International Journal of Cardiology 259 (2018) 76–81

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Second-generation cryoballoon ablation as a first-line treatment of symptomatic atrial fibrillation: Two-year outcome and predictors of recurrence after a single procedure

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

[a] Dept. of Cardiology, Kerckhoff Heart Center, Bad Nauheim, Germany
[b] Med. Clinic I, Justus Liebig University, Giessen, Germany

ARTICLE INFO

Article history:
Received 25 August 2017
Received in revised form 17 October 2017
Accepted 3 November 2017

Keywords:
First-line catheter ablation
Predictors
Pulmonary vein isolation
Second-generation cryoballoon
Symptomatic atrial fibrillation
Two-year outcome

ABSTRACT

Introduction: Antiarrhythmic drug (AAD) therapy of patients with atrial fibrillation (AF) has limitations. We investigated the 2-year outcome and pre-procedural predictors of recurrence for first-line catheter ablation using the second-generation cryoballoon (CB-Adv) in a large cohort of patients with symptomatic AF.
Methods and results: For this prospective observational study, we enrolled 457 patients with symptomatic AF (278 paroxysmal, 179 persistent) who had no history of AAD use and who underwent pulmonary vein isolation (PVI) with the CB-Adv at our institution. Follow-up data, including Holter-ECGs, were collected during outpatient clinic visits. The impact of several variables on outcome was evaluated in univariate and multivariate analyses and Cox proportional hazards regression models. Median follow-up duration was 28 (interquartile range 15/42) months. PVI was sufficient in restoring and maintaining sinus rhythm in 79.2% ($n = 362$) of patients. The median procedure and fluoroscopy times were 90 (72/120) and 16 (12/21) min, respectively. Phrenic nerve injury occurred in 16 (3.5%) patients, persisting until hospital discharge in 6 (1.3%) patients; phrenic nerve function recovered in all patients during follow-up. Seven patients developed groin hematomas (1.5%). Cox regression analysis showed that left atrial area >21 cm^2 independently predicted recurrence.
Conclusion: This is the first demonstration that PVI with CB-Adv is safe and effective as a first-line treatment of symptomatic AF. Sinus rhythm persisted in 79.2% of patients even 2 years after ablation. The success rate was lower in patients with enlarged left atria.

1. Introduction

According to current guidelines [1], pulmonary vein isolation (PVI) is a Class I/A recommendation for symptomatic, drug-refractory, paroxysmal atrial fibrillation (AF). First-line ablation, prior to antiarrhythmic drug (AAD) therapy, is also an option for symptomatic paroxysmal AF. Treatment with PVI using the radiofrequency (RF) technique prior to AAD therapy in paroxysmal AF patients is superior [2–4] or at least non-inferior [5] to medical treatment. Complication rates are similar when ablation is performed by experts. Consequently, first-line PVI is considered to be a Class IIa/B recommendation for symptomatic paroxysmal AF suitable for patients preferring PVI or for those with contraindications for AAD therapy [1]. First-line RF ablation and cryoballoon (CB) ablation showed similar short-term outcomes in paroxysmal AF patients [6], but CB ablation offers some advantages over RF ablation [7]. In addition, the second-generation CB (CB-Adv) is more effective than the first-generation device for acute PVI and is associated with better clinical outcomes [8]. Short- to midterm studies employing the CB-Adv show acceptable rates of freedom of AF: 67% [9] to 83.6% [10] for patients with drug-refractory paroxysmal AF and 56% [11] to 69% [12] for patients with persistent AF. Not surprisingly, PVI with the CB-Adv is being increasingly performed as a first-line therapy [6]. Here we present the first report of 2-year outcomes and pre-procedural predictors of arrhythmia recurrence after first-line CB-Adv PVI for treatment of paroxysmal and persistent AF in a large cohort of patients.

2. Methods

2.1. Study population

For this prospective observational study, we enrolled all patients (May 2012–June 2016) with symptomatic AF who did not have a history of rhythm control with AADs, owing either to contraindications or refusal of chronic drug therapy (first-line ablation). Medical histories were obtained during clinic visits and all medical records, including ECGs and Holter-ECG recordings showing AF episodes, were reviewed. The study was approved by the institutional ethics committee and complied with the principles of the Declaration of Helsinki. We excluded patients who presented with acute reversible causes of AF, moderate-to-severe valvular stenosis or regurgitation, congenital 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).

https://doi.org/10.1016/j.ijcard.2017.11.011
0167-5273/

myocardial infarction or coronary artery bypass graft surgery within the 3 months before ablation, severe respiratory insufficiency, known bleeding diathesis or intolerance for heparin or oral anticoagulation, left atrial (LA) thrombus at the time of ablation, pregnancy, severe comorbidity, or New York Heart Association class III or IV heart disease.

2.2. Pre-procedural management

Transesophageal echocardiography before PVI excluded intracavitary thrombi. LA area was measured by transthoracic echocardiography; left ventricular ejection fraction was calculated by the modified Simpson's method from apical 4- and 2-chamber views [13]. 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. All patients gave written informed consent before the procedure.

2.3. Ablation procedure

CB ablation was performed under conscious sedation or general anesthesia. We used biplane fluoroscopy with 60° left and 30° right anterior oblique views. After single transseptal access with an SL-1 sheath (St. Jude Medical, Minneapolis, MN, USA) using the modified Brockenbrough technique (BRK-1, St. Jude Medical), an exchange wire was placed in the left superior pulmonary vein (PV). The SL-1 sheath was then replaced with a steerable sheath (FlexCath Advance™, Medtronic, Minneapolis, MN, USA). 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. Diagnostic mapping was conducted with a 6-Fr decapolar catheter (IBI, St. Jude Medical). Through the steerable sheath, a 15- or 20-mm-diameter inner lumen mapping catheter (Achieve™, Medtronic) was placed proximal to each PV ostium to record PV signals before ablation. The 28-mm CB-Adv (Arctic Front Advance™, Medtronic) was advanced over the Achieve catheter, inflated, and positioned at each PV ostium. Selective contrast injections revealed any vessel occlusion or atrial backflow. If occlusion was acceptable, a ≥180-sec freeze-thaw cycle was initiated. The Achieve catheter was used actively during cryoablation; time to PV isolation ("time-to-effect") was recorded "online" when PV potentials completely disappeared or were dissociated from LA activity. During septal PV ablation, the decapolar catheter was positioned in the superior vena cava for diaphragm stimulation via electrical pacing of the ipsilateral phrenic nerve (2500-msec cycle). Phrenic nerve function loss was detected using diaphragmatic compound motor action potentials or by tactile feedback of diaphragmatic contraction.

For periprocedural AF without conversion to sinus rhythm (SR), electrical cardioversion was performed. Finally, isolation of all PVs with verified exit and entrance blocks for ≥30 min after initial PVI was documented as procedural endpoint. 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. Post-procedural management

Patients were monitored by telemetry for ≥24 h. In patients with persistent phrenic nerve palsy (PNP) at procedure end, phrenic nerve function was assessed via chest radiography of diaphragmatic movement before discharge. Oral anticoagulation was prescribed for at least 3 months postprocedurally and according to the CHA_2DS_2-VASc score thereafter. Periprocedural complications were defined as described in the consensus statement [16].

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 fulfills the latest recommendations [14]. Patients were monitored via resting ECGs, 7-day Holter-ECGs, and echocardiography during follow-up visits at 3-month intervals in the first year and every 6 months thereafter. Follow-up was also monitored by structured telephone interviews to assess additional adverse events and complications. Symptoms of arrhythmia recurrence were evaluated, and cases with AFLAT documented by a Holter study or ECG were added to the database. If arrhythmias recurred during the blanking period, AADs were prescribed until the end of the 3-month follow-up period.

2.6. Statistical analysis

Continuous data are presented as means and medians with standard deviation and interquartile (25/75) range (IQR); categorical variables are given as numbers and percentages. Effects of discrete variables were studied using Kaplan-Meier survival analysis with the log-rank test. Univariate association of continuous variables, including constructed scores with outcome, was analyzed using receiver operating characteristic curves; parameters were dichotomized at the optimal cut-off point determined from the maximum sum of specificity and sensitivity. The impact of discrete variables on outcome was determined with positive and negative prediction accuracy and hazard ratio. To avoid model over-fitting, only parameters significantly associated with outcome in the univariate analyses were included in the multivariate Cox regression model performed using the 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

The study included 457 consecutive patients with symptomatic AF (278 paroxysmal, 179 persistent) without a history of AAD use for rhythm control. Patients with persistent AF had a significantly larger LA area than those with paroxysmal AF (median LA area 22.9 cm^2 vs. 18.7 cm^2, $P < 0.01$). In most of the patients, AF history was ≤3 years. The baseline characteristics of all patients are summarized in Table 1.

3.2. Procedural characteristics

We isolated 1788 PVs with a median of 8 (5/9) freezes per patient. Online mapping was available for 1045 (58.4%) PVs; single-shot isolation was achieved in 1599 (89.4%) of the targeted PVs. The minimal nadir temperature was registered in the right superior PV. The median fluoroscopy time and procedure time (from groin puncture to extraction of all catheters) were 16 (12/21) and 90 (72/120) min, respectively. At the beginning of the procedure, 144 (31.5%) patients presented with AF; among these, procedural conversion to SR occurred in 26 (5.7%), and SR was restored by external electrical cardioversion in the other 118 (25.8%) patients. In all patients, complete circumferential PVI was achieved in all veins with the 28-mm CB-Adv without additional RF-based touch-up lesions. However, all procedures were performed by highly experienced operators, which might explain the high degree of procedural success and short procedure and fluoroscopy times. Procedural characteristics are displayed in Table 2.

3.3. Complications

There were no periprocedural deaths, atrio-esophageal fistulas, or PV stenoses. PNP occurred in 16 (3.5%) patients and persisted until hospital discharge in 6 (1.3%) patients. By the 6-month follow-up, phrenic nerve function recovered in all patients. All instances of PNP occurred

Table 1
Baseline clinical and demographic characteristics of all patients ($n = 457$).

Baseline characteristics	
Patients, n	457
Demographic variables	
Age, y (IQR 25/75)	61 (54/68)
Female gender, n (%)	177 (38.7)
Medical history	
Paroxysmal AF, n (%)	278 (60.8)
Structural heart disease, n (%)	44 (9.6)
History of AF, months (IQR 25/75)	19 (6/36)
Episode duration of AF, h (IQR 25/75)	43 (5/150)
Right atrial flutter, n (%)	49 (10.7)
Hypertension, n (%)	306 (77.0)
Diabetes, n (%)	44 (10.1)
BMI, kg/m^2 (IQR 25/75)	27.3 (24.9/30.7)
History of stroke/TIA, n (%)	25 (5.5)
Sleep apnea, n (%)	16 (3.5)
Vitamin K antagonists, n (%)	76 (16.6)
Novel oral anticoagulants, n (%)	221 (48.4)
CHA_2DS_2-Vasc Score, mean ± SD	1.5 ± 1.2
Echocardiography	
LVEF, % (IQR 25/75)	62 (57/62)
LA area, cm^2 (IQR 25/75)	20.5 (17.3/23.9)
Laboratory data	
GFR, ml/min/1.7 m^2 (IQR 25/75)	93.8 (79.1/105.5)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; IQR, interquartile range; GFR, glomerular filtration rate; LA, left atrial; PV, pulmonary vein; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; SD, standard deviation; TIA, transient ischemic attack.