Conclusions: In patients with repeat ablation of AF, index RFC or CB ablation are equally effective in terms of freedom from AF. Although CB ablation results in shorter index procedures times, durations of repeat ablation are significantly longer.

KEYWORDS
atrial fibrillation, clinical outcomes, cryoballoon ablation, radiofrequency current ablation, repeat ablation of atrial fibrillation

1 INTRODUCTION

Catheter ablation (CA) is an effective treatment for patients suffering from atrial fibrillation (AF). The target of ablation is the antral aspect of the pulmonary veins (PVs) and complete isolation of the PV is the key procedural endpoint for all patterns of AF. The two most commonly used approaches for pulmonary vein isolation (PVI) are radiofrequency current (RFC) ablation in conjunction with three-dimensional (3D) electroanatomic mapping and cryoballoon (CB) ablation. RFC ablation allows for individual point-by-point ablation guided by the patient’s anatomy, but it demands a long learning curve. CB ablation is a “single-shot” device with a fixed diameter of either 23 or 28 mm and a relatively simple, time-saving application with a short learning curve. Despite these differences, both methods have been shown to be equally effective and safe for the treatment of paroxysmal AF. However, taking account of both energy sources, CA for AF is still limited by a considerably high rate of atrial arrhythmia recurrences (AAR). Consequenly, there is a large number of patients undergoing repeat ablation procedures aiming at stable sinus rhythm (SR) maintenance. The main reason for AAR following CA is the electrical reconnection of the PV. In contrast to index ablation procedures, in which extensive CA is performed to achieve electrical isolation of the PV from the atrial myocardium, repeat ablation aiming at reisolation of the PVs mostly demands only a limited number of energy applications along the areas of electrical reconnection; therefore, the treatment of choice in repeat ablation procedures is point-by-point RF ablation. Of note, gap localizations of initially isolated PVs differ considerably in patients who underwent CB ablation from patients being treated with RFC. The impact of these different characteristics of both energy sources on clinical success rates is under continuous investigation.

The current study was designed to assess the effects of a hybrid ablation approach (CB ablation as index procedure followed by repeat ablation using RFC) as compared with the exclusive use of RFC ablation on clinical outcomes of patients with repeat ablation for the treatment of AF.

2 METHODS

2.1 Inclusion and exclusion criteria

Patients with symptomatic paroxysmal AF (as defined by 2016 ESC guidelines), who underwent an index ablation procedure applying either cryothermal energy or RFC and repeat ablation for the treatment of AAR using exclusively RFC, were included into the current study. Exclusion criteria were an LA diameter of more than 60 mm, severe valvular heart disease and contraindications to postinterventional oral anticoagulation.

The current study constitutes a retrospective analysis based on institutional databases. The study was approved by the local ethical boards and performed in accordance with the Declaration of Helsinki of 2013.

2.2 Periprocedural management

Transesophageal echocardiography was performed before CA in all patients to rule out intracardiac thrombi and to assess the LA diameter. No further preprocedural imaging was performed.

2.3 Intraprocedural management

The intraprocedural management has been described in detail before. In brief, in patients on vitamin K antagonists, the procedure was performed under therapeutic INR values of 2 to 3. Novel oral anticoagulants were stopped the day before the procedure and continued 6 hours postablation. All procedures were performed under deep sedation using midazolam, sufentanil, and propofol. One or two diagnostic catheters were introduced via the femoral vein and/or the left subclavian vein and positioned within the coronary sinus and/or along with the His bundle. Transseptal puncture was performed via the femoral vein under fluoroscopic guidance, using a modified Brockenbrough technique and an 8.5 French transseptal sheath (SL1; St Jude Medical Inc, St Paul, MN). After a transseptal puncture, heparin boluses were administered in 30-minute intervals targeting an activated clotting time of ≥300 seconds. Selective angiographies were performed to identify the individual PV Ostia.

2.4 Ablation protocol: CB-based PVI

The 28-mm second-generation CB was utilized exclusively. The transseptal sheath was exchanged over a guidewire for a 12F steerable sheath (FlexCath Advance; Medtronic Inc), through which the CB was advanced into the LA. Guiding of the CB to the target PV was performed over a 20-mm spiral mapping catheter (Achieve;
Medtronic Inc) and complete occlusion of the PV ostium was verified by contrast injection through the central lumen of the inflated CB.

Patients were treated based on a “time-to-isolation” (TTI) guided ablation protocol. This means, after live verification of PVI, freezing was continued for an additional 120 seconds; if the TTI could not be recorded, the freeze-cycle duration was set at 180 seconds; no additional bonus-freeze cycle was applied after successful PVI. An esophageal temperature probe (Sensitherm; St Jude Medical Inc and Circa; Circa Scientific Inc) was inserted and positioned according to the individual CB position to provide esophageal temperature monitoring during energy delivery. The intraluminal esophageal temperature cut-off was set at $15^\circ C$.12

During CB ablation along the septal PVs, continuous phrenic nerve (PN) pacing was performed using a diagnostic catheter positioned along the superior vena cava (6F, Inquiry; St Jude Medical Inc). PN capture was monitored by tactile feedback of diaphragmatic contraction by placing the operator’s hand on the patient’s abdomen. In addition, the continuous motor action potential (CMAP) was monitored and refrigerant delivery was stopped immediately if weakening or loss of diaphragmatic movement was noted or the amplitude of the CMAP decreased by $\geq 30\%$.13,14

2.5 | Ablation protocol: RFC ablation

In patients undergoing irrigated RFC as index ablation procedure, circumferential PVI was performed in conjunction with 3D electroanatomic mapping, as previously described.15 The procedural endpoint was the absence of any PV potential recorded by a spiral mapping catheter (Lasso; Biosense Webster, Diamond Bar, CA) placed along the ostium of the respective PV.

2.6 | Ablation protocol: repeat procedures

Repeat ablation procedures were performed in patients with AAR. Electrical reconduction gaps of reconnected PVs were identified and closed with RFC ablation aiming at PV reisolation. Additional ablation strategies beyond PVI were only performed in patients with (a) AT that was not related to PV reconduction gaps; (b) recurrence of AF despite durable isolation of the PVs; or (c) AF that could not be converted to SR by reisolation of the PVs or direct current cardioversion. Additional ablation strategies included bidirectional conduction block of the anterior line, complex fractionated atrial electrogram ablation, bidirectional conduction block of the mitral valve isthmus line, and/or bidirectional conduction block of the LA roofline. In the case of focal AT or non-PV triggers for AF, RFC ablation was performed aiming at substrate/trigger elimination.

2.7 | Postprocedural care

Transthoracic echocardiography was performed in all patients to rule out pericardial effusion. All patients were treated with proton-pump inhibitors for 6 weeks. Low-molecular-weight heparin was administered in patients on vitamin K antagonists and an international normalized ratio (INR) less than 2.0 until a therapeutic INR of 2 to 3 was reached. Novel oral anticoagulants were reinitiated 6-hour postablation. Anticoagulation was continued for at least 3 months and thereafter based on the individual CHA$_2$DS$_2$-VASc score. Previously ineffective antiarrhythmic drugs were continued for 3 months.

2.8 | Follow-up

Following a blanking period of 3 months, patients completed outpatient clinical visits at 3, 6, and 12 months and in 6-month intervals thereafter; the clinical visits included ECGs and 24-hour Holter ECGs. In addition, regular telephone interviews were performed and outpatient clinical visits were immediately initiated in case of symptoms suggestive of recurrent arrhythmia.

2.9 | Endpoints

The primary endpoint was a recurrence of a symptomatic and/or documented episode of AAR with a duration of more than 30 seconds outside the 3-month blanking period. Secondary endpoints were acute procedural characteristics and major complications (transient ischemic attack, stroke, pericardial tamponade, PN palsy, and severe bleeding requiring blood transfusion).

2.10 | Statistics

All data were evaluated retrospectively. Continuous data are described as mean and standard deviation if normally distributed; otherwise, the median and interquartile range (IQR [first quartile; third quartile]) are reported. Categorical data are described with absolute and relative frequencies. Based on a logistic regression model (global test of no-regression) baseline variables were simultaneously compared between the two groups.

Differences in logarithmic-transformed procedural data were analyzed with two-sample t tests. Freedom from AAR was estimated with the Kaplan-Meier method. Differences in recurrence-free survival were analyzed with the logrank test.

All P values were two-sided and a P value of less than .05 was considered significant. All calculations were performed with the statistical analysis software R (R Core Team, 2018).

3 | RESULTS

3.1 | Patients

A total of 195 patients with symptomatic paroxysmal AF underwent PVI applying either RFC ablation (n = 138) or 28-mm second-generation CB
ablation (n = 57). All 195 patients underwent repeat ablation applying exclusively RFC. There were no statistically significant differences in baseline characteristics or comorbidities between the two cohorts (P = 1.0). The patients' baseline characteristics are given in Table 1.

### 3.2 Procedural characteristics: index ablation procedures

In the 195 patients, all PVs were successfully isolated during the index ablation procedure. Median procedure times were significantly shorter in the CB group (95 [80; 140] vs 140 [115; 164] minutes, P ≤ .001), whereas fluoroscopy times and dose area products (DAP) were shorter in the RFC group (16 [11; 22] vs 19 [14; 25] minutes, P = .003; 1862 [1203; 2922] vs 3148 [1756; 5888] cGycm², P ≤ .001). Moreover, the amount of contrast dye was significantly lower in the RFC group (92 ± 32 vs 123 ± 33 mL, P ≤ .001). Neither RF ”touch up” ablation in patients being treated with the CB nor additional ablation strategies (beyond PVI) were performed during the first ablation procedure. Procedural parameters are given in Table 2.

### TABLE 1 Baseline patient characteristics

| Characteristics               | First procedure RFC (n = 138) | First procedure CB (n = 57) |
|-------------------------------|-------------------------------|----------------------------|
| Age, y                        | 70 [59; 75]                   | 70 [58; 75]                 |
| Female gender                 | 58 (42)                       | 26 (46)                    |
| CHA2DS2-VASc score            |                               |                            |
| 0                             | 18 (13)                       | 6 (11)                     |
| 1                             | 20 (14)                       | 8 (14)                     |
| 2                             | 28 (20)                       | 13 (23)                    |
| 3                             | 33 (24)                       | 12 (21)                    |
| 4                             | 25 (18)                       | 11 (19)                    |
| 5                             | 10 (7)                        | 4 (7)                      |
| 6                             | 3 (2)                         | 1 (2)                      |
| 7                             | 1 (1)                         | 1 (2)                      |
| 8                             | 0                             | 1 (2)                      |
| BMI, kg/m²                    | 27 ± 4                        | 28 ± 4                     |
| LA diameter, mm               | 46 ± 6                        | 46 ± 5                     |
| LVEF, %                       | 58 ± 7                        | 58 ± 7                     |
| Coronary artery disease       |                               |                            |
| GFR                           | 74 [61; 87]                   | 76 [65; 88]                 |

Note: Values are mean ± standard deviation, median [first quartile; third quartile] or n (%). Abbreviations: BMI, body mass index; CB, cryoballoon; GFR, glomerular filtration rate; LA, left atrium; LVEF, left ventricular ejection fraction; RFC, radiofrequency current.

Calculations on the basis of a logistic regression model revealed no difference between the two groups (P = 1).

### 3.3 Procedural characteristics: repeat ablation procedures

All patients underwent repeat ablation for the treatment of AAR by the use of RFC. Durable PVI of all PVs was documented in 36 of 138 (26%) patients in the RFC group and in 12 of 57 (21%) patients in the CB group. The remaining patients of both groups showed electrical reconnection of at least one PV.

In the 138 patients of the RFC group and the 57 patients of the CB group, repeat ablation strategies included reisolation of PVs with electrical reconnection following the index ablation procedure (RFC group: 102 patients [74%]; CB group: 45 patients [79%]), ablation of complex fractionated atrial electrograms (CFAE) with creation of linear lesions (RFC group: 30 patients [22%]; CB group: 10 patients [18%]), and sole CFAE ablation (RFC group: 9 patients [7%]; CB group: 3 patients [5%]).

In the RFC group, repeat ablation procedure times were significantly shorter as compared with patients being originally treated with the CB (115 [85; 145] vs 125 [105; 150] minutes, P = .007). However, overall combined procedures times (considering index and repeat ablation) remained shorter in the CB group (230 [190; 290] vs 260 [220; 302] minutes, P = .042).

There was a trend towards higher durability of PVI following CB ablation without meeting statistical significance (P = .074). PV reconnection rates are given in Table 3.

### 3.4 Periprocedural complications

Complications occurred in a total of 12 procedures (3%). Major complications during the index procedure did not occur. Minor complications during the index procedure were four pericardial effusions that were conservatively treated (RFC group: three patients; CB group: one patient) and one false aneurysm in the right groin (following RFC ablation). During repeat ablation procedures with exclusive use of RFC, major complications included four cardiac tamponades (three requiring pericardiocentesis; one requiring cardiac surgery). Minor complications were two pericardial effusions with conservative treatment and one false aneurysm in the right groin. No atrioesophageal fistula, no stroke or transient ischemic attack, no symptomatic PV stenosis, and no procedure-related deaths were observed. Complications are shown in Table 4.

### 3.5 Clinical follow-up

Estimated arrhythmia-free survival at 1, 2, and 3 years after repeat ablation in the RFC group was 72% (95% confidence interval [CI], 64%-81%), 56% (95% CI, 47%-65%), and 48% (95% CI, 39%-57%), respectively. In the CB group, estimated arrhythmia-free survival at 1, 2, and 3 years after repeat ablation was 73% (95% CI, 63%-84%), 58% (95% CI, 45%-70%), and 47% (95% CI, 34%-60%), respectively. The logrank test confirmed no
Differences between the two groups ($P = .78$). Recurrence-free survival is shown in Figure 1.

4 | DISCUSSION

4.1 | Main findings

The current study reports on clinical outcomes of repeat ablation aiming at PVI in patients with recurrent paroxysmal AF following CA. Index procedures were performed with the 28-mm second-generation CB or with the use of RFC guided by 3D mapping. Repeat ablation was exclusively performed with RFC. Main findings are (a) the arrhythmia-free survival did not differ between the cohorts of patients; (b) index procedure times were significantly shorter in the CB group, whereas fluoroscopy times, DAP, and the amount of contrast dye were lower in the RFC group; (c) repeat ablation procedure times were significantly shorter in patients being exclusively treated with RFC; and (d) CB ablation appears to result in a higher rate of durable PVI.

4.2 | Catheter ablation for paroxysmal AF

CA is the most effective treatment for patients with symptomatic AF.\(^1\) In the FIRE AND ICE trial, CB ablation was noninferior to RFC ablation in terms of efficacy and safety.\(^2\) However, AAR was still high with one-third of the patients had experienced a recurrence of AF at 1-year of FU.\(^2\) Although repeat ablation increases the arrhythmia-free survival substantially,\(^3,16,17\) the effects of the energy source applied during the index procedure have not yet been well investigated.

The characteristics of cryo- and RFC-lesions are considerably different. Cryothermal lesions are homogeneous and precisely circumscribed. In contrast, RFC energy creates a higher grade of inflammation, more extensive endothelial cell destruction and a less clearly circumscribed lesion formation.\(^18\) Moreover, CB and RFC ablation do not just differ in terms of the energy source. During CB ablation, energy is delivered to the tissue via the entire distal hemisphere of the balloon. The fixed diameter of the CB results in a mismatch of the PV and the CB. Therefore, the level of isolation solely depends on the individual size of the PV Ostia. This aspect results in wide-area PVI with additional LA

| TABLE 2 | Procedural data |
|----------|----------------|
| **Characteristics** | 1st First procedure RFC ($n = 138$) | 1st First procedure CB ($n = 57$) | $P$ values |
| Index ablation | | | |
| Total procedure time, min | 140 [115; 164] | 95 [80; 140] | <.001 |
| Fluoroscopy time, min | 16 [11; 22] | 19 [14; 25] | .003 |
| Dose area product, cGycm\(^2\) | 1862 [1203; 2922] | 3148 [1756; 5888] | <.001 |
| Contrast dye used, mL | 92 ± 32 | 123 ± 33 | <.001 |
| Repeat ablation | | | |
| Total procedure time, min | 115 [85; 145] | 125 [105; 150] | .007 |
| Fluoroscopy time, min | 15 [11; 20] | 16 [12; 21] | .200 |
| Dose area product, cGycm\(^2\) | 1570 [883; 2648] | 1814 [1023; 3032] | .312 |
| Contrast dye used, mL | 78 ± 21 | 75 ± 18 | .319 |

Note: Values are mean ± standard deviation or median [first quartile; third quartile].

Abbreviations: CB, cryoballoon; RFC, radiofrequency current.

| TABLE 3 | Reconnected pulmonary veins following the initial cryoballoon or radiofrequency ablation |
|----------|---------------------------------|
| **PV Characteristics** | RSPV | RIPV | LSPV | LIPV | LCPV |
| PVs initially treated with RF ablation | 138 | 138 | 134 | 134 | 4 |
| PVs isolated during the index procedure | 138 | 138 | 134 | 134 | 4 |
| PVs with electrical reconnection after successful index ablation procedure\(^a\) | 62/138 (45) | 62/138 (45) | 67/134 (50) | 59/134 (44) | 1/4 (25) |

Note: Values are $n$ (%).

Abbreviations: CB, cryoballoon; LCPV, left common pulmonary vein; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein; PVI, pulmonary vein isolation; RF, radiofrequency; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

\(^a\)Calculations on the basis of a mixed logistic regression model revealed a trend toward higher durability of PVI following CB ablation without reaching statistical significance ($P = .074$).
There was no difference between the two groups regarding clinical outcomes ($P = .78$). Noteworthily, despite repeat ablation, was performed in all patients, AAR was still considerably high. The main driver for AAR following CA is reconnection of previously isolated PVs; however, Kuck et al. reported on a surprisingly high AAR rate of 57% also in patients with proof of durable PVI. Considering these results, efforts are needed not just to increase the rate of durable PVI, but also to identify patients for whom additional ablation strategies are beneficial. In those patients, improved mapping and ablation of extrapulmonary vein triggers for AF might be an additional key aspect to increase clinical outcomes.

### Procedural aspects

During index ablation, procedure times were significantly shorter in patients undergoing CB ablation as compared to RFC ablation; in contrast, fluoroscopy times, DAP and the amount of contrast dye used during the index procedure were significantly higher for CB ablation. These findings are in accordance with previous reports and explained by the fact that RFC is guided by 3D mapping, whereas CB ablation is only guided by fluoroscopy and sufficient occlusion during freeze applications of the PV is verified by injection of contrast dye. The lower demand of contrast dye in RFC ablation can be a useful consideration when treating patients with chronic kidney disease.

In our study, repeat ablation procedures were significantly shorter in patients undergoing originally RFC ablation. In CB ablation, conduction gaps of initially isolated PV are mainly the result of a poor tissue balloon contact. Since the CB is a “single-shot” device, the area of electrical reconnection can involve a larger aspect of the PV. In contrast, PV conduction gaps following RFC ablation are oftentimes strictly circumscribed and might thereby be easier (and time-saving) identified. However, considering index and repeat ablation, overall combined procedures times remained significantly shorter in the CB group.

### TABLE 4 Complications

| Complications                              | RFC  | CB  |
|--------------------------------------------|------|-----|
| Total                                      | 11 (3.3)$^a$ | 1 (1.8)$^b$ |
| Index ablation procedure                   | 4 (2.9)$^c$ | 1 (1.8)$^d$ |
| Pericardial effusion with conservative     | 3 (2.2)$^c$ | 1 (1.8)$^d$ |
| treatment                                   |      |     |
| False aneurism at the puncture side         | 1 (0.7)$^c$ | 0   |
| Repeat ablation procedure                   | 7 (3.6)$^d$ | ... |
| Cardiac tamponade with pericardiocentesis   | 3 (1.5)$^d$ | ... |
| pericardiocentesis                         |      |     |
| Cardiac tamponade with cardiac surgery      | 1 (0.5)$^d$ | ... |
| Pericardial effusion with conservative     | 2 (1.0)$^d$ | ... |
| treatment                                   |      |     |
| False aneurism at the puncture side         | 1 (0.5)$^d$ | ... |

Note: Values are n (%).

Repeat ablation was exclusively performed with use of RFC.

Abbreviations: CB, cryoballoon; RFC, radiofrequency current.

$^a$Relative values in percentage refer to the 333 RFC procedures.

$^b$Relative values in percentage refer to the 57 CB procedures.

$^c$Relative values in percentage refer to the 138 index RFC procedures.

$^d$Relative values in percentage refer to the 195 repeat ablation procedures.

## FIGURE 1

Freedom from atrial arrhythmia recurrence after index plus repeat RFC ablation (orange curve) and after index CB-based PVI with repeat RFC ablation (blue curve). CB, cryoballoon; PVI, pulmonary vein isolation; RFC, radiofrequency current.
4.4 | Limitations

The current study is an observational, single-center, nonrandomized analysis. Repeat ablation was exclusively performed by the use of RFC ablation; no information can be given regarding clinical outcomes of patients undergoing repeat ablation with the use of CB ablation. At our center, RFC ablation is more frequently used for index PVI as compared with CB ablation. This aspect resulted in different numbers of patients being included in the two groups and might have biased the findings.

4.5 | Conclusions

In patients with repeat ablation of AF, the exclusive use of RFC ablation and the use of CB with subsequent RFC ablation are equally effective in terms of freedom from AAR. Although CB ablation results in shorter index ablation procedures times, durations of repeat ablation are significantly longer as compared to patients being initially treated with RFC. CB ablation appears to ensure a higher rate of durable PVI.

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