Journal of Arrhythmia 33 (2017) 81–85

Contents lists available at ScienceDirect

Journal of Arrhythmia

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

Original Article

A multicenter study of the need of additional freezing for cryoballoon ablation in patients with atrial fibrillation: The AD-Balloon study

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ARTICLE INFO

Article history:
Received 12 May 2016
Received in revised form
14 June 2016
Accepted 27 June 2016
Available online 27 July 2016

Keywords:
Cryoballoon
Paroxysmal atrial fibrillation
Pulmonary vein isolation

ABSTRACT

Background: Pulmonary vein isolation (PVI) is a cornerstone of catheter ablation in patients with paroxysmal atrial fibrillation (PAF), and balloon-based ablation has been recently performed worldwide. Ablation using the second-generation cryoballoon (CB2) (Arctic Front Advance™, Medtronic, MN, USA) is useful for PVI; however, there is some debate concerning the optimal freezing time and number of cycles after PVI is achieved.

Methods: The AD-Balloon study was designed as a prospective, multicenter, randomized clinical trial to evaluate the optimal strategy (freezing cycles) of CB2 ablation (UMIN Clinical Trials Registry UMIN000020130). The main objective of this study is to investigate the need for an additional freezing cycle after PVI in patients treated with CB2 ablation. Patients will be randomly assigned in a 1:1 ratio to treatment with additional freezing (AD group) or without additional freezing (non-AD group). In the AD group, 3 min of additional freezing time will be applied in all pulmonary veins after PVI is confirmed at the previous freezing cycle. In the non-AD group, no additional freezing will be applied in all pulmonary veins after PVI is confirmed. The primary endpoint of this study is the occurrence of atrial tachyarrhythmias within a 1-year follow-up period. We will enroll 110 consecutive patients with PAF. We will also investigate the usefulness of delayed-enhancement magnetic resonance imaging to assess the ablation lesions caused by CB2 ablation.

Results: The results of this study are currently under investigation.

Conclusion: The AD-Balloon study would assess the need for an additional freezing cycle after PVI is achieved. Our findings may contribute to further improvement of the CB2 ablation procedure.

1. Introduction

Pulmonary vein isolation (PVI) is an established strategy of paroxysmal atrial fibrillation (PAF) ablation [1–3]. Radiofrequency catheters have been the standard for AF ablation; however, PVI using balloon-based ablation has been increasingly adopted by electrophysiology laboratories around the world [4–6]. The second-generation cryoballoon (CB2) (Arctic Front Advance™, Medtronic, MN, USA), which is designed to achieve more uniform cooling across the entire distal hemisphere of the balloon, has been recently launched on the market for the treatment of PAF. CB2 ablation is effective for the treatment of PAF; however, there is some debate concerning the optimal number of freezing cycles, the ideal freezing duration of each cycle, and the appropriate patient characteristics for CB2 ablation. No prospective, randomized clinical CB2 trials have been conducted to investigate the need for an additional (bonus) freezing cycle after PVI is achieved. We therefore conducted an investigation of the optimal freezing cycles in AF patients treated with CB2 ablation.

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http://dx.doi.org/10.1016/j.joa.2016.06.005

2. Material and methods

2.1. Objectives

The AD-Balloon study was designed as a prospective, multicenter, randomized clinical trial of the optimal strategy (freezing cycles) of CB2 ablation (UMIN Clinical Trials Registry UMIN000020130). The objectives of this study are, firstly, to investigate the need for an additional freezing cycle after PVI in patients treated with CB2 ablation; and secondly, to investigate the usefulness of delayed-enhancement magnetic resonance imaging (MRI) to assess the ablation lesions created by CB2 ablation.

2.2. Study design

The patients will be randomly assigned in a 1:1 ratio to treatment with an additional freezing (AD group) cycle or without additional freezing (non-AD group). In the AD group, 3 min of additional freezing time will be applied in all pulmonary veins (PVs) after PVI is confirmed during the previous freezing cycle. In the non-AD group, no additional freezing will be applied in any of the PVs after PVI is confirmed.

We will use Efron's biased coin design to allocate patients to either group with computer generated random numbers in order to reduce the predictability and selection bias. Researchers will obtain allocation results by registering subjects in a computer system. The system generating the random allocation was created by an independent third party.

The primary endpoint of this study is the occurrence of atrial tachyarrhythmias (ATs) at 1 year with a blanking period of 90 days after CB2 ablation. Based on previous studies in PAF patients, the incidence of recurrent ATs after a single CB2 ablation procedure with a blanking period of 90 days will be assumed to be 20% [4,7,8]. Considering the primary endpoint as a binary outcome, 55 patients in each group, and 110 patients in total will be required to achieve a 90% confidence interval in this study. Approximately 3–5 centers across Japan will participate in this study. The secondary efficacy endpoint is repeat ablation for ATs at 1 year without the blanking period. The secondary safety endpoints include procedural complications, total procedure time, and total fluoroscopy time.

The study protocol must be approved by each of the participating institutions. All participants are required to provide written informed consent (M26-159, Nov 27, 2015).

2.3. Study population

We will enroll 110 consecutive patients with PAF. The patient inclusion criteria for enrollment are as follows: (1) a diagnosis of PAF in accordance with the 2014 AHA/ACC/HRS guideline on the management of patients with atrial fibrillation [3]; (2) treatment with CB2 ablation for PAF; and (3) aged 20–85 years, regardless of the sex.

The exclusion criteria of this study are as follows: (1) aged $<$ 20 or $\geq$ 85 years, (2) the presence of an intra-cavitary thrombus, (3) uncontrolled heart failure, (4) PV anomaly such as left common PV and confluent inferior PV, and (5) any contraindication to the procedure. Patients will be enrolled after confirming these exclusion criteria.

2.4. CB2 ablation procedure

Transesophageal echocardiography will be performed prior to CB2 ablation to exclude the presence of any thrombi in the atrium, including the left atrial appendage. The patients will also undergo a pre-procedural computed tomography to investigate the detailed left atrial and PV anatomies.

Details of the CB2 ablation procedure have been described in previous studies [4–6,9]. In brief, the 28-mm CB will be advanced into the left atrium (LA) via a 15F steerable sheath (FlexCath Advance™, Medtronic). The CB will be inflated proximal to each PV and pushed gently, aiming for an optimal balloon-to-PV ostium contact. Contrast medium will be injected through the central lumen of the CB to confirm a complete occlusion of the PV ostium or leak detection. The inner lumen mapping catheter (Achieve™, Medtronic) will be used to obtain the PV potential recordings for real time monitoring during the CB2 ablation.

We will conduct a 180-s freeze per cycle using the CB2 in both groups. The CB2 freezing will be terminated when the temperature decrease is colder than $-55\,^{\circ}C$ to avoid any deeper tissue injury [9]. When the initial freezing fails to isolate the PV, a second freezing cycle will be applied to the same PV in both groups. In the AD group, an additional 180-s freezing cycle will also be applied to each PV after the PVI. To avoid any deeper tissue injury, the additional freezing will be applied at a more antral site of the PV, which Su et al. have described as having a “golf ball on a tee” appearance [9]. When PVI is difficult by cryoballoon ablation, a touch up ablation (additional focal ablation) will be performed. The timing of touch up ablation and the catheter used will be determined by the operator (Freezor Max, Medtronic; FlexAbility™, St. Jude Medical, MN, USA; Cool Flex™, St. Jude Medical; Cool Pass Duo™, St. Jude Medical; ThemoCool Smart Touch, Biosense Webster, CA, USA; ThermoCool Surround Flow, Biosense Webster; Therapy™, St. Jude Medical, or Fantasista, Japan Lifeline, Tokyo, Japan).

Confirmation of the LA to PV electrical connection and PVI will be conducted with a circular mapping catheter (Optima™, St. Jude Medical; Lasso, Biosense Webster; or Libero, Japan Lifeline) at a proximal site in the ostium in each vein before and after CB2 ablation. Exit block from each PV will also be confirmed after PVI by pacing from the circular catheter within the PV.

All patients will receive therapeutic warfarin or direct oral anticoagulation (DOAC) at least 30 days before the procedure. Warfarin will be continued through the procedure. DOAC will be discontinued on the evening before the procedure or on the morning of the procedure, and resumed on the evening of the procedure or the morning after the procedure, depending on the kind of DOAC and whether the procedure is performed on the morning or afternoon.

2.5. Safety considerations

To avoid right phrenic nerve (PN) injury, we will ensure that the CB2 position is as antral as possible. The PN will be paced at twice the capture threshold using a deflectable circular catheter positioned at the superior vena cava, and palpation of the strength of the diaphragmatic excursions during PN pacing will be monitored [10]. The diaphragmatic excursion will also be confirmed visually by intracardiac echocardiography [11]. In addition, monitoring of the diaphragmatic compound motor action potentials will also be monitored [9,10]. PN pacing will be performed during the CB2 application to the right superior PV and right inferior PV. CB2 ablation will be terminated using a “double stop” technique immediately after any PN injury occurs.

To avoid esophageal injury, we will monitor both the CB2 and luminal esophageal temperature (LET) [12,13]. CB2 ablation will be terminated when the LET decreases to more than $-15\,^{\circ}C$.

2.6. Protocol of MRI acquisition

The details have been described in our previous work [14]. In brief, delayed-enhancement MRI will be performed 1–2 months after discharge using a 1.5-T scanner (MAGNETOM Sonata, Siemens, Erlangen, Germany) with a 6-channel body array coil. An intravenous bolus of 0.15 mmol/kg gadolinium contrast will be administered 20 min before a 3-dimensional (3D) electrocardiographically gated inversion-recovery gradient-echo sequence applied in the axial orientation. The cardiac MRI image will be reconstructed and analyzed using the software module workstation (Ziostation2; Ziosoft, Tokyo, Japan). The ablation scar will be extracted by tracing the hyperenhanced area on a source image, and the 3D volume-rendering images of the magnetic resonance angiography overlaid with the PV-LA scars will be reconstructed. The overlaid 3D images will be analyzed in terms of whether each PV is completely encircled by the scar and where the suspicious gaps in the lesions are located.

2.7. Follow-up

After discharge from the hospital, the patients will be scheduled for follow-up visits at 1 month, and then every 1–3 months, during which 12-lead electrocardiograms (ECGs), 24-h Holter recordings (3 and 12 months after the procedure), and/or cardiac event recordings will be obtained.

Discontinuation of antiarrhythmic drugs (AADs) is recommended after the CB2 ablation procedure; however, the decision to restart AADs after CB2 ablation will be determined by the patient's physician. All documented AT episodes of >30 s after the index procedure recorded by a standard ECG, 24-h ECG Holter monitoring, or cardiac event recorder during both a planned and symptom driven consultation will be considered as a recurrence. A 3-month blanking period will be employed after the ablation. When an AT recurrence occurs and the patient agrees, a second catheter ablation will performed.

2.8. Evaluations

The patient characteristics and status of the medical treatment at baseline in each group will be collected as presented in Table 1. The CB2 ablation procedures, results, complications, status of medical treatment after CB2 ablation, and follow-up data in each group will be collected as presented in Tables 2 and 3.

Registration for this study will be conducted by the medical staff of each center, who will be required to fill out a hard copy data sheet at enrollment and send it to the secretary of this study. The secretary of this study will assign the patients a specific ID for this study, which will be shared electronically with the medical staff at each center. The Medical staff may input the patient data into the website via their personal computers or hard copy data sheet. The follow-up data will be collected by each participating center.

The data will be provided via traditional or electronic mail using only the specific ID without the patient's name, and personal confidentiality will be protected. The data collection will begin after the ethical aspects of this study have been approved by the ethics committees at each center. All patients will be prospectively followed-up by the participating centers for at least 1 year.

2.9. Statistical analysis

The sample size was calculated based on the precision-based method. A sample size of 55 patients per group (equally sized-groups) will provide a two-sided 95% confidence interval (CI) for the difference in population proportions with a width that is equal to 0.35 when the two estimated group sample proportions are equally 0.20.

Analyses will be done according to an intention-to-treat (ITT) principle. Analysis of the per-protocol set will be also done to assess the robustness of the ITT analysis. Patient demographic data will be analyzed descriptively; categorical variables will be assessed with the chi-square test or Fisher's exact test, whereas continuous variables will be assessed with the Student's *t*-test or the Wilcoxon rank-sum test, as appropriate. The difference in the occurrence rate of AT between the two groups will be calculated with the 95% CI, and the two occurrence rates will be compared using the chi-square test. Also, the AT-free survival will be summarized using the Kaplan–Meier method in each group, and the survival curves will be compared by the log rank test. An additional exploratory logistic regression or Cox regression model will be fitted for planned subgroup analysis in which the odds ratio or hazard ratio will be stratified as described and, when applicable, with treatment as a covariate.

Table 1
Patient characteristics at baseline.

Age, years, *n* (%)
Age 65–74 years
Age >75 years
Male sex, *n* (%)
Height, cm
Weight, kg
Blood pressure, mmHg
Heart rate, /min
Duration of atrial fibrillation, months
Congestive heart failure, *n* (%)
Hypertension, *n* (%)
Diabetes mellitus, *n* (%)
Stroke and/or transient ischemic attack, *n* (%)
Structural heart disease, *n* (%)
Coronary artery disease
Valvular heat disease
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Valvular heart disease
Others
Post-open heart surgery
$CHADS_2$ score
CHA_2DS_2-VASc score
Echocardiographic data
Left ventricular ejection fraction, %
Left atrial dimension, mm (%)
PV anatomy, *n* (%)
Left common ostium
Right-sided early branching
History of anti-arrhythmic drug use, *n* (%)
Disopyramide
Cibenzoline
Aprindine
Pilsicainide
Flecainide, *n* (%)
Propafenone, *n* (%)
Bepridil, *n* (%)
Sotalol, *n* (%)
Amiodarone, *n* (%)
Verapamil, *n* (%)
Beta-blocker, *n* (%)
Digitalis, *n* (%)
Others, *n* (%)
Laboratory data

Abbreviations: PV, pulmonary vein.

3. Results

The results of this study are currently under investigation.

Table 2
The CB2 ablation procedure, results, complications.

Procedure time (groin puncture to catheter extraction), min
Fluoroscopic time, min
LSPV
Freezing cycles, *n*
Total freezing time, s
Time to isolation, s
Minimum balloon temperature, °C
Minimum LET during freezing, °C
The need for touch up RF ablation, *n*
LIPV
Freezing cycles, *n*
Total freezing time, s
Time to isolation, s
Minimum balloon temperature, °C
Minimum LET during freezing, °C
The need for touch up RF ablation, *n*
RSPV
Freezing cycles, *n*
Total freezing time, s
Time to isolation, s
Minimum balloon temperature, °C
Minimum LET during freezing, °C
The need for touch up RF ablation, *n*
RIPV
Freezing cycles, *n*
Total freezing time, s
Time to isolation, s
Minimum balloon temperature, °C
Minimum LET during freezing, °C
The need for touch up RF ablation, *n*
Cavotricuspid isthmus ablation, *n* (%)
Other adjunctive ablation, *n* (%)
Use of 3D mapping system, *n* (%)
Complications, *n* (%)
Total
Pericardial effusion requiring drainage
Pericardial effusion not requiring drainage
Transient ischemic attack
Cerebral infarction
Transient phrenic nerve paralysis
Prolonged phrenic nerve paralysis
Severe pulmonary vein stenosis
Hematoma at the puncture site
Pseudoaneurysm at the puncture site
Gastric hypomotility
Death
Discharge prescription, *n* (%)
Oral anticoagulant
Vitamin-K antagonist
Direct oral anticoagulant
Anti-platelet agents
Antiarrhythmic drugs
Disopyramide
Cibenzoline
Aprindine
Pilsicainide
Flecainide
Propafenone
Bepridil
Sotalol
Amiodarone
Verapamil
Beta-blocker
Digitalis
Others
Angiotensin converting enzyme inhibitor
Angiotensin II receptor blocker
Statin

Abbreviations: CB2, second-generation cryoballoon; RF, radiofrequency; 3D, three-dimensional.

4. Discussion

CB2 ablation provides more reproducible results and reduced procedural times than conventional radiofrequency catheter ablation [15,16]. In addition, some studies have reported a high rate of PVI durability and a high long-term AF free rate of about 80% using the CB2 ablation procedure [17].

Some clinical reports describing cryobiology stress the need for repetitive freezing cycles to extend the lethal effect at the periphery of the target tissue [18,19]. On the other hand, recent studies on the CB2 have shown that a single 3-min freezing cycle may be sufficient for a durable PVI [7,20]. Chierchia et al. reported the initial experience of 3-min freeze cycles using the CB2 [7]. Fifty-two consecutive patients were included in the study. In the first 24 (46%) consecutive patients, an additional freezing cycle after PVI was performed, and it was not given in the subsequent 28 patients (54%). As a result, there were no differences in the recurrence rate between patients with and without an additional freezing cycle after PVI. However, patients were not randomly assigned, and the learning curve might have affected the results in the study about the initial experience with CB2 ablation. We therefore assess the optimal freezing cycles in AF patients treated with CB2 ablation in this prospective, multicenter, and randomized clinical trial.

Table 3
MRI acquisition.

LSPV
The presence of lesion gaps
The location of gaps
The length of gaps
Lesion volume, ml
LIPV
The presence of lesion gaps
The location of gaps
The length of gaps
Lesion volume, ml
RSPV
The presence of lesion gaps
The location of gaps
The length of gaps
Lesion volume, ml
RIPV
The presence of lesion gaps
The location of gaps
The length of gaps
Lesion volume, ml

Abbreviations: MRI, magnetic resonance imaging.

5. Conclusions

The AD-Balloon study will be the first prospective investigation to assess the need for an additional (bonus) freezing cycle after PVI is achieved. Our findings may contribute to further improvement of the CB2 ablation procedure.

Role of the funding source

The AD-Balloon study is partly supported by the Intramural Research Fund (25-4-7, Kusano) for Cardiovascular Diseases of National Cerebral and Cardiovascular Center. There is no specific sponsor that has a role in the study design or conduct of the study, collection of the data, its analysis or its interpretation, or in the preparation of the present manuscript. The authors have full access to all data and take full responsibility for the integrity of the data in this study, and for the decision to submit this manuscript for publication.

Conflict of interest

All authors declare no conflict of interest related to this study.

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