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Outcome of cryoballoon ablation for atrial fibrillation

Medium-term follow-up from a single center

Cryoballoon ablation (CBA) is widely used in the management of patients with atrial fibrillation (AF), as is radiofrequency catheter ablation (RFCA). At the Deutsches Herzzentrum Berlin (DHZB) the CBA procedure has been performed for the past 6 years and is always guided by three-dimensional atrial rotational angiography imaging. Our previous studies showed CBA to be safe and effective for patients with AF after short-term follow-up [1]. The present retrospective study analyzes the medium-term follow-up after single CBA and investigates the clinical risk factors that can predict AF recurrence.

Patients and methods

Study population

Patients who received CBA for AF for the first time at the DHZB between January 2009 and July 2013 were included in this retrospective study. The data collected consisted of inpatient and outpatient parameters and details of the CBA procedure. According to the current consensus, AF was divided into two types: paroxysmal atrial fibrillation (ParAF) and persistent atrial fibrillation (PerAF) [2]. The $CHADS_2$, CHA_2DS_2-VaSc, and HAS-BLED scores as well as the body mass index (BMI) were calculated from the inpatient records [3]. The left atrial diameter (LAD) and left ventricular ejection fraction (LVEF) were measured by transthoracic echocardiography before the CBA procedure. LAD was measured in the parasternal long-axis view from the trailing edge of the posterior aortic root–anterior LA complex to the posterior LA wall at end-systole. LVEF was calculated on the basis of the difference between the left ventricular end-diastolic and end-systolic volume by Simpson's two-dimensional methodology.

Electrophysiological study and CBA procedure

The electrophysiological study and CBA procedure were performed as in our previous reports [1, 4]. In brief, the whole procedure was completed with patients under general anesthesia. Following left femoral vein puncture, a 6-F decapolar catheter (Inquiry, St. Jude Medical, St. Paul, Minn.) and a 5-F bipolar catheter (Josephson, C.R. Bard, Murray Hill, N.J.) were individually inserted into the coronary sinus and the right ventricular apex. After successful single transseptal puncture with a 15-F steerable sheath (FlexCath Advance™, Medtronic, Minneapolis, Minn.), a 6-F pigtail catheter was inserted into the LA for three-dimensional LA rotational angiography (EP navigator, Phillips, Best, The Netherlands). The LA anatomic image was reconstructed and the location of each PV ostium and the LA was overlaid directly onto the real-time X-ray screen ([5], **Fig. 1**). A 28-mm cryoballoon (ArcticFront or, since September 2012, ArcticFront Advance, Medtronic) was transferred to each PV ostium and a 4-polar or 10-polar (ProMAP, ProRhythm Inc., Ronkonkoma, N.Y.) or 8-polar circular mapping catheter (Achieve™, 15 mm, Medtronic) was inserted into each PV to record the pulmonary vein potential (PVP). During the cryoablation of the left superior pulmonary vein (LSPV), left inferior pulmonary vein (LIPV), and left common pulmonary vein (LCPV), PV

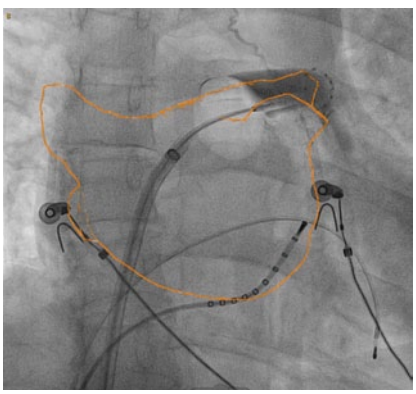

Fig. 1 ▲ Three-dimensional reconstruction of left atrium, left atrial appendage, and pulmonary vein based on intraprocedural rotational angiography and overlaid on an X-ray real-time fluoroscopic screen. The pulmonary vein angiogram shows good contact between the cryoballoon and left superior pulmonary vein

Tab. 1 Baseline characteristics of patients enrolled in study

Male (n/%)	159/75%
Age	61±10
BMI	28 [23, 37]
AF type	
– ParAF (n/%)	151/71.23%
– PerAF (n/%)	61/28.77%
Hypertension (n/%)	137/63.6%
Diabetes mellitus (n/%)	23/10.85%
Heart failure (n/%)	21/9.91%
Coronary disease (n/%)	40/18.87%
Hyperlipidemia (n/%)	80/37.74%
Previous ablation	
– PVI (n/%)	19/8.96%
– Right isthmus ablation (n/%)	18/8.49%
CHA_2DS_2-VaSc score	2 [0.5]
HAS-BLED score	1 [0.3]
LAD (mm)	45±6
LVEF (%)	62±9

AF atrial fibrillation, *BMI* body mass index, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction, *ParAF* paroxysmal atrial fibrillation, *PerAF* persistent atrial fibrillation, *PVI* pulmonary vein isolation

angiography was done to confirm good contact between the balloon and the PV ostium [1], or rapid right ventricular pacing with a cycle length of 300 ms lasting for 30 s was used to achieve good contact between the cryoballoon and the PV ostium [4]. Cryoablation of the right superior pulmonary vein (RSPV) and the right inferior pulmonary vein (RIPV) was completed under continuous right phrenic nerve pacing and was stopped immediately when the phrenic muscle movement became weak. The endpoint of cryoablation for each PV was pulmonary vein isolation (PVI), which was confirmed by pacing stimulation from the LA and the respective PV. The duration of cryomapping and cryoablation during each procedure was recorded, as was the X-ray exposure time. The procedure time was calculated from the beginning of puncture to occlusion of the peripheral vessel. The main complications related to cryoablation were also recorded: phrenic nerve palsy (PNP), stroke or transient ischemic attack (TIA), pericardial effusion or tamponade, symptomatic pulmonary vein stenosis, and atrial-esophageal fistulas.

Anticoagulation during CBA procedure and antiarrhythmic drugs

Oral anticoagulation (OAC) medication was continued at an effective therapeutic dosage until the CBA procedure. During CBA, unfractionated heparin was given and the active coagulation time (ACT) was kept between 250 and 300 s. Anticoagulation was resumed on the afternoon after the CBA procedure and generally lasted for 3 months. Whether or not anticoagulation was stopped depended on the patient's $CHADS_2$ or CHA_2DS_2-VaSc score. A proton pump inhibitor was prescribed for 4 weeks to prevent esophagus injury.

Antiarrhythmic drugs (AADs) were not stopped before cryoablation. During the ablation procedure, AADs were not used and electrical conversion was performed if atrial arrhythmia had not terminated after ablation. The AADs were again given, as before the procedure, for 2–3 months to maintain sinus rhythm and then were stopped to evaluate the efficiency of CBA.

Clinical follow-up

After the cryoablation procedure, patients were asked at regular 3-monthly outpatient visits whether the AF-related symptoms had recurred and complications were recorded. Twelve-lead electrocardiography (ECG) and 24-h Holter monitoring were done routinely at each appointment to detect evidence of atrial tachycardia (AT), atrial flutter (AFL), or AF. These procedures were also done every year for patients without AA recurrence. Once AT, AFL, or AF lasting >30 s was recorded after 3 months, the cryoablation procedure was regarded as having failed and the date was recorded as the recurrence date. Otherwise, the treatment was considered successful.

Statistical analysis

The variables with normal distribution are reported as mean ± standard deviation and were compared by the Student's t test. The variables with non-normal distribution are reported as median (5% quartile, 95% quartile) and were compared by Wilcoxon's test. Discrete variables were compared by chi-square or Fisher's exact test, as appropriate. The receiver operating characteristic curve (ROC) of the LAD was used to test the best cut-off value and the area under the curve (AUC) for the prediction of AF recurrence. Multivariate analysis was performed to identify independent predictors of failure of CBA treatment using a forward stepwise procedure with a criterion of $p<0.05$ for inclusion and $p>0.05$ for removal from the model. Adjusted odds ratios and 95% confidence intervals were determined for the variables associated with each outcome. The Kaplan–Meier curve was prepared to estimate the difference in success rate between the two groups in follow-up. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed with the SAS (Version 9.1, SAS Institute Inc., Cary, NC).

Results

Baseline data

A total of 212 patients were enrolled in this retrospective study, and 166 patients with full follow-up data were included in the analysis of predictive risk. There were no

differences in clinical characteristics between the two groups (Tab. 1).

CBA procedure

A total of 678 PVs were targeted, which included ten left common PVs. The success rates of PVI on LSPV, LIPV, RSPV, RIPV, and LCPV were 94.92% (187/197), 94.76% (181/191), 95.85% (185/193), 97.70% (85/87), and 100% (10/10), respectively. The mean rate of total PVI after cryoablation was 87.74% (186/212).

The mean time of the total CBA procedure, X-ray exposure, cryomapping, and cryoablation was 120 min [75, 183], 21 min [13, 39], 52 min [30, 82], and 35 min [20, 55], respectively.

Complications

The complication rate was 2.83%. There were three patients (1.42%) with PNP; in two of them palsy resolved immediately when cryoablation stopped, and in the other patient PNP completely resolved until 7 months after the procedure. One patient (0.47%) had pericardial effusion and two patients (0.94%) suffered a transitory ischemic attack (TIA); these all resolved spontaneously. No pulmonary vein stenosis, cardiac tamponade, or atrium-esophagus fistula occurred.

Follow-up outcomes

In all, 46 patients were lost to follow-up. Among the 166 patients who completed the follow-up, there were 76 (45.8%) who remained in sinus rhythm (SR) during the mean 28±15-month follow-up period. Among the 90 patients with a recurrence, ten patients had AFL, two patients AT, and 78 patients AF. The patients with AFL or AT recurrence were completely cured by re-ablation with RFCA. Patients in the failed-treatment group had larger LAD (47±6 mm vs. 43±5 mm, p<0.0001, Tab. 2); there were no differences in the other clinical characteristics between groups.

Among the patients with treatment failure, 76 (84.4%) experienced an AA recurrence during the first year after ablation. The rate of late recurrence was only 15.6%.

Abstract · Zusammenfassung

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Outcome of cryoballoon ablation for atrial fibrillation. Medium-term follow-up from a single center

Abstract

Objective. We analyzed the medium-term follow-up of cryoballoon ablation (CBA) for atrial fibrillation (AF) and the clinical risk factors predicting outcome.

Methods. AF patients treated for the first time with CBA in a 4.5-year period were studied retrospectively. Pulmonary vein isolation (PVI) was achieved via a single cryoballoon with diameter of 28 mm. Left atrial diameter (LAD) was measured by transthoracic echocardiography. Failure of cryoablation treatment was defined as detection of an episode of AF, atrial flutter, or atrial tachycardia lasting more than 30 s during the 3-month follow-up.

Results. A total of 212 patients were enrolled and in 87.7% patients PVI was achieved by CBA. The complication rate was 2.83%. The mean follow-up was 28±15 months; in 166 patients follow-up was complete. The rate of successful treatment for primary CBA was 45.8%. The percentage of patients who experienced atrial arrhythmia recurrence in the first 12 months was 84.44%. Patients in whom treatment failed had a larger LAD (47±6 mm vs. 43±5 mm, p<0.0001). The Kaplan–Meier curve showed that the patients with LAD <45 mm had a higher success rate than patients with LAD ≥45 mm [57.9% (44/76) vs. 35.6% (32/90), log rank =5.492, p=0.019]. The LAD [odds ratio, OR =−0.1053(0.303, 12.2040), p=0.0005] was shown in logistic regression analysis to be independently predictive of CBA treatment failure.

Conclusion. The CBA procedure for AF patients is safe and effective. Most atrial arrhythmia recurrences occurred during the first 12 months after CBA. The LAD can independently predict failure of CBA treatment.

Keywords

Cryoballoon ablation · Atrial fibrillation · Medium-term follow-up · Risk factors · Outcome

Ergebnis der Kryoballonablation bei Vorhofflimmern. Mittelfristige Nachbeobachtung durch ein einzelnes Zentrum

Zusammenfassung

Ziel. Untersucht wurden der mittelfristige Verlauf nach Kyroballonablation (CBA) bei Vorhofflimmern (VF) und die klinischen Risikofaktoren, die das Ergebnis prognostizieren.

Methoden. Retrospektiv untersucht wurden VF-Patienten, bei denen erstmals in einem 4,5-Jahres-Zeitraum eine CBA erfolgte. Die Pulmonalvenenisolation (PVI) wurde mittels eines einzelnen Kryoballons mit einem Durchmesser von 28 mm erzielt. Der linksatriale Durchmesser (LAD) wurde transthorakal echokardiographisch gemessen. Das Versagen der Kryoablationstherapie war definiert durch den Nachweis einer Phase von VF, Vorhofflattern oder Vorhoftachkardie mit einer Dauer >30 s während des 3-monatigen Follow-up.

Ergebnisse. In die Studie aufgenommen wurden 212 Patienten, und bei 87,7% wurde eine PVI per CBA erzielt. Die Komplikationsrate betrug 2,83%. Das durchschnittliche Follow-up lag bei 28±15 Monaten; bei 166 Patienten wurde es vollständig durchgeführt. Die Therapieerfolgsrate der primären CBA betrug 45,8%. Der Anteil der Patienten, bei denen es in den ersten 12 Monaten zu einem Rezidiv der Vorhofarrhythmie kam, lag bei 84,44%. Patienten mit Therapieversagen wiesen einen größeren LAD auf (47±6 mm vs. 43±5 mm; p<0,0001). Die Kaplan-Meier-Kurve zeigte, dass bei Patienten mit einem LAD <45 mm die Erfolgsrate höher war als Patienten mit einem LAD ≥45 mm [57,9% (44/76) vs. 35,6% (32/90), Log Rank =5,492; p=0,019]. Die LAD [Odds Ratio, OR =−0,1053 (0,303; 12,2040), p=0,0005] erwies sich in der logistischen Regressionsanalyse als unabhängiger Prädiktor des Therapieversagens der CBA.

Schlussfolgerung. Das Verfahren der CBA bei Patienten mit VF ist sicher und wirksam. Die meisten Rezidive im Hinblick auf Vorhofarrhythmien traten in den ersten 12 Monaten nach CBA auf. Der LAD ist ein unabhängiger Prädiktor des Therapieversagens der CBA.

Schlüsselwörter

Kryoballonablation · Vorhofflimmern · Mittelfristiges Follow-up · Risikofaktoren · Ergebnis

Tab. 2 Differences in clinical characteristics between patients with successful and failed treatment

	Successful treatment (n=76)	Failed treatment (n=90)
Male (n/%)	56/73.68%	69/76.67%
Age	63±10	61±10
BMI	27 [22, 36]	28 [23, 37]
AF type		
– ParAF (n/%)	56/73.68%	58/64.44%
– PerAF (n/%)	20/26.32%	32/35.56%
Hypertension (n/%)	46/60.53%	66/73.33%
Diabetes mellitus (n/%)	10/13.16%	7/7.78%
Heart failure (n/%)	5/6.58%	12/13.33%
Coronary disease (n/%)	12/15.79%	21/23.33%
Hyperlipidemia (n/%)	24/31.58%	41/45.56%
Previous ablation		
– PVI (n/%)	8/10.53%	9/10.00%
– Right isthmus ablation (n/%)	9/11.84%	8/8.89%
CHA_2DS_2-VaSc score	2 [0.5]	2 [0.5]
HAS-BLEED score	1 [0.3]	1 [0.3]
LAD (mm)	43±5	47±6*
LVEF (%)	62±9	61±10
AAD used		
– Beta-blocker	62/81.6%	71/78.9%
– Flecainide	13/17.1%	10/11.1%
– Amiodarone/dronedarone	12/15.8%	14/15.6%
– Propafenone	4/5.3%	9/10%
PVI success (n/%)	69/90.8%	76/84.4%

*p<0.01. See Table 1 for abbreviations

Relationship between LAD and outcome of CBA

The ROC curve of the LAD to predict the outcome of CBA was prepared, and the AUC was 66.4% (58.2%, 74.5%). When a cut-off value of the LAD of 45 mm was chosen, the sensitivity and specificity were 63.3 and 63.2%, respectively. The Kaplan–Meier curve showed that the successful treatment rate in patients with an LAD <45 mm was higher than in patients with an LAD ≥45 mm [57.9% (44/76) vs. 35.6% (32/90), log rank =5.492, p=0.019] (**Fig. 2**).

Predictor for outcome of CBA

A logistic regression analysis that included LAD, hypertension, AF type, age, LVEF, PVI success, and BMI showed that the LAD [OR =−0.1053(0.303, 12.2040), p=0.0005] was an independent predictor of outcome after CBA.

Discussion

The main findings of the present study were: (1) CBA was safe for patients with AF and was effective after 2-year follow-up. (2) The LAD could independently predict failed CBA treatment. (3) In most patients with AA recurrence, this recurrence happened during the first 12 months after CBA.

The unique characteristic of CBA for AF, as compared with RFCA, is its good safety profile. Just as in our previous study [1], the main complication of CBA rate in the present study, which has more patients, is only 2.8%. Although PNP is a common complication of CBA, its incidence in this study was only 1.4%, which is far lower than in other reports [6, 7, 8]. Our experience is that the right PV cryoablation must be done under consistent right phrenic nerve pacing, and cryoablation must be stopped once the phrenic muscle movement becomes weaker but before it disappears. Another factor related to the lower incidence is that we chose only a 28-mm cryoballoon [7].

The effectiveness of PVI as achieved by CBA is similar to that of RFCA. In this study, the successful rate of PVI on different PVs was higher than 95%. The success rate of PVI for the LCPV, which is difficult to ablate with RFCA, is higher at 100%. In the German Ablation Registry, the acute success rate of CBA and RFCA is the same [9], showing that CBA is an effective form of management of patients with AF.

The success rate of CBA for AF is still not high after single ablation (45.8%) in the present study. The reasons for the low success rate may include the following: (1) We analyzed the outcome after single ablation and not the follow-up after re-ablation for patients with AF recurrence. Our results are similar to those recently reported by Giovanni et al. [10] The 1-year follow-up showed the freedom from AF without AAD after a single procedure to be 58% with the first generation of cryoballoon. The STOP AF trial [6] also found a success rate of 57.7% after the single procedure, reaching 69.9% in the 19% of patients who received repeat cryoablation. (2) We considered AF or AFL or AT recurrence all as failure of CBA treatment. The expert consensus statement on catheter ablation of AF [2] considers, as the criterion of successful CBA treatment, only freedom from AF, which is not sufficient to testify to cryoablation as a curative tool. (3) Our medium-term follow-up had a mean duration of 3 years; longer follow-up of catheter ablation is associated with a lower success rate [2]. A prospective study of long-term outcome after CBA also showed that the success rate decreases with follow-up duration [11].

LAD is a common index of LA anatomic remodeling and is the main influential factor of RFCA for patients with AF. The present study showed that patients with a larger LAD have a lower rate of successful treatment after CBA therapy. Logistic regression analysis also showed that the risk of failed treatment is increased and positively related with LAD value. This phenomenon was also observed by Neumann et al. [12], who showed that normalized LA is the sole independent predictor for the outcome of CBA. Aytemir et al. [13] also reported that LAD can individually

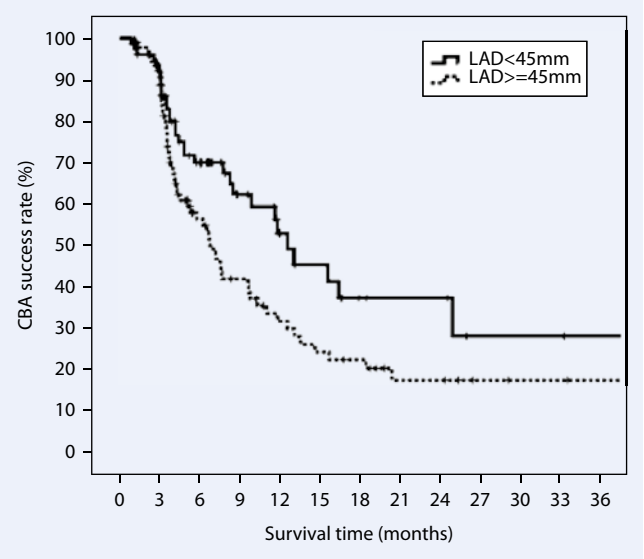

Fig. 2 ◀ Kaplan–Meier curve of the successful treatment rate based on the best cut-off value of the left atrial diameter (*LAD*) of 45 mm. *CBA* cryoballoon ablation

predict AF recurrence after cryoablation (HR, 2.42; 95% CI, 1.64–5.88). Therefore, the LAD is still an important reference tool when screening the appropriate patients for CBA therapy.

Recurrence is still a common phenomenon after CBA therapy. Our results show that AA recurrence increases with follow-up time, as indeed it does after RFCA [14]. However, it is interesting to note that most recurrences (nearly 85%) occurred during the first 12 months after CBA. Vogt et al. [11] also reported that the recurrence rate during the first 12 months is twice as high as after a further 12 months (22.4% vs. 10.6%). The North American STOP AF study [6] also found that the success rate decreased greatly during the first year after CBA. The 5-year follow-up of a single CBA for patients with ParAF reported by Neumann et al. [12] showed a marked recurrence rate (30%) during the first year.

Therefore, the AA recurrence after CBA for AF during the first postprocedural year is a problem that requires further research.

Limitations

There are many limitations to this retrospective study. A high rate of loss to follow-up because of patients coming from foreign countries can lower the power of the evidence. Further, the 24-h Holter ECG, not a 7-day or remote ECG, can miss an asymptomatic AA attack and therefore an AA recurrence.

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Compliance with ethical guidelines

Conflict of interest. J. Liu, J. Kaufmann, C. Kriatselis, E. Fleck, and J. Gerds-Li state that there are no conflicts of interest. All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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