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Original Research

Influence of excess weight and obesity on performance and outcome of pulmonary vein isolation with the cryoballoon

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Pulmonary vein isolation (PVI) has become a cornerstone therapy in the treatment of atrial fibrillation (AF). Patients with overweight or obesity suffer more often from AF, and studies investigating the safety and feasibility of PVI in these patients have shown varying results. In this study we analyzed PVI performed with the 2nd generation cryoballoon (CB) with regard to safety, procedure and fluoroscopy time in patients with normal weight, overweight and obesity. We analyzed 228 consecutive patients treated with CB PVI in our hospital in 2018 and 2019. Fifty nine (25.88%) patients presented with normal weight (body mass index (BMI) of <25), 115 (50.44%) patients with overweight (BMI between 25 and 29.9) and 54 (23.68%) were obese patients (BMI >30). All pulmonary veins (PV) were isolated successfully. Concerning procedural parameters, neither complications, procedural time, nor fluoroscopy time differed significantly. There was a significant increase of dose area product (DAP) in obese patients compared to normal weight and overweight patients (2035.5 ± 1930.1 μGym^2 vs. 975.3 ± 814.9 vs. 1325.1 ± 2081.3, $p = 0.001$) but no significant difference between overweight and normal weight patients ($p = 0.611$). Our follow-up data of 168 patients (73.68%) observed for 12 months showed no differences in the recurrence of AF in the three BMI groups [80.9% vs. 83.3% ($p = 0.733$) vs. 86.55% ($p = 0.460$)]. In conclusion, CB PVI in overweight and obese patients is safe with similar levels of complications and recurrence of AF as patients of normal weight. However, obese patients and operators are exposed to higher radiation doses.

Keywords

Atrial fibrillation; Ablation; Arrhythmia; Overweight; Cryoballoon

1. Introduction

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia with increasing incidence and prevalence and is associated with increased morbidity and mortality [1]. Pulmonary vein isolation (PVI) has become a cornerstone therapy in the treatment of AF [2]. Its benefit has also been shown in patients with heart failure [3]. Besides radiofrequency (RF) ablation, cryoballoon (CB) PVI is a widely used technique especially since the parity to RF PVI was proven [4]. Obesity is increasing in almost every country worldwide [5]. It is associated with premature death and a heavy impact on healthcare expenses [6]. Since the 1980s the prevalence of obesity has doubled in more than 70 countries [7]. Obesity is associated with an increase of AF leading to atrial remodeling [8]. Furthermore, epicardial fat seems to play a key role in the development of AF [9]. Mahajan *et al.* [10, 11] showed that obesity leads to not only fibrosis and conduction abnormalities but also to the development of epicardial fat depots that serve as a substrate for AF. On the other hand, several studies point out that losing weight leads to a decrease of AF incidence. The LEGACY study by Pathak *et al.* [12] showed that patients who were offered a weight management program showed a significant reduction of AF burden when achieving a persistent weight loss of more than ten percent. Several studies on the safety of RF PVI in obese patients have been published showing a longer procedure time, greater radiation dose and impact on the patients outcome [13, 14]. Our study sought to investigate the influence of overweight and obesity on the performance of CB PVI with respect to both procedure and fluoroscopy time, dose area product (DAP), and safety.

2. Material and methods

2.1 Study design and procedural characteristics

We retrospectively analyzed 228 consecutive patients who underwent CB-PVI between 01/2018 and 12/2019 in our hospital. The choice of performing either CB or RF PVI had been at the operator's discretion. Patient body weight was assessed by weighing and body size was self-reported. The Body Mass Index (BMI) was calculated (kg/m^2). Patients were categorized as normal weight (BMI <25), overweight (BMI 25–29.9), and obese (BMI >30) in accordance with current definitions [15]. All patients were administered oral anticoagulants for a minimum of four weeks prior to the procedure. Phenprocoumon was continued during PVI. The administration of direct oral anticoagulants (DOAC) was

stopped on the day of the procedure for one dose in the morning on the day of the procedure. All patients, regardless of actual sinus rhythm or AF, underwent transesophageal echocardiography (TOE) to exclude intracardiac thrombus especially within the left atrial appendage before the procedure. Written informed consent was obtained from all patients before the procedure. All PVIs were performed by one of four experienced (>100 PVIs per year) investigators. PVI was conducted under deep sedation using midazolam and propofol. Transseptal puncture was performed with a fixed, 8F sheath (SL1; SJM, St. Paul, MN, USA) using a BRK-1 XS needle (SJM) under fluoroscopy and pressure monitoring. Afterwards, a stiff wire (Amplatz super stiff; Boston Scientific, Marlborough, MA, USA) was placed as a guiding wire into the left superior pulmonary vein (LSPV). Then, the fixed 8F sheath was exchanged for the 12F steerable CB sheath (Flexcath advance, Medtronic, Fridley, MN, USA) over the wire and the 28 mm CB (2nd generation, Arctic Front Advance, Medtronic, Fridley, MN, USA) was inserted in the LA targeting the PVs with a spiral catheter (Achieve, Medtronic, Fridley, MN, USA). After inflation, the correct occlusion of the targeted vein was made evident by dye injection. The freeze duration protocol was 240 seconds per freeze. Shortening of the freeze was necessary when the temperature of the esophagus decreased under 15–17 degrees Celsius or when the stimulation of the phrenic nerve was disturbed. The temperature of the esophagus was monitored using a temperature probe (Sensitherm; St. Jude Medical, St Paul, MN, USA). The phrenic nerve was monitored by stimulation and simultaneous palpation during the freezes of the right pulmonary veins.

Directly after the procedure pericardial effusion (PE) was excluded and the patient was monitored by telemetry for 24 hours. DOACs were re-administered the day of the procedure as long with phenprocoumon. Before discharge PE was excluded again by echocardiography. Anticoagulation medication was continued for a minimum of three months post ablation and then stopped or continued depending on the patients' CHA2DS2VASC score. Patients were advised to present to their cardiologists or to our outpatient clinic after 1, 3, 6 and 12 months for a follow-up with anamnesis of symptoms, a 12 lead ECG and a 24-hour Holter-ECG. AF recurrence within a three-month period after ablation (blanking time) was not considered.

2.2 Statistical analysis

For global test statistics we used a significance level of 5%. Continuous data is shown as mean ± standard deviation (SD). The exact Fisher-Test, Kruskal-Wallis-Test, Cox Regression, Kaplan-Meier plots and the Mann-Whitney-U-Test were used when appropriate. The exact Fisher-Test was used to test for independence of the three BMI group and categorical data (global test). The distributions of continuous data of the three BMI groups were compared by Kruskal-Wallis-Test (global test). For procedural data BMI groups were compared pairwise by either exact Fisher-Test or Mann-Whitney-U-Test when the p-value of the global test was below the level of significance. Data analysis was performed using Stata/IC 16.1 for Unix (StataCorp 4905 Lakeway Drive, College Station, TX 77845, USA).

3. Results

In all, successful PVI was performed and isolation of all PVs was achieved for 228 Patients (70.2% male, 29.8% female). No major complications occurred. In 19 patients, a common ostium of the left pulmonary veins was observed (cLPV; 8.3%). Fifty-nine (25.88%) patients presented with normal weight (BMI <25), 115 patients (50.44%) were overweight (BMI 25–29.9), and 54 (23.68%) patients had obesity. The patients' characteristics displayed in Table 1 showed no significant differences by sex (69.5% vs. 73.3% vs. 63.0% male, $p = 0.335$), age (59.9 ± 10.9 vs. 61.2 ± 10.1 vs. 60.7 ± 9.0 years, $p = 0.649$), body size (173.12 ± 10.05 vs. 174.41 ± 10.28 vs. 172.72 ± 9.87 cm, $p = 0.95$), type of AF (72.9% vs. 70.4% vs. 64.8% paroxysmal AF, $p = 0.628$), LA diameter (42.6 ± 6.2 vs. 44.5 ± 6.7 vs. 45.4 ± 7.7 mm, $p = 0.120$), symptoms (European Heart Rhythm Association [EHRA] score, $p = 0.817$) and comorbidities like arterial hypertension (45.8% vs. 44.3% vs. 53.7%, $p = 0.499$), diabetes mellitus (15.3% vs. 9.6% vs. 13.0%, $p = 0.491$), coronary artery disease (11.9% vs. 13.0% vs. 16.7%, $p = 0.766$) or dyslipidemia (22.0% vs. 18.3% vs. 24.1%, $p = 0.619$).

Obese patients took betablockers significantly more often and DOACs significantly less often compared to the other groups. Furthermore, the CHA2DS2VASC score was significantly elevated in obese patients.

Table 2 displays procedural parameters. There were no significant differences for most measures examined. Complications (3.4% vs. 1.7% vs. 1.9%, $p = 0.840$), nadir freeze temperature for all veins, procedural time (77.1 ± 18.8 vs. 78.1 ± 18.8 vs. 80.6 ± 18.6 min, $p = 0.424$) and fluoroscopy time (17.2 ± 7.5 vs. 17.1 ± 7.2 vs. 18.4 ± 7.6 min, $p = 0.662$) were similar across groups. Complications were few in the study sample. In the normal weight group, we observed one pseudoaneurysm without need of surgery and one phrenic nerve palsy which recovered by the end of the procedure. In the overweight group, we observed one pseudoaneurysm without need for surgery and a phrenic nerve palsy which recovered by discharge from the hospital and one pseudoaneurysm without surgical need in the obesity group.

There was a significant increase of DAP in obese patients compared to patients with normal weight and overweight (2035.5 ± 1930.1 μGym^2 vs. 975.3 ± 814.9 vs. 1325.1 ± 2081.3, $p = 0.001$) but no significant increase was observed comparing overweight and normal weight patients ($p = 0.611$).

Follow-up data was obtained for 168 (73.68%) patients presenting to our outpatient clinic. In this cohort, 47 (27.98%) were normal weight, 84 (50.00%) patients and 37 (22.02%) patients had overweight and obesity, respectively.

Table 1. Patient's characteristics of the three body mass index groups.

	BMI <25 (n = 59)	BMI 25–29.9 (n = 115)	BMI >30 (n = 54)	*p*-value
Age (years)	59.9 ± 10.9	61.2 ± 10.1	60.7 ± 9.0	0.649
Sex (male)	41 (69.5%)	85 (73.3%)	34 (63.0%)	0.335
Paroxysmal AF	43 (72.9%)	81 (70.4%)	35 (64.8%)	0.628
Body size (cm)	173.12 ± 10.05	174.41 ± 10.28	172.72 ± 9.87	0.95
Body weight (kg)	69.09 ± 9.94	83.26 ± 10.75	99.61 ± 12.85	<0.001*§¥
CHA2DS2VASC	1.6 ± 1.5	1.7 ± 1.4	2.2 ± 1.5	0.047
EHRA score (2, 3, 4)	25 (42.4%), 26 (44.1%), 8 (13.6%)	41 (35.7%), 58 (50.4%), 16 (13.9%)	17 (31.5%), 29 (53.7%), 8 (14.8%)	0.817
LA-Diameter (mm)	42.6 ± 6.2	44.5 ± 6.7	45.4 ± 7.7	0.120
Anticoagulation (DOAC)	56 (94.9%)	110 (95.7%)	44 (81.5%)	0.008*§
Betablocker	44 (74.6%)	76 (66.1%)	47 (87.0%)	0.0014*§
Arterial hypertension	27 (45.8%)	51 (44.3%)	29 (53.7%)	0.499
Diabetes mellitus II	9 (15.3%)	11 (9.6%)	7 (13.0%)	0.491
Coronary artery disease	7 (11.9%)	15 (13.0%)	9 (16.7%)	0.766
Dyslipidemia	13 (22.0%)	21 (18.3%)	13 (24.1%)	0.619

Legend: *: *p*-value for BMI >30 vs. BMI >25–29.9: <0.005; §: *p*-value for BMI >30 vs. <25: <0.005; ¥: *p*-value for BMI 25–29.9 vs. BMI <25: <0.005.

Table 2. Procedural data of the three body mass index groups.

	BMI <25 (n = 59)	BMI 25–29.9 (n = 115)	BMI >30 (n = 54)	*p*-value
Complications	2 (3.4%)	2 (1.7%)	1 (1.9%)	0.840
Temp LSPV (°C)	−49.3 ± 6.1	−49.6 ± 4.9	−49.0 ± 6.4	0.772
Temp LIPV (°C)	−45.2 ± 4.8	−46.4 ± 5.1	−45.4 ± 5.6	0.202
Temp cLPV (°C)	−53.7 ± 7.6	−52.6 ± 5.6	−55.8 ± 3.5	0.598
Temp RSPV (°C)	−51.7 ± 5.0	−51.9 ± 5.9	−50.7 ± 6.6	0.478
Temp RIPV (°C)	−49.4 ± 6.2	−49.4 ± 6.4	−47.7 ± 7.2	0.172
Procedure time (min)	77.1 ± 18.8	78.1 ± 18.8	80.6 ± 18.6	0.424
Fluoroscopy time (min)	17.2 ± 7.5	17.1 ± 7.2	18.4 ± 7.6	0.662
DAP (μGym²)	975.3 ± 814.9	1325.1 ± 2081.3	2035.5 ± 1930.1	0.001*,§

Legend: *: *p*-value for BMI >30 vs. BMI >25–29.9: <0.005; §: *p*-value for BMI >30 vs. <25: <0.005.

Patients' characteristics of the three BMI groups showed no significant differences by age, sex, symptoms, type of AF or comorbidities.

After a 12-month follow-up, 80.9% of the patients with normal weight were free of AF, as were 83.3% of the overweight patients ($p = 0.733$) and 86.5% of the obese patients ($p = 0.460$). There were no significant differences in the characteristics of the three groups. The corresponding Kaplan-Meier plot is shown in Fig. 1.

4. Discussion

Obesity has been and continues to increase rapidly in adults and children all over the world [6, 16]. Patients with obesity suffer more often from AF than patients with normal weight [8, 17]. In 2018, Middeldorp *et al.* [18] showed that patients in the LEGACY study with lasting obesity progressed most often from a status of paroxysmal AF to persistent AF (REVERSE-AF study). On the other hand, patients with a significant reduction of BMI progressed less often to persistent AF or even transited from persistent to paroxysmal AF or sinus rhythm. The ARREST-AF study analyzed the benefit of risk factor reduction according to current guidelines after ablation of AF. It was shown that aggressive risk factor reduction led to less AF recurrence after ablation [19]. Several studies examined the procedural outcome of patients with morbid obesity (BMI >40) that underwent PVI. It was shown that these patients, especially women, suffered more often from complications, and had more AF recurrence; furthermore 4 of the 6 major complications were vascular complications [20]. The outcome of patients with morbid obesity improved significantly after bariatric surgery [21]. In our hospital we usually do not ablate patients with a BMI >35 so we were not able to explore this weight group.

In our study, only 59 patients presented with normal weight (25.88%). This high prevalence of obesity and overweight, which can be found in many other studies, underscores the imperative of addressing this issue with the patients. Furthermore, in this study obese patients had a significantly higher CHA2DS2VASC score. Concerning complications, we did not find any significant differences across weight groups. Of note, only minor complications occurred. Data on the relationship of BMI, body size and the diameter of the pulmonary veins is rare. Our patients did not undergo computed tomography or MRI before ablation so we cannot provide data on the PV diameter. The three patient groups showed no differences in body size.

In our study, patients with obesity and overweight showed no significant differences for procedure time or fluoroscopy

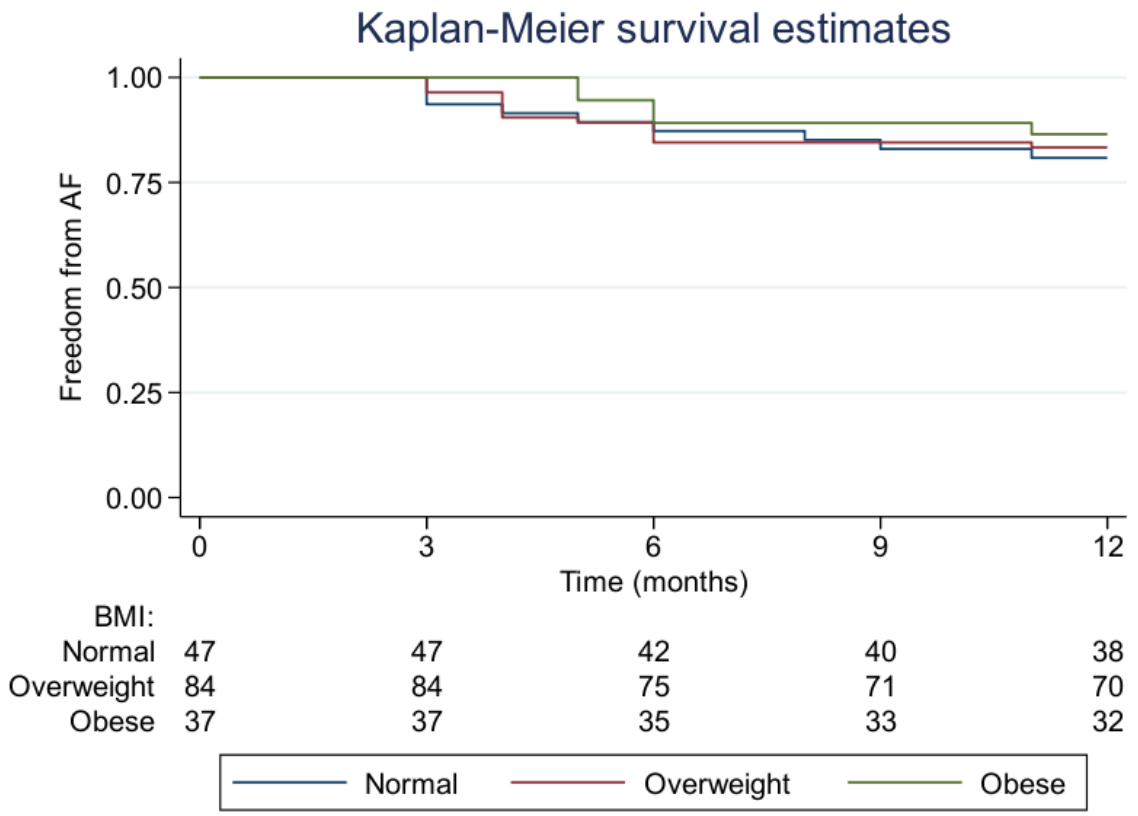

Fig. 1. Kaplan Meier plot at 12 months follow-up of the three body mass index groups.

time compared to normal weight patients. As expected, the dose area product (DAP) was significantly higher in the obesity group. but not when comparing the overweight and the normal weight group. We think that these group differences may become significant with a larger number of patients. It has been widely shown that obesity has a major impact on radiation exposure of both patients and the operator [22, 23]. Reduction of radiation with special protocols and being aware of different radiation exposure in different system angulations is important for every intervention but must especially kept in mind in obese patients [24, 25]. In our laboratory we reduce the frame rate per second (fps) to 3 fps whenever possible, collimate the beam, keep the distance of the detector and the patient as low as possible and try to store taken fluoroscopy loops instead of filming again.

Contradictory data has been published on the recurrence of AF in overweight and obese patients, mostly analyzing patients after RF PVI. Glover *et al.* [26] analyzed 3333 patients and reported a higher AF recurrence rate after PVI in obese patients. Providência *et al.* [27] showed in their study of nearly 2500 PVIs consisting of almost 30% CB PVIs that obesity is associated with an increased risk of recurrent AF and goes along with higher rates of persistent AF. Furthermore, in a sub-analysis they discussed that CB PVI may be a feasible alternative to RF PVI in obese patients [27]. In another study of Winkle *et al.* [13] analyzed 2715 patients after PVI, it was likewise shown that BMI >35 predicts a worse outcome of PVI and that patients had more often persistent than paroxysmal AF. Furthermore, a higher BMI did not lead to more major complications [13].

Concerning the different types of AF in specific settings, Nuzzi *et al.* [28] presented data on more than 1100 patients with dilated cardiomyopathy with a median follow up of more than ten years. They could show that permanent AF had a low incidence and prevalence but had a negative prognostic impact on patients' outcome [28].

Recently, Malaspina *et al.* [29] reported on more than 2000 patients who underwent CB PVI. They did not find a worse outcome during their follow-up among patients with increased BMI. Furthermore, they found persistent AF was an independent predictor of AF recurrence after ablation [29]. Data on suboptimal outcome after PVI in patients with persistent AF with respect to AF recurrence has been reported before [30, 31].

In our study, we had access to 168 patients presenting for their follow up in our outpatient clinic. We found no differences across groups in recurrence of AF that may be due to our smaller sample size. Conversely, our findings are consistent with a recent published study. Weinmann *et al.* [32] analyzed 600 patients after CB PVI and also found no impact of weight on procedure time and complication rate. In contrast to our study, they experienced a significantly higher fluoroscopy time in obese patients. They also found no differences with respect to recurrence of AF at follow up [32]. A

potential benefit of CB in obese patients might be its good stability during the application which makes it less susceptible to respiratory disorders often found in obese patients.

Thus, further studies may be needed to focus on the impact of weight on the recurrence of AF in overweight and obese patients after CB PVI whether this PVI method is preferable to use in obese patients. Additional data on the impact of CB PVI in obese patients concerning the outcome in different types of AF is needed. Irrespective of these findings the need of weight managing programs and education of patients regarding lifestyle and risk factor management has to be underscored.

5. Limitations

This study has several notable limitations due to its retrospective character. Furthermore, it is a single-center non-randomized study with a small cohort. We can only provide retrospective follow-up data of 168 patients presenting to our outpatients' clinic. Due to the conventional mapping, we do not have data on atrial fibrosis. Lastly, we do not have data on patients with morbid obesity (BMI $>$40). Only the second-generation CB was used in our study; furthermore, we used a 240 sec protocol and not a time-to-isolation guided protocol which has been introduced recently [33]. During follow-up no re-assessment of BMI was conducted. Patients had no electronic device for rhythm monitoring. We cannot provide data on the efficacy of antiarrhythmic drugs in obese patients and their impact on rhythm control strategies in this specific cohort. We cannot provide data on the use of antiarrhythmic drugs during follow-up that may be used more often in obese patients due to their comorbidities.

6. Conclusions

CB PVI in overweight and obese patients is safe and feasible. We found no differences in complications, procedure time and fluoroscopy time among these patients. Dose area product was significantly higher in obese patients. In addition, we found no differences in recurrence of AF between normal weight, overweight and obese patients. Further studies should be conducted to evaluate whether CB PVI is a preferable approach in obese patients compared to RF PVI.

Abbreviations

AA, antiarrhythmic drug; AF, atrial fibrillation; ATH, arterial hypertension; BMI, body mass index; CB, cryoballoon; DM, diabetes mellitus; CAD, coronary artery disease; DAP, dose area product; DOAC, direct oral anticoagulant; FT, fluoroscopy time; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; cLPV, common os left pulmonary vein; PE, pericardial effusion; PT, procedure time; PV, pulmonary vein; PVI, pulmonary vein isolation; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; TOE, transesophageal echocardiography.

Author contributions

CB and DS designed the research study and wrote the manuscript. JG and BK collected and analyzed the data. HW and AB performed and supervised statistical analysis. MS supervised the study and supervised the analysis and provided help on writing the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Ärztekammer Nordrhein, Düsseldorf, Germany (approval number: 327/2020). All treatments and assessments were performed after the informed consent of patient.

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Conflict of interest

The authors declare no conflict of interest.

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