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Five-year outcome and predictors of success after second-generation cryoballoon ablation for treatment of symptomatic atrial fibrillation

Ersan Akkaya [a,*], Alexander Berkowitsch [a], Sergej Zaltsberg [a], Harald Greiss [a], Christian W. Hamm [a,b], Johannes Sperzel [a], Malte Kuniss [a], Thomas Neumann [a]

[a] Department of Cardiology, Kerckhoff Heart Center, Bad Nauheim, Germany
[b] Medical Clinic I, Justus-Liebig University, Giessen, Germany

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ABSTRACT

Introduction: Data on long-term outcomes of cryoballoon ablation for treatment of atrial fibrillation (AF) are sparse. Here, we report the first 5-year follow-up results and predictors of outcome for pulmonary vein isolation (PVI) using the second-generation cryoballoon (CB-Adv) in patients with symptomatic AF.

Methods and results: For this prospective observational study, we enrolled 178 patients with paroxysmal (132/178 [74.2%] patients) or persistent AF who underwent PVI with CB-Adv at our institution during 2012. Clinical success was defined as freedom from AF, atrial flutter or atrial tachycardia recurrence >30-s following the 3-month blanking period. Follow-up data were collected during outpatient clinic visits and included Holter-ECG recordings. The impacts of several variables on outcome were evaluated by means of univariate and multivariate analyses and Cox proportional hazards regression models.

PVI was sufficient in restoring and maintaining sinus rhythm in 59.0% (n = 105) of patients (paroxysmal AF: 81/132 (61.4%) patients; persistent AF: 24/46 (52.2%) patients, P = 0.20). The median procedure and fluoroscopy times were 126 (interquartile range 114/150) and 20 (16/26) min, respectively. Cox regression analysis showed that left atrial area ≤21 cm^2 and the absence of diabetes independently predicted outcome.

Conclusions: Sinus rhythm was maintained in a substantial proportion of patients even 5 years after CB-Adv ablation. Patients with a non-enlarged left atrium without diabetes had the best outcome.

1. Introduction

Atrial fibrillation (AF) is the world's most common cardiac arrhythmia. Pulmonary vein isolation (PVI) via cryoballoon (CB) ablation is an effective, safe therapy for symptomatic AF [1]. Compared with the first-generation CB, the second-generation CB (CB-Adv; Arctic Front Advance™, Medtronic, Minneapolis, MN, USA) is more effective in acute PVI and is associated with at least equivalent [2] or better clinical outcomes [3]. The improvements are attributed to the altered arrangement and number of injectors in the CB-Adv increases the coolant flow rate and effective treatment area. PVI with the CB-Adv is increasingly performed on patients with paroxysmal or persistent AF. However, most studies have limited follow-up periods (2 or 3 years, or even less), and no outcome data beyond 3 years is available [3–7]. The long-term (5-year) success rate of PVI with the CB-Adv, when carried out according to the HRS/EHRA/ECAS Expert Consensus Statement [8], is not well-known. Herein, we report the 5-year outcome and predictors of success after treatment of symptomatic paroxysmal or persistent AF by PVI with the CB-Adv.

2. Methods

2.1. Study population

For this prospective observational study, we enrolled 178 consecutive patients undergoing PVI with the CB-Adv for treatment of symptomatic paroxysmal (episodes <7 days) or persistent AF (>7-day and ≤one-year episodes) at our institution in the year 2012. A medical history was obtained from outpatient visit data collected by thoroughly reviewing medical records, including electrocardiograms (ECGs) and Holter ECG recordings of AF episodes.

The diagnostic criteria of diabetes mellitus were a fasting plasma glucose level of ≥126 mg/dl, a HbA1c of ≥6.5%, or a random plasma glucose level of ≥200 mg/dl [9].

The study was approved by the institutional ethics committee and was performed according to the Declaration of Helsinki principles. Exclusion criteria were acute reversible causes of AF, moderate-to-severe valvular stenosis or insufficiency, congenital heart disease, myocardial infarction or coronary artery bypass graft surgery <3 months before ablation, severe respiratory insufficiency, bleedi'ng diathesis or intolerance to heparin or oral anticoagulation, left atrial (LA) thrombus at time of ablation, pregnancy, severe comorbidity, or New York Heart Association class IV heart disease.

* Corresponding author at: Department of Cardiology, Kerckhoff Heart Center, Benekestr. 2-8, 61231 Bad Nauheim, Germany.
E-mail address: e.akkaya@kerckhoff-klinik.de (E. Akkaya).

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2.2. Preprocedural management

Transesophageal echocardiography before PVI excluded the presence of intracavitary thrombi. LA area was measured by transthoracic echocardiography, and left ventricular ejection fraction was calculated by the modified Simpson's method from apical 4- and 2-chamber views [10].

The LA measurement was performed at end-systole using an apical 4-chamber view, just before the opening of the mitral valve. Therefore, the inner border of the LA was traced, excluding the area under the mitral valve annulus and the inlet of the pulmonary veins. Peripheral venous blood samples were collected after an overnight fast on the day of hospital admission. Oral anticoagulation therapy included interrupted phenprocoumon with heparin bridging or continuous phenprocoumon, targeting an internationally normalized ratio >2 before PVI. Depending on the number of daily doses, patients on novel oral anticoagulants received their last dose 12–24 h before PVI. The risks of ablation were discussed in detail with the patients, all of whom provided written informed consent before the procedure.

2.3. Ablation procedure

All CB-Adv ablations were performed under conscious sedation or general anesthesia. After a single transseptal access with an SL-1 sheath (Abbott, Chicago, IL, USA) by means of the modified Brockenbrough technique (BRK-1, Abbott), an exchange wire was placed in the left superior pulmonary vein (PV). The SL-1 sheath was replaced with a steerable sheath (FlexCath Advance™, Medtronic). LA and PV anatomy were visualized by PV angiography. The PV anatomy was classified as normal or atypical according to the absence/presence of a common ostium or additional veins. When the PV united before entering the outer left atrial contour to form a common truncus, the ostium was defined as a common ostium. Additional or accessory PVs were defined as those entering the left atrium in separate ostia. Through the steerable sheath, a 15- or 20-mm-diameter Achieve™ inner lumen-mapping catheter (Medtronic) was placed proximal to each PV ostium to record baseline PV signals before ablation. The 28-mm CB-Adv was advanced over the Achieve catheter, inflated, and positioned at each PV ostium. Vessel occlusion and backflow into the atrium were assessed by selective contrast injection. If occlusion was acceptable, a freeze-thaw cycle was initiated. The Achieve catheter was used actively during cryoablation, and the time to PV isolation ("time-to-effect") was recorded "online" when PV potentials disappeared or were dissociated from LA activity. If online signals were unavailable due to distal positioning of the Achieve catheter, it was retracted after completion of the freeze-thaw cycle to a more proximal position at which PV potentials had been recorded before the ablation. During ablation of septal PVs (beginning with the right inferior PV), a decapolar catheter (IBI, Abbott) was positioned in the superior vena cava for diaphragmatic stimulation by electrical pacing of the ipsilateral phrenic nerve. Phrenic nerve capture was monitored by tactile feedback of diaphragmatic contraction. Energy delivery was interrupted immediately if weakening or loss of diaphragmatic contraction was noted.

In cases in which periprocedural AF persisted after isolation of all PVs, sinus rhythm (SR) was restored by electrical cardioversion. Finally, isolation of all PVs with a verified exit and entrance block for ≥30 min was documented. Patients with a history of typical atrial flutter also underwent cavotricuspid isthmus RF ablation with a 4-mm irrigated-tip catheter (Thermocool, Biosense Webster, Diamond Bar, CA, USA). Pericardial effusion was excluded by echocardiography immediately after ablation.

2.4. Postprocedural management

Patients were monitored by telemetry for ≥24 h. In patients with persistent phrenic nerve palsy (PNP) at the end of the procedure, phrenic nerve function was assessed via chest radiography of diaphragmatic movement before discharge. Oral anticoagulation was prescribed for 3 months postprocedurally and according to CHA_2DS_2-VASc score thereafter. Periprocedural complications were defined as described in the consensus statement [8].

2.5. Follow-up

Clinical success was defined as freedom from AFLAT (AF, atrial flutter, or atrial tachycardia [AT]) recurrence >30-s following the 3-month blanking period from the date of the ablation procedure in the absence of AAD therapy. Our strict follow-up protocol is consistent with the latest recommendations [8]. Patients were monitored via resting ECG, 7-day Holter-ECG, and echocardiography during follow-up visits at 3- or 6-month intervals in the first year. Late follow-up (>1 year post-intervention) was performed once a year. Follow-up was additionally monitored by structured telephone interviews to assess any additional adverse events and complications. Symptoms of arrhythmia recurrence were evaluated, and in cases with AFLAT documented by a Holter study or ECG, the data were added to the database.

2.6. Statistical analysis

Continuous data are presented as means and medians with standard deviation and interquartile ranges, and categorical variables are given as numbers and percentages. The effects of discrete variables were studied by means of Kaplan-Meier survival analysis with the log-rank test. Univariate associations of continuous variables were tested by means of receiver operating characteristic analysis, and parameters were dichotomized at the optimal cut-off point determined from the maximum sum of specificity and sensitivity. The impacts of discrete variables on outcomes were determined with positive and negative prediction accuracy and hazard ratio. To avoid model over-fitting, only parameters significantly associated with the outcome in the univariate analyses were included in the multivariate Cox regression model performed by means of a step-down procedure. Two-tailed P-values ≤0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline patient characteristics

A total of 178 patients with a history of paroxysmal (132/178 [74.2%] patients) or persistent AF (46/178 [25.8%] patients) underwent CB-Adv ablation. The baseline characteristics of all patients are summarized in Table 1.

3.2. Procedural characteristics

All cryoablations were performed with the 28-mm CB-Adv, which allowed isolation of all veins without the need for additional focal catheter ablations. A freeze-cycle of 240-s duration was applied to all patients, whereby 51 aborted freezes were documented. After successful PVI one additional bonus-freeze-cycle was applied in the first 168 patients, while a single freeze approach was admitted to the last 11 patients. PVI was achieved with a median of 2 freezes/vein in the 693 veins identified. Online mapping was available in 382 (55.1%) PVs, and "single-shot" isolation was achieved in 549 (79.2%) of the targeted PVs. The minimal nadir temperature was achieved in the right superior PV. The median procedure and fluoroscopy times were 126 (114/150) and 20 (16/26) min, respectively. At the beginning of the procedure, 154 patients (86.5%) were in SR, and 24 (13.5%) presented with AF. Conversion to SR occurred during ablation in 9 of the 24 patients. In the remaining 15 patients, SR was restored by external electrical cardioversion. Procedural characteristics are displayed in Table 2.

3.3. Complications

There were no periprocedural deaths, strokes, atrioesophageal fistulas, pericardial effusions/tamponades or PV stenoses. PNP, the most common complication, was present in 14 (7.9%) patients, of which 2 (1.1%) had recovered by hospital discharge; PNP occurred during right superior PV cryoablation in all 14 patients. Early termination of cryoenergy application during right phrenic pacing did not prevent the subsequent occurrence of PNP. In all patients, right phrenic nerve function was fully recovered within 12 months of follow-up. One patient had a transient air embolism, resulting in transient ST-segment elevation in the inferior leads and chest pain for several seconds. The clinical symptoms and ECG changes self-resolved without further consequences. Three (1.7%) additional patients had vascular complications (minor groin hematoma), which were treated conservatively.

3.4. Follow-up

The 5 years success rate after CB-Adv ablation procedure was 59.0% in the abscense of AADs (Fig. 1A) with recurrences due to AF (n = 67, 91.8%), AT (n = 6, 8.2%) or typical atrial flutter (n = 1, 1.4%). One patient showed AF with coexisting AT. Out of 132 patients with paroxysmal AF, 81 (61.4%) were AFLAT-free compared to 24 of 46 (52.2%) patients with persistent AF (Fig. 1B, P = 0.20). Arrhythmia-free survival rates after a single ablation procedure were 90.9%, 82.6%, and 71.1% at 1, 2 and 3 years.

Electrical cardioversion was performed in 5 patients during follow-up. After the blanking period, 17 patients received AAD therapy (six of them until repeat ablation) as follows: flecainide (n = 13, 7.3%), amiodarone (n = 2, 1.1%), dronedarone (n = 1, 0.6%) and sotalol (n = 1, 0.6%). The daily dosages administered were: flecainide 100/200 mg (2/11 patients),