

# Safety and Efficacy of Cryoballoon Ablation for the Treatment of Atrial Fibrillation in Diabetic Patients

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## Abstract

**Background:** Cryoballoon based catheter ablation (CB-CA) is an established therapy for treatment of symptomatic atrial fibrillation (AF). However, data about AF ablation using the CB in the diabetic population is sparse. The aim of this single center retrospective study is to evaluate the safety and efficacy of CB ablation in patients with diabetes mellitus (DM) as compared to patients without DM.

**Methods and results:** Between July 2015 and December 2017, 397 consecutive patients underwent CB-CA for AF. Forty-eight consecutive patients with DM (DM group, study group) were compared with propensity score-matched patients without DM (n=48, control group). All patients underwent pulmonary vein isolation (PVI) using the second-generation CB (CB2). The mean age in the DM group was 66.9±9.5 years and 69.5±8.8 in the non-DM group (p=0.18). During a follow-up of 12.7±5.1 months, single procedure success rate for the DM and the non-DM group was 68.7% and 70.8%, respectively (p=0.82). The most common complication was transient phrenic nerve palsy (4 DM group vs. 0 non-DM group, p=0.04). No severe complication such as procedure related deaths, atrio-esophageal fistula or cerebrovascular embolic events occurred.

**Conclusions:** Our data strengthen the value of CB2 based ablation for the treatment of AF as an effective and safe procedure in DM patients, with similar success rates when compared with a non-DM population.

## Introduction

The prevalence of atrial fibrillation (AF) is markedly increased in patients with diabetes mellitus (DM) <sup>[1,2]</sup>. This risk of AF occurrence is increased due to macro- and microvascular dysfunction, diabetic autonomic neuropathy and systemic inflammation leading consequently to atrial remodeling and fibrosis <sup>[1]</sup>.

## Key Words

Atrial fibrillation, Cryoballoon, Catheter ablation, Diabetes mellitus

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Catheter ablation (CA) of symptomatic patients with AF by targeting the pulmonary veins (PV) is widely used as recommended by current guidelines <sup>[3-5]</sup>. Single shot techniques such as the cryoballoon (CB) technology have been developed to facilitate the ablation procedure and to improve outcome <sup>[6-8]</sup>. In the last years, CB based PV isolation (PVI) is increasingly performed <sup>[7,8]</sup>. CB-CA has been proven to be non-inferior to the current gold standard of manual point by point mapping and radiofrequency (RF) CA for AF with respect to success and complication rates <sup>[6,9]</sup>. Additionally, CB-CA has recently been shown to be an effective strategy for paroxysmal as well as persistent AF <sup>[4,6-8]</sup>.

The necessity of treating DM patients with AF is noticeably growing, as the prevalence of DM population increases [10-12]. DM has been associated with worse outcome after cardiac surgery and interventions [2,10]. The abnormal glucose metabolism in DM patients, has been shown to affect the atrial substrate properties with an intra-atrial conduction delay and a low voltage area formation, resulting in higher AF recurrence rate after RF based CA [13]. Despite the fact that several non-randomized clinical studies have addressed the issue of CA in DM and have shown favorable rates of success [11,12], little is known about the results of CB-CA in this population.

In this study, we aimed to assess the safety and efficacy of AF ablation using the second-generation CB (CB2, Arctic Front Advance, Medtronic, Inc. Minneapolis, MN, USA) in patients with DM compared to a non-DM group of patients and to analyze predictors of arrhythmia recurrence.

## Methods

Between July 2015 and December 2017, 397 patients with symptomatic paroxysmal or persistent AF and an indication for AF ablation according to current guidelines, who were scheduled for PVI using the CB2, were enrolled in this retrospective single center study. Patients with left atrial (LA) thrombus, uncontrolled thyroid dysfunction, contraindication to anticoagulation, pregnancy, previous AF-ablation, severe valvular disease and a LA size >60 mm were excluded. Severity of symptoms was recorded according to European Heart Rhythm Association (EHRA) score. Informed consent was taken from each patient before the procedure. The study was in compliance with the principals outlined in the Declaration of Helsinki and approved by the local Ethics Committee (No. 17-298). Patients were divided into a study group with diagnosed type 1 or type 2 DM (DM group) and a control group (non-DM group).

## Preprocedural management

Transesophageal echocardiography was performed in all patients prior to the procedure. Apart from echocardiography, no additional

**Table 1: Baseline characteristics of study patients.**

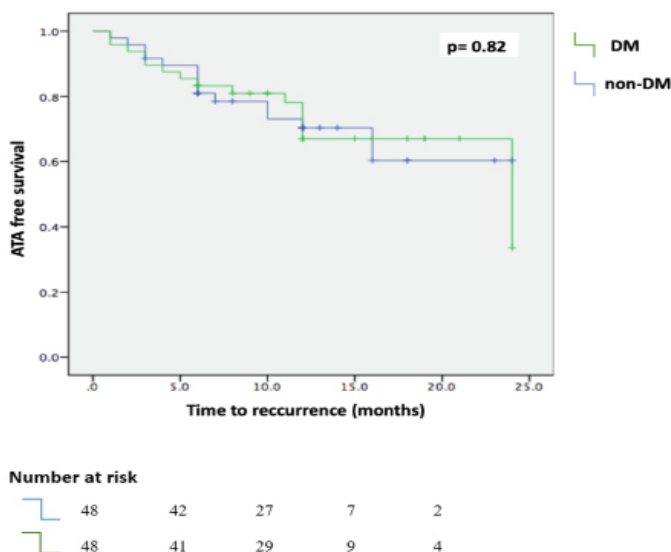
	Non-DM	DM	P value
Number of patients	48	48	
Age (years)	69.5 ± 8.8	66.9 ± 9.5	0.18
Male gender, n	27 (56.2%)	26 (54.1%)	0.83
Height (cm)	173.2±10.6	174.8±10.1	0.42
Weight (kg)	85.9±16.7	93.7±15.7	0.04
Hypertension, n	42 (87.5%)	44 (87.5%)	0.50
LA diameter (mm)	41.1±8.2	41.3±9.7	0.93
LVEF %	51.2±8.1	48.6±8.6	0.12
CHA2DS2VASc score	3.0±1.5	3.8±1.5	0.01
EHRA score	2.5±0.6	2.5±0.6	0.82
Previous Stroke/TIA, n	4 (8.3%)	5 (10.4%)	0.54
Previous MI, n	6 (12.5%)	14 (29.1%)	0.04
Cardiomyopathy, n	9 (18.7%)	11 (22.9%)	0.31
• Non-Ischemic	5 (10.4%)	7 (14.5%)	0.53
• Ischemic	4 (8.3%)	4 (8.3%)	1.00
Mean duration of AF (months)	16.8±21.9	20.8±23.9	0.40
Follow up period (months)	11.8±4.7	13.6±5.55	0.87
Persistent AF, n	29 (60.4%)	35 (72.9%)	0.13

LA: left atrium, LVEF: left ventricular ejection fraction, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary bypass grafting operation, AF: atrial fibrillation. EHRA: European heart rhythm association. TIA: transient ischemic attack. CTI: cavotricuspid isthmus.

pre-procedural imaging was performed. In patients on vitamin K antagonists, anticoagulation was continued throughout the procedure aiming at an INR of 2-3. In patients treated with novel oral anticoagulants (NOACs), the drug was discontinued up to 24 hours prior to the procedure and re-initiated 6 h post-ablation at half the regular dose, and at full dose the following day.

## Procedural management

All procedures were performed under deep sedation using midazolam, fentanyl, and propofol [14]. One 10-pole diagnostic catheter (Webster® CS Uni-Directional, Biosense Webster, Inc., CA, USA) was introduced via the right femoral vein and positioned within the coronary sinus. A single transseptal puncture was performed via the right 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, USA or PREFACE Biosense Webster). Heparin was administered after transseptal puncture to maintain an activated clotting time of ≥ 300 seconds. The transseptal sheath was then exchanged over a guidewire with a 12 French steerable sheath (Flexcath Advance, Medtronic). In order to identify all PV ostia, selective PV angiography was performed. In all patients, an esophageal temperature probe (Sensitherm, St Jude Medical, Inc. or CIRCA S-CATH™) was inserted and positioned according to the individual CB position to facilitate esophageal temperature monitoring during energy delivery. All ablation procedures were conducted with the 28 mm CB2. The 28 mm CB2 was advanced into the LA via the 12 French steerable sheath and a spiral mapping catheter (20 mm diameter; Achieve, Medtronic) was advanced into the target PV to record electrical activity. The CB2 was inflated proximal to the PV ostium and gently pushed against the PV ostium to facilitate complete antral sealing. Contrast medium injected through the central lumen of the CB2 was used to verify complete occlusion of



**Figure 1: Comparison of ATA free survival for DM vs non-DM patients**

**Table 2: Baseline characteristics of study patients.**

	Non-DM	DM	P value
Number of patients	48	48	
Additional CTI during the procedure, n	2 (4.1%)	2 (4.1%)	1.00
PV abnormality, n	14 (29.1%)	6 (12.5%)	0.03
• LCPV	8 (16.6%)	3 (6.2%)	0.10
• RMPV	6 (12.5%)	3 (6.2%)	0.62
Total procedure time (min)	122.5±33.3	127.5±38.3	0.50
Fluoroscopy time (min)	24.1±10.7	27.8±10.8	0.61
Freezes in LSPV (times)	1.2±0.4	1.3±0.7	0.23
Freezes in LIPV (times)	1.3±0.5	1.2±0.4	0.20
Freezes in RSPV (times)	1.3±0.5	1.3±0.5	0.85
Freezes in RIPV (times)	1.6±0.7	1.3±0.5	0.06
LSPV freeze duration (seconds)	251.8±95.6	264.7±126.7	0.57
LIPV freeze duration (seconds)	266.7±121.2	252.5±93.9	0.47
RSPV freeze duration (seconds)	250.9±138.9	257.5±143.5	0.82
RIPV freeze duration (seconds)	317.2±157.1	282.2±131.2	0.23
Minimum temperature in LSPV (°C)	48.6±6.2	48.6±6.6	0.98
Minimum temperature in LIPV (°C)	46.9±6.5	46.8±7.3	0.84
Minimum temperature in RSPV (°C)	48.8±6.5	48.8±6.7	0.97
Minimum temperature in RIPV (°C)	47.6±6.2	45.5±6.6	0.99
Balloon temperature <-60 °C (n)	8 (14.1%)	7 (12.2%)	0.42
Initial sinus rhythm, n	316 (92.9%)	52 (91.2%)	0.4
Cardioversion during procedure, n	24 (50.0%)	23 (47.9%)	0.83
Recurrence in blanking period, n	9 (18.7%)	8 (16.6%)	0.78
Late recurrence, n	14 (29.1%)	15 (31.2%)	0.82

LIPV: left inferior pulmonary vein; LSPV: left superior pulmonary vein; RIPV: right inferior pulmonary vein; RMPV: right middle pulmonary vein; RSPV: right superior pulmonary vein.

the PV ostium. Each freeze cycle duration lasted 180 seconds. If the time to PVI was longer than 60 seconds or no real time PV isolation recording could be obtained, 240 seconds freeze cycle and one more 180 seconds bonus freeze cycle were applied as per discretion of the operator. In patients demonstrating AF at the time of the procedure, electrical cardioversion was performed after the final freeze cycle and PVI was re-confirmed in sinus rhythm (SR). During energy delivery along the right PVs, continuous phrenic nerve pacing at maximum output and pulse width (12 mA, 2.9 ms) at a cycle length of 1000 ms was performed, using a diagnostic catheter positioned in the superior vena cava. Phrenic nerve capture was monitored by intermittent fluoroscopy and by tactile feedback of diaphragmatic contraction by the operator's hand positioned on the patient's abdomen. In addition, the continuous motor action potential (CMAP) was monitored. Refrigerant delivery was stopped immediately if weakening or loss of diaphragmatic movement, or the reduction of CMAP amplitude was noted. If phrenic nerve palsy (PNP) occurred, no additional freeze cycle was applied along the septal PVs. Cavotricuspid isthmus ablation (CTI), using an open irrigated radiofrequency catheter (Celsius ThermoCool or ThermoCool -SF, Biosense Webster), was solely performed in patients with documented or induced common type atrial flutter during the index procedure. PV abnormality was defined as left common ostium and/or a right middle PV.

### Postprocedural management

Following ablation, all patients underwent transthoracic

**Table 3: Parameters included in univariate analysis**

	P value
Gender	0.83
Age	0.79
hypertension	0.50
PV abnormality	0.03
LA diameter	0.32
LVEF	0.46
Early recurrence during BP	0.78
Diabetes mellitus	0.07
Cardiomyopathy of any type	0.31
Persistent AF	0.13
Mean duration of AF	0.26
Documented atrial flutter	0.56
Previous MI	0.04
CV during procedure	0.83

LA: left atrium, LVEF: left ventricular ejection fraction, MI: myocardial infarction, AF: atrial fibrillation, PV: pulmonary vein, CV: cardioversion, BP: blanking period.

**Table 4: Cox regression analysis. Predictors of ATA recurrence after multivariate analysis.**

	β	SE	Wald	df	Significance level	HR	CI 0.95	HR
Recurrence in blanking period	1.863	0.396	22.138	1	0.001	12.5	7.04	22.2
Persistent AF	1.171	0.543	4.662	1	0.03	2.45	1.41	4.27

SE: Standard error, df: degree freedom, HR: Hazard Ratio, AF: atrial fibrillation

echocardiography to rule out a pericardial effusion. All patients were treated with proton-pump inhibitors twice daily after the procedure until discharge and once daily for 6 weeks thereafter. Anticoagulation was continued for at least 3 months and thereafter based on the individual CHA<sub>2</sub>DS<sub>2</sub>-VASC score. To prevent early recurrence, antiarrhythmic drugs (ADD) were administered throughout a 3-month blanking period (BP). Our institutional approach strongly recommends the administration of AAD and discontinuation after BP. Due to patient preference or referring physician preference AAD was continued. Follow-up was performed either by the outpatient clinic or the referring cardiologist at 3, 6, and 12 months after the index procedure, as well as in case of symptoms suggestive of arrhythmia recurrence and included a ≥24 h-Holter recording and interrogations of implanted devices, if present. Symptoms suggestive of recurrent atrial tachyarrhythmia (ATA) prompted additional outpatient clinic visits.

Repeat ablation was offered to patients with symptomatic ATA recurrence after the BP, or symptomatic drug-refractory recurrent ATA within the BP that could not be managed without intervention. Repeat procedure was performed using a 3D Navigation system (CARTO-3, Biosense Webster). PVs were assessed for reconnection and re-isolation of the PVs was performed in case of recovered conduction. In case of AT, electro-anatomical mapping and entrainment mapping were performed to verify the mechanism and to guide the following RF ablation.



The primary endpoint of this study was any episode of documented ATA recurrence lasting longer than 30 seconds after a 3-month BP or triggering a repeat ablation within the blanking period. Secondary endpoints were complications related to the procedure, such as pericardial tamponade, PNP, cerebrovascular events, and groin complications.

### Statistical Analysis

Continuous data are presented as mean  $\pm$  standard deviation, skewed continuous parameters were expressed as median (interquartile range defined as Q1–Q3). Overall, 48 patients with DM were matched to 48 patients without DM. Propensity score matching was on a logistic regression model including age, sex, type of AF, hypertension, LVEF, LA size and prior transient ischemic attack (TIA)/stroke. Categorical data were summarized as frequencies and percentages and were compared using  $\chi^2$  test. Comparisons between baseline characteristics were performed by independent Student's t-test, Mann–Whitney rank-sum, Fisher exact, or  $\chi^2$  tests where appropriate. To analyze the association between baseline and procedural parameters on AF recurrence, binary logistic regression analysis was used. Parameters that were found to be univariately associated with the outcome and those that show a slight association with the outcome with  $P < 0.20$  were included in the multivariable analysis. Kaplan Meyer and cox regression analysis were performed to describe ATA free survival. Statistical analyses were performed using SPSS statistical software (version 22.0; SPSS Inc., Chicago, IL, USA). A 2-tailed  $P < 0.05$  was considered statistically significant.

### Results

A total of 397 patients with paroxysmal (180/397; 45.4%) and persistent (217/397; 55.6%) AF [30 (7.5%) patients had concomitant documented typical atrial flutter] undergoing PVI using the 28mm CB2 were included in the analysis; 48/397 (12%) patients had DM. The control group was selected by propensity score matching from patients without DM. It was based on a logistic regression model including age, sex, type of AF, hypertension, LVEF, LA size, and prior TIA/stroke. Baseline characteristics of the study population are summarized in Table 1. Patients in the DM group had a higher CHA<sub>2</sub>DS<sub>2</sub>-VASC score ( $3.8 \pm 1.5$  vs  $3.0 \pm 1.5$   $p = 0.01$ ) and a higher prevalence of previously known myocardial infarction (MI) (29.1% vs 12.5%,  $p = 0.04$ ). Additionally, there was a higher trend of persistent AF in DM group (72.9% vs 60.4 %,  $p = 0.13$ ). All targeted veins were isolated. Procedural characteristics are presented in Table 2. Anatomical PV abnormalities were observed in 6 patients (12.5%) in the DM group and 14 (29.1%) patients in the non-DM group ( $p = 0.03$ ). Total procedural time in the DM and non-DM groups were  $127.5 \pm 38.3$  vs  $122.5 \pm 33.3$  minutes ( $p = 0.50$ ).

### Clinical follow-up

Overall, during  $12.7 \pm 5.4$  months of follow-up, single procedure success rate was 70.8 % in the DM group and 72.9% in the non-DM group ( $p = 0.82$ ) (Figure 1). Early recurrence of ATA within the first 3 months after the index CB-CA occurred in 16.6% of patients in the DM group and 18.7% in the non-DM group ( $p = 0.78$ ). In multivariate analysis age, gender, hypertension, DM, PV abnormality, LA diameter, LVEF, cardioversion during procedure, early recurrence during the BP, Previous MI, cardiomyopathy of any type, documented atrial flutter, mean duration of AF and persistent AF, were included

as these parameters had  $p < 0.20$  in univariate analysis (Table 3). After multivariable Cox regression analysis, persistent AF ( $p = 0.03$ ) and early recurrence during the BP ( $p = 0.001$ ), but not DM, were found to be predictors of recurrence of ATA (Table 4). AAD was prescribed to all patients after the index procedure.

### Adverse events

Seven groin complications occurred (7 hematoma) in 4 DM patients and 3 in the non-DM group patients ( $p = 0.71$ ). Transient PNP occurred in 4 patients in the DM group (4 vs 0,  $p = 0.04$ ). PNP had no effect on prolongation of hospital stay. All PNP cases resolved spontaneously during follow-up. In one case pericardial tamponade occurred, that was managed by pericardial puncture (one in the non-DM group,  $p = 0.73$ ), but hospital stay was not prolonged in this patient. There were no severe complications (procedure related deaths, atrio-esophageal fistula or cerebrovascular embolic events).

### Discussion

This retrospective analysis investigated the safety and efficacy of CB2-CA in DM patients with paroxysmal and persistent AF and assessed predictors of ATA recurrence. The current analysis demonstrates that CB2-CA is a feasible and safe procedure in DM patients with similar success and complication rates as compared to a non-DM population. Persistent AF and early recurrence during the BP were found as predictors of recurrence of ATA.

Diabetic patients with AF have a worse cardiovascular outcome than those without, regarding mortality and hospitalizations [15,16]. Consequently, a rhythm control approach may be preferred in this group of patients to improve cardiovascular outcome [10,17].

However, data investigating the effect of CB<sub>2</sub>-CA in DM patients were limited by non-randomized small studies and limited number of patients [2,11,17].

The long-term outcome of CA in patients with AF and DM was studied in a meta-analysis by Anselmino and colleagues [11]. In this meta-analysis 15 studies with 1464 patients were included. Mean follow-up was 27 months. The overall complication rate was between 1.5–5.0 % and overall long-term success rate of maintaining SR was 66 (58–73) %. Advanced age, higher body mass index, and higher basal glycated haemoglobin level were found to be predictors of recurrence of ATA. In our analysis, the complication and success rates were similar to previous publications without significant differences between the both groups [11, 18, 19].

Recently, Bogossian et al. evaluated the efficacy and safety of CA for AF and atrial flutter (AFlut) in patients with DM [2]. Between 2007 and 2010, 8175 patients who underwent CA for AFlut or AF were included in this multicenter prospective registry. Patients with DM ( $n = 944$ ) were compared to patients without DM ( $n = 7231$ ). After a follow-up period of 366 days, there was no significant difference between AF groups in terms of major adverse cardiac and cerebrovascular events. CA of AF was mostly done with RF CA. CB-CA was the most frequent alternative energy source (DM: 17.1%, non-DM: 17.5%) [2].

The AF prevalence and the risk of AF recurrence are increased in

patients with DM due to atrial remodeling and fibrosis <sup>[1,10]</sup>. This correlation was also proven in our analysis where patients with DM presented more often with persistent AF and persistent AF was a predictor of recurrence of ATA. However, during our follow-up, single procedure success rate was similar between both groups. Similar ATA free survival in diabetic patients with more complex substrate can be attributed to additional ablative effects of CB-2. Besides ostial PV isolation, application of CB-2 results in large atrial lesion formation causing substrate modification, especially in the posterior LA wall. The spherical shape of CB-2 may cause a mismatch between the balloon and PV ostia during optimal contact causing additional atrial wall ablation that may eliminate components responsible for more diseased LA such as CFAEs, rotors, and vagal ganglia as well <sup>[20]</sup>. Recently the left atrial appendage was identified as a possible target for catheter ablation and radiofrequency and CB-2 based LAAI has been shown to improve clinical outcome. <sup>[21,22,23]</sup>

Phrenic nerve palsy was found to be more common in DM patients. In all cases, PNP resolved spontaneously during follow-up and did not prolonged hospital stay. However, DM itself may cause neuropathy and phrenic nerves of diabetic patients may be more sensitive to cryoenergy compared to nondiabetic individuals <sup>[1,2]</sup>.

The results of our analysis as well as of the abovementioned studies suggest that in patients with DM, CB2-CA is a safe and effective treatment strategy for symptomatic AF. Moreover, DM patients with good functional status and controlled glycemic levels <sup>[19]</sup> should be carefully evaluated and highly considered to receive CB2-CA with a favorable success rate and similar complication rate in comparison to non-DM patients.

There are some limitations of this study that need to be acknowledged. This analysis is retrospective in nature with moderate number of patients and without preprocedural cardiac imaging. Moreover, our follow-up did not include routine continuous monitoring with implanted devices or 7-day Holter recording and therefore our success rate may be overestimated. Nevertheless, follow up included 24-hour Holter monitoring, and/or device interrogations (if present), at three, six and 12 months. The effect of DM type, duration of DM, and HbA1c levels on CB2-CA outcome has not been assessed. Finally, no systematical esophagoscopy was performed in this study. Consequently, no data about the incidence of esophageal injury is available.

## Conclusions

Our data strengthen the value of CB2-CA for the treatment of AF as an effective and safe procedure in DM patients, with similar success and complications rates compared to non-DM population.

## Conflicts of interests

CHH received travel grants and research grants by Medtronic, Pfizer, Novartis, Claret Medical, SentreHeart, Biosense Webster, Boston Scientific and Cardiofocus. He received speaker's honoraria from Cardiofocus, Boston Scientific and Novartis. RRT received travel grants from St. Jude Medical, Topera, Biosense Webster, Daiichi Sankyo, SentreHeart and speaker's honoraria from Biosense Webster, Biotronik, Pfizer, Topera, Bristol-Myers Squibb; Bayer, Sano Aventis and research grants by Cardiofocus. CE received

travel grants and educational grants by Medtronic. KHK received travel grants and research grants from Biosense Webster, Stereotaxis, Prorhythm, Medtronic, Edwards, Cryocath, and is a consultant to St. Jude Medical, Biosense Webster, Prorhythm, and Stereotaxis. He received speaker's honoraria from Medtronic. All other authors have no relevant disclosures.

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