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The established and the challenger: a direct comparison of current cryoballoon technologies for pulmonary vein isolation

Dissertation

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ORIGINAL ARTICLE

WILEY

The established and the challenger: A direct comparison of current cryoballoon technologies for pulmonary vein isolation

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Abstract

Introduction: Cryoballoon (CB) ablation for pulmonary vein isolation (PVI) is an effective treatment of atrial fibrillation (AF). Recently, a novel cryoablation system was introduced. The aim of the study was to compare the safety, efficacy and biophysical characteristics of a novel cryoablation system (POLARx™; Boston Scientific) to a commonly used and clinically well characterized system (Arctic Front Advance Pro™, AFA; Medtronic).

Methods and Results: Fifty consecutive patients with symptomatic AF, who underwent CB-based ablation with the POLARx were compared to 50 consecutive patients treated with the AFA. Acute PVI was achieved in 99.8% (POLARx 99.5%, AFA 100%, $p = 1.00$). Time to isolation (TTI) was comparable in both groups (POLARx 35 [27, 48] s, AFA 30 [21, 43] s, $p = 0.165$). The POLARx showed a lower balloon temperature at TTI (POLARx −44 [−50, −36] °C, AFA −31 [−38, −21] °C, $p < 0.001$) and lower nadir temperature (POLARx −60 [−65, −55] °C, AFA −48 [−54, −45] °C, $p < 0.001$). Procedure time (POLARx 80 [60, 105] min, AFA 62 [42, 80] min, $p < 0.001$), fluoroscopy time (POLARx 17 [13, 22] min, AFA 11 [7, 16] min, $p < 0.001$) and freeze cycles per patient (POLARx 5 [4, 6], AFA 4.5 [4, 5], $p = 0.002$) were higher in the POLARx group. Two cerebral ischemic events occurred in the POLARx group, two patients in each group had phrenic nerve injury.

Conclusion: Both systems enable effective isolation of pulmonary veins. The POLARx required longer procedure and fluoroscopy times. Larger, prospective and randomized studies are needed to assess long-term efficacy and safety of this technology.

KEYWORDS

atrial fibrillation, catheter ablation, cryoballoon technology, pulmonary vein isolation

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia and is associated with an increased risk of stroke, heart failure and death.[1] Catheter ablation aiming at pulmonary vein isolation (PVI) is an effective intervention to achieve rhythm control therapy in patients with AF. In addition to reducing symptoms, rhythm control therapy can improve morbidity and mortality in patients with heart failure and in patient with recently diagnosed AF.[2–4] While radiofrequency (RF) was the initial energy source to achieve PVI, cryoballoon (CB)-based AF ablation using the Arctic Front Advance™ cryoballoon (AFA; Medtronic) is an equally effective energy source associated with shorter procedure times.[5,6]

Recently, a novel cryoablation system (POLARx™; Boston Scientific) was launched on the European market. Early experience showed similar safety and efficacy with different biophysical characteristics when compared to the benchmark AFA system.[7–10] The aim of this study was to directly compare acute efficacy and periprocedural safety of the POLARx with the established AFA and to report biophysical characteristics.

2 | METHODS

2.1 | Study population

In this cohort study, we enrolled 100 consecutive patients with symptomatic persistent or paroxysmal AF, who underwent cryoablation at our institution. We compared clinical characteristics and procedural outcomes of the 50 patients undergoing CB-PVI before introduction of the POLARx system with the first 50 patients undergoing POLARx-based CB ablation. The procedures of both groups were performed by the same experienced operators and our institutional standards for CB ablation were not changed during the study period.[11] No training cases before the study with the new balloon system were performed. All patients provided written informed consent and the study was performed in accordance to the Declaration of Helsinki.

2.2 | Procedural management

Transesophageal echocardiography was performed before the procedure to exclude left atrial (LA) thrombi. No additional preprocedural imaging was performed. AF ablation was performed on uninterrupted oral vitamin K-anticoagulation with an INR of 2.0–3.0 on the day of the procedure. In patients treated with novel oral anticoagulants, anticoagulation was interrupted for 12 h before the procedure. The procedure was performed under deep sedation using midazolam, fentanyl and propofol or general anesthesia. A temperature probe (CIRCA S-CATH; Circa Scientific) was placed in the esophagus to monitor esophageal temperatures during the freeze cycles. After vascular access, a multipolar catheter was positioned in the coronary sinus and a single transseptal puncture was performed. After transseptal puncture intravenous heparin was given with a targeted activated clotting time of more than 300 s. Selective angiography was performed with a multipurpose catheter to identify individual pulmonary vein (PV) ostia. The 28 mm CB (AFA-Pro™ 8 mm tip, Medtronic or POLARx™ 5 mm or 12 mm tip, Boston Scientific) was inserted through a steerable sheath (15-F FlexCath Advance™ Medtronic or 15.9-F POLARSHEATH™, Boston Scientific). A 20 mm circular mapping catheter (Achieve Advance™, Medtronic or POLARMAP™, Boston Scientific) was used in all patients to guide the CB within the LA and to attempt real-time recordings from the targeted PV. Contrast injections via the central lumen of the inflated CB were used to assess occlusion of the PV ostium. A time to isolation (TTI)-based ablation protocol was applied. Following TTI, freeze-cycles were continued for another 120 s. If TTI was not achieved in ≤60 s. the respective freeze-cycle was stopped and a better CB position and/or occlusion was attempted. If PV-signals could not be visualized online, a standard freeze of 180 s. was applied. Cryoablation was stopped prematurely, when: (1) minimal predefined balloon temperature (−60°C for the AFA, −70°C for the POLARx) was reached (2) reduced diaphragmatic excursion was noticed (3) the intraluminal esophageal temperature reached the 15°C cutoff. During cryoablation of the right PVs, phrenic nerve (PN) pacing was performed using a diagnostic catheter positioned in the superior vena cava and diaphragmatic excursion was assessed by tactile feedback and compound motor action potential (CMAP) visualization. PVI was confirmed by entrance block during and after cryoablation of each PV. After the procedure antiarrhythmic drugs were stopped at the discretion of the operator.

Patient demographic data were obtained from reviewing the medical records, procedural characteristics were collected during and at the end of the procedure. In addition, the cryoablation data stored in the cryoablation system were used to analyze various biophysical parameters. Ablation-related complications were described by individual narratives and classified as: (1) life-threatening complications; (2) severe complications; (3) or moderate or minor complications;

2.3 | Statistical analysis

Continuous variables are presented by mean and *SD* or median and interquartile range as appropriate. Categorical variables are presented by absolute and relative frequencies. Group comparisons were performed using Student's *t*-test or nonparametric tests (Mann–Whitney *U* for continuous variables and Pearson's chi-square test or Fisher exact test for categorical variables). Statistical analysis was performed using SPSS. All statistical tests were two-sided. All *p* values less than 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

The POLARx group had a higher proportion of male patients when compared to the AFA group (POLARx 82% vs. 62%, $p = 0.045$). Other baseline variables were similar between the groups (Table 1).

TABLE 1 Patient baseline characteristics

	POLARx ($n = 50$)	AFA ($n = 50$)	p value
Age, years	64.5 [57, 74]	67 [55, 75]	0.947
Age ≥75 years (%)	9 (18)	13 (26)	0.469
Age 65–75 years (%)	16 (32)	13 (26)	0.659
Gender, male (%)	41 (82)	31 (62)	**0.045**
Persistent AF (%)	22 (44)	30 (60)	0.161
Body mass index	27 [24, 32]	28 [24, 31]	0.895
Implanted cardiac device (%)	4 (8)	8 (16)	0.336
Left ventricular ejection fraction (%)	57 [44, 60]	55 [45, 60]	0.788
CHA_2DS_2VASc Score	2 [1.25, 3]	3 [2, 4]	0.217
Congestive heart failure	17 (34)	14 (28)	0.665
Hypertension (%)	30 (60)	37 (74)	0.202
Coronary artery disease (%)	11 (22)	14 (28)	0.644
Diabetes mellitus (%)	10 (20)	8 (16)	0.795
History of stroke/TIA (%)	5 (10)	4 (8)	1.00
Classes I and III antiarrhythmic drugs	11 (22)	14 (28)	0.488
Beta-blocker	42 (84)	41 (82)	0.793

Note: Continuous data are summarized as means ± *SD*s or as medians (25th and 75th percentiles). Categorical data are presented as n (%). Bold values was considered statistically significant $p < 0.05$.

Abbreviations: AF, atrial fibrillation, TIA, transient ischemic attack.

3.2 | Procedural characteristics

When compared with the AFA group, the POLARx group had significantly longer procedure times (POLARx: 80 [60, 105] min vs. AFA: 62 [42, 80] min, $p < 0.001$) and longer fluoroscopy times (POLARx: 17 [12, 22] min vs. AFA: 11 [7, 16] min, $p < 0.001$). The amount of contrast dye used was higher in the POLARx group (POLARx: 70 [45, 85] ml vs. 60 [40, 69] ml, $p = 0.015$). Detailed procedural characteristics are given in Table 2.

3.3 | Acute procedural outcome and biophysical characteristics

A total of 393 PVs (POLARx: 197 PVs, AFA 196 PVs) were targeted. Complete PVI confirmed by entrance block with the circumferential multipolar catheter was achieved in 196/197 PVs with the POLARx and in 196/196 PVs with the AFA ($p = 1.00$). In one patient of the POLARx group the right inferior PV was not accessible and no freezing cycle was employed. Procedures conducted with the POLARx system required more freeze cycles than procedures conducted with the AFA system (POLARx 5 [4, 6] vs. 4.5 [4, 5], $p = 0.002$). This difference was mainly driven by more freezing cycles delivered in the right superior PV (POLARx 1.6 ± 0.9, AFA 1.1 ± 0.3, $p = 0.001$). Complete isolation of all PVs with one freeze cycle per PV (first-pass) was not significantly different between both groups (POLARx: 28%, AFA: 48% $p = 0.064$). Acute success rates per individual freeze cycle are shown in Table 3.

While TTI was similar in both groups (POLARx 35 [27, 48] s, AFA 30 [21, 43] s, $p = 0.165$), the POLARx was associated with a lower balloon temperature at TTI (POLARx −44 [−48, −27] °C, AFA −31 [−38, −21] °C, $p < 0.001$) and lower nadir temperature (POLARx −60 [−65, −55] °C, AFA −48 [−54, −45] °C, $p < 0.001$), in line with the lower target temperatures set for the POLARx system. The rate of real-time recordings was similar in both groups (POLARx 55,8%, AFA 52,6%, $p = 0.378$). Cryoablation procedural details per PV is presented in Table 4.

Four patients in both cohorts had early recurrence of AF and underwent cardioversion before hospital discharge. All patients were discharged in sinus rhythm.

TABLE 2 Procedural characteristics

	POLARx ($n = 50$)	AFA ($n = 50$)	p value
Initial rhythm AF, n (%)	27 (54)	24 (48)	0.613
Total procedure time, min	80 [60, 105]	62 [42.25, 80]	**<0.001**
Total fluoroscopy time, min	17 [13, 22]	11 [7, 16]	**<0.001**
Cumulative radiation dose, cGycm2	528 [341.9, 844.5]	422 [269.35, 622.25]	0.054
Contrast dye, ml	70 [47, 85]	60 [40, 68.75]	**0.015**

Note: Continuous data are summarized as median (25th and 75th percentiles). Bold values was considered statistically significant $p < 0.05$.

Abbreviation: AF, atrial fibrillation.

TABLE 3 Acute success rates per individual freeze cycle

	POLARx (*n* = 50)					AFA (*n* = 50)				
Isolation of pulmonary vein (%)	**LSPV (*n* = 47) 100**	**LIPV (*n* = 47) 100**	**LCV (*n* = 3) 100**	**RIPV (*n* = 50) 98**	**RSPV (*n* = 50) 100**	**LSPV (*n* = 46) 100**	**LIPV (*n* = 46) 100**	**LCV (*n* = 4) 100**	**RIPV (*n* = 50) 100**	**RSPV (*n* = 50) 100**
Isolation with 1st freeze (%)	70	83	33	56	64	85	83	75	82	88
Isolation with 2nd freezes (%)	26	15	0	36	20	13	13	25	14	12
Isolation with 3rd or more freezes (%)	4	2	67	6	16	2	4	0	4	0

Abbreviations: LCV, left common vein; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

TABLE 4 Cryoablation procedural details for pulmonary veins

	POLARx	AFA	*p* value
LSPV	47	46	
Freeze cycles (min; max)	1.4 ± 0.6 (1; 4)	1.2 ± 0.4 (1; 3)	0.103
Occlusion grade 4, *n*	30	32	0.987
Live signals (%)	31 (66)	32 (70)	0.881
Time to isolation, s	41 [29, 52]	32 [24, 45]	0.116
Temperature at isolation (°C)	−46 [−54, −39]	−35 [−40, −30]	**0.001**
Total freezing duration, s	180 [180, 240]	180 [180, 195]	0.240
Minimal temperature (min; max)	−62 [−66, −58]	−49 [−55, −47]	**<0.001**
Min. esophageal temp (°C)	34 [31, 35]	34 [32, 35]	0.256
LIPV	47	46	
Freeze cycles (min; max)	1.2 ± 0.5 (1;3)	1.2 ± 0.5 (1;3)	0.796
Occlusion grade 4, *n*	29	31	1.00
Live signals (%)	33 (70)	25 (54)	0.172
Time to isolation, s	31 [23, 47]	25 [18, 31]	0.125
Temperature at isolation (°C)	−40 [−48, −28]	−27 [−30, −14]	**<0.001**
Total freezing duration, s	180 [180, 204]	180 [180, 180]	0.769
Minimal temperature (min; max)	−58 [−62, −55]	−46 [−50, −43]	**<0.001**
Min. esophageal temperature (°C)	32 [24, 35]	34 [21, 35]	0.295
LCV	3	4	
Freeze cycles (min; max)	2.7 ± 1.5 (1; 4)	1.25 ± 0.5 (1; 2)	0.135
Occlusion grade 4, *n*	3	4	n/a
Live signals (%)	2 (67)	3 (75)	1.00
Time to isolation, s	81 [66, 96]	35 [28, 37]	0.083
Temperature at isolation (°C)	−53 [−58, −47]	−36 [−37, −28]	0.083
Total freezing duration, s	436 [338, 554]	180 [168, 225]	0.074
Minimal temperature (min; max)	−60 [−60, −63]	−55 [−58, −51]	0.108
Min. esophageal temperature (°C)	24 [22, 28]	33 [32, 33]	0.077
RSPV	50	50	
Freeze cycles (min; max)	1.6 ± 0.9 (1;4)	1.1 ± 0.3 (1;2)	**0.001**

TABLE 4 (Continued)

	POLARx	AFA	*p* value
Occlusion grade 4, n	34	31	0.958
Live signals (%)	23 (46)	29 (58)	0.230
Time to isolation, s	29 [24, 35]	30 [20, 53]	0.849
Temperature at isolation (°C)	−42 [−50, −34]	31 [−41, −24]	**0.015**
Total freezing duration, s	180 [180, 247]	180 [160, 180]	0.125
Minimal temperature (min; max)	−62 [−65, −55]	53 [−56, −48]	**<0.001**
Min. esophageal temperature (°C)	34 [34, 35]	34 [34, 35]	0.234
RIPV	50	50	
Freeze cycles (min; max)	1.5 ± 0.6 (1; 3)	1.3 ± 0.66 (1; 4)	0.130
Occlusion grade 4, *n*	29	35	1.00
Live signals (%)	22 (44)	14 (28)	0.124
Time to isolation, s	42 [34, 48]	38 [24, 61]	0.479
Temperature at isolation (°C)	−49 [−50, −45]	−33 [−37, −27]	**0.001**
Total freezing duration, s	180 [180, 242]	180 [180, 180]	0.162
Minimal temperature (min; max)	−60 [−67, −56]	−47 [−52, −45]	**<0.001**
Min. esophageal temperature (°C)	34 [29, 35]	35 [33, 35]	0.123

Note: Continuous data are summarized as means ± SDs or as medians (25th and 75th percentiles). Categorical data are presented as *n* (%). Bold values was considered statistically significant $p < 0.05$.

Abbreviations: LCV, left common vein; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

3.4 | Procedure-related complications

In two patients within the POLARx group (4%) a cerebral ischemic event occurred, with demarcation of infarct areas in CT and MRI. PN palsy occurred in two patients in the POLARx group (4%) and in two patients in the AFA group (4%), in both groups during energy delivery targeting the right superior PV. No cardiac tamponade, atrioesophageal fistula or death occurred in both groups. Procedure-related complications are shown in Table 5.

4 | DISCUSSION

Our main findings are:

(1) The POLARx is as effective for acute PVI as the AFA with very high acute efficacy and similar TTI.

TABLE 5 Procedure-related complications

	POLARx (*n* = 50)	AFA (*n* = 50)	*p* value
Life-threatening complications			
Oesophageal perforation/ fistula	0 (0)	0 (0)	n/a
Periprocedural thromboembolic event	2 (4)	0 (0)	0.159
Cardiac tamponade	0 (0)	0 (0)	n/a
Severe complications			
Persistent phrenic nerve palsy	2 (4)	2 (4)	1.00
Vascular complications	0 (0)	0 (0)	n/a
Moderate or minor complications			
Various	0 (0)	0 (0)	n/a

Note: Ablation-related complications classified according to the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation.[1]

(2) Procedure duration and fluoroscopy times were longer in patients treated with the POLARx.
(3) The number of freeze cycles was higher in the POLARx cohort, mainly due to more freezes needed in the right superior PV.
(4) The nadir CB temperature and the temperature at time of isolation was significantly lower in the POLARx group.
(5) The rate of complications in the POLARx group is numerically higher when compared to the AFA group.

CB-ablation for PVI, with the AFA-CB being by far the most frequently used balloon device, has an established track record of both safety and efficacy. Particularly the incidence of cardiac tamponade is significantly lower in balloon procedures as compared to RF-based procedures.[12] The novel POLARx CB has been designed as another ablation balloon system.

In our study, the rate of complications was statistically not significantly different between the groups. However, in two patients (4%) treated with the POLARx, a thrombo-embolic event occurred. Symptoms occurred directly after the procedure and the diagnosis of a periprocedural stroke was confirmed by CT and MRI. In both cases, the complication was procedure related—whether it was also directly device related cannot be answered. Yap et al.[7] report of one patient (1.8%), experiencing a transient left sided hemiparesis due to a transient ischemic attack after the procedure with the POLARx. CT and MRI imaging showed no demarcation of infarct areas. In the POLARx cohort by Tilz et al.[8] a transient ST-elevation for <10 min was observed in one of 25 patients (4%). Due to the shortness of the ST-elevation, an air embolism was presumed. The reported stroke rate in larger cohorts using AFA is 0.5%.[5] The sheath of the Boston cryoablation system (POLAR sheath) is slightly larger in diameter (15.9 F compared to 15 F Medtronic Flexcath Advance), which might

potentially increase the risk for air embolism. However, current data are too limited to draw a final conclusion.

The rate of PN palsy was similar between the two groups (two patients in each group, $p = 1.00$). This is comparable with the incidence of PN palsy reported in the literature.[12] PN capture was monitored by tactile feedback of diaphragm contraction during pacing using a diagnostic catheter in the superior vena cava and assessment of the right diaphragmatic CMAP. The Boston system offers a novel diaphragmatic movement sensor (DMS), which is based on an accelerometer technology and is placed on an electrode below the right-sided costal cartilage. DMS can only assess diaphragm movement adequately, when palpation of PN capture is not performed on the chest or abdomen. As some of the operators relied on tactile feedback by placing the hand on the abdomen, DMS was not routinely used to monitor PN function. The rate of PN palsy reported by Tilz et al.[8] and Yap et al.[7] was similar, despite using the DMS. (POLARx 4%, AFA 4% $p = 0.999$ and POLARx 3.5%, AFA 3,7%, $p = 1.00$). A potential benefit of this additional tool might be shown in future studies.

We also systematically measured intraluminal esophageal temperatures during cryoablation. Cryoablation was stopped when intraluminal esophageal temperature reached the predefined 15°C cutoff.[13] There was no difference between the luminal esophageal temperature despite significantly lower balloon temperatures with the POLARx.

There are several key differences in the balloon and sheath design of the POLARx with the intent to improve experience in the ablation procedure. The POLARx has lower inner balloon pressure and it does not increase in size during cryoablation. Moreover, the POLARSHEATH is softer and more flexible when being compared to the Medtronic Flexcath sheath. This difference in design and materials results in a slightly different approach for balloon positioning at the PV ostium. Optimal coaxial alignment and less push is needed to achieve adequate balloon-to-tissue contact. In our study, the grade of PV occlusion and the rate of PVI was similar between the groups. One right inferior PV in the POLARx group could not be reached and therefore was not isolated.

The AFA shows a high rate of acute PVI after the first freeze. First pass isolation of left common PVs was only 33% when using the PolarX and thus is considerably low in this patient cohort. A potential explanation could be less mechanical stability provided by the PolarX sheath. However, larger patient numbers will be mandatory before final conclusions regarding this aspect can be drawn. Differences between both technologies as well as less experience with the PolarX system as compared to that with the AFA might have influenced our results.

There is a significant difference of the biophysical parameters during cryoablation with the two technologies. The mean nadir balloon temperature reached with the POLARx was significantly lower than that with the AFA, however, this was not translated to lower minimal intraluminal esophagus temperatures or a difference in TTI. This finding might be explained by a slightly different position of the temperature probe within the POLARx, different materials or differences in pressure within the balloon. This actual tissue temperature seems not to be significantly different. The rate of real time recording, as it is commonly utilized for time-to-effect-based dosing strategy, was not different between the groups. The unique biophysical parameters raise the need for further investigation to optimize dosing.

5 | STUDY LIMITATIONS

This cohort study has inherent limitations. As such, no randomization has been performed. The POLARx group had a higher proportion of male patients when compared to the AFA group. Anatomical differences between the male and female patients have been reported and as such may influence the outcome.[14] To prevent selection bias consecutive patients were included and the procedure was done by the same experienced operators. However, the level of experience with both technologies was different: while all operators had vast experience with the AFA, they just started collecting first experiences with the POLARx. Although the basic principals of both systems are similar, a certain learning curve cannot be excluded and might have influenced the reported results. The thawing time as a potential predictor for durable PVI has not been investigated. Furthermore, due to the recent launch of the system, only acute procedural efficacy and safety data in a relatively limited number of patients are reported. Evaluation of durable PVI with the POLARx cryoablation system as well as clinical outcome data needs further investigation.

6 | CONCLUSION

Both systems enable effective isolation of the PVs. The POLARx required longer procedure and fluoroscopy times. Larger, prospective and randomized studies are needed to assess long-term efficacy and safety of this technology.

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CONFLICT OF INTERESTS

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Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in AF, and has received honoraria from several such companies in the past, but not in the last 3 years. P. Kirchhof is listed as inventor on two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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2 Introduction (Einleitung)

Atrial fibrillation (AF) is the most common arrhythmia and is associated with an increased risk of stroke, heart failure and death.[1] Catheter ablation aiming at pulmonary vein isolation (PVI) is an effective intervention to achieve rhythm control therapy in patients with AF. In addition to reducing symptoms, rhythm control therapy can improve morbidity and mortality in patients with heart failure and in patient with recently diagnosed AF.[2-4] While radiofrequency (RF) was the initial energy source to achieve PVI, cryoballoon (CB)-based AF ablation using the Arctic Front Advance™ cryoballoon (AFA, Medtronic, St Paul, MN, USA) is an equally effective energy source associated with shorter procedure times.[5,6]

Recently, a novel cryoablation system (POLARx™, Boston Scientific, Marlborough, MA, USA) was launched on the European market. Early experience showed similar safety and efficacy with different biophysical characteristics when compared to the benchmark AFA system.[7-10] The aim of this study was to directly compare acute efficacy and periprocedural safety of the POLARx with the established AFA and to report biophysical characteristics.

3 Methods (Methoden)

3.1 Study population

In this cohort study, we enrolled 100 consecutive patients with symptomatic persistent or paroxysmal AF, who underwent cryoablation at our institution. We compared clinical characteristics and procedural outcomes of the 50 patients undergoing CB-PVI prior to introduction of the POLARx system with the first 50 patients undergoing POLARx-based CB ablation. The procedures of both groups were performed by the same experienced operators and our institutional standards for CB ablation were not changed during the study period.[11] No training cases prior to the study with the new balloon system were performed. All patients provided written informed consent and the study was performed in accordance to the Declaration of Helsinki.

3.2 Procedural management

Transesophageal echocardiography was performed prior to the procedure to exclude left atrial (LA) thrombi. No additional pre-procedural imaging was performed. AF ablation was performed on uninterrupted oral vitamin K-anticoagulation with an INR of 2.0-3.0 on the day of the procedure. In patients treated with novel oral anticoagulants (NOACs), anticoagulation was interrupted for 12 hours before the procedure. The procedure was performed under deep sedation using midazolam, fentanyl and propofol or general anesthesia. A temperature probe (CIRCA S-CATH; Circa Scientific, Englewood, CO, USA) was placed in the esophagus to monitor esophageal temperatures during the freeze cycles. After vascular access, a multipolar catheter was positioned in the coronary sinus and a single transseptal puncture was performed. After transseptal puncture intravenous heparin was given with a targeted activated clotting time of more than 300 seconds. Selective angiography was performed with a multipurpose catheter in order to identify individual pulmonary vein (PV) ostia. The 28mm CB (AFA-Pro^{TM} 8mm tip,

Medtronic or POLARx™ 5mm or 12mm tip, Boston Scientific) was inserted through a steerable sheath (15-F FlexCath Advance™ Medtronic or 15.9-F POLARSHEATH™, Boston Scientific). A 20mm circular mapping catheter (Achieve Advance™, Medtronic or POLARMAP™, Boston Scientific) was used in all patients to guide the CB within the LA and to attempt real-time recordings from the targeted PV. Contrast injections via the central lumen of the inflated CB were used to assess occlusion of the PV ostium. A time to isolation (TTI)-based ablation protocol was applied. Following TTI, freeze-cycles were continued for another 120 seconds (sec). If TTI was not achieved in ≤60 sec. the respective freeze-cycle was stopped and a better CB position and/or occlusion was attempted. If PV-signals could not be visualized online, a standard freeze of 180 sec. was applied. Cryoablation was stopped prematurely, when: (1) minimal predefined balloon temperature (-60°C for the AFA, -70 °C for the POLARx) was reached (2) reduced diaphragmatic excursion was noticed (3) the intraluminal esophageal temperature reached the 15°C cutoff. During cryoablation of the right PVs, phrenic nerve (PN) pacing was performed using a diagnostic catheter positioned in the superior vena cava and diaphragmatic excursion was assessed by tactile feedback and compound motor action potential (CMAP) visualization. PVI was confirmed by entrance block during and after cryoablation of each PV. After the procedure antiarrhythmic drugs were stopped at the discretion of the operator.

Patient demographic data were obtained from reviewing the medical records, procedural characteristics were collected during and at the end of the procedure. In addition, the cryoablation data stored in the cryoablation system were used to analyze various biophysical parameters. Ablation-related complications were described by individual narratives and classified as: (1) life-threatening complications; (2) severe complications; (3) or moderate or minor complications;

3.3 Statistical analysis

Continuous variables are presented by mean and standard deviation or median and interquartile range as appropriate. Categorical variables are presented by absolute and relative frequencies. Group comparisons were performed using Student's t-test or nonparametric tests (Mann-Whitney U for continuous variables and Pearson's chi-square test or Fisher exact test for categorical variables). Statistical analysis was performed using SPSS. All statistical tests were two-sided. P values less than 0.05 were considered statistically significant.

4 Results (Ergebnisse)

4.1 Baseline characteristics

The POLARx group had a higher proportion of male patients when compared to the AFA group (POLARx 82% vs. 62%, p= 0.045). Other baseline variables were similar between the groups (**Table 1**).

Table 1: Patient baseline characteristics

	POLARx (n=50)	**AFA** (n=50)	p-value
Age, years	64.5 [57, 74]	67 [55, 75]	0.947
Age ≥ 75 years (%)	9 (18)	13 (26)	0.469
Age 65-75 years (%)	16 (32)	13 (26)	0.659
Gender, male (%)	41 (82)	31 (62)	**0.045**
Persistent AF (%)	22 (44)	30 (60)	0.161
Body Mass Index	27 [24, 32]	28 [24, 31]	0.895
Implanted cardiac device (%)	4 (8)	8 (16)	0.336
Left ventricular ejection fraction (%)	57 [44, 60]	55 [45, 60]	0.788
CHA_2DS_2VASc Score	2 [1.25, 3]	3 [2, 4]	0.217
Congestive heart failure	17 (34)	14 (28)	0.665
Hypertension (%)	30 (60)	37 (74)	0.202
Coronary artery disease (%)	11 (22)	14 (28)	0.644
Diabetes mellitus (%)	10 (20)	8 (16)	0.795
History of stroke/TIA (%)	5 (10)	4 (8)	1.00
Class I & III antiarrhythmic drugs	11(22)	14 (28)	0.488
Beta-blocker	42 (84)	41 (82)	0.793

Continuous data are summarized as means ± standard deviations or as medians (25^{th} and 75^{th} percentiles). Categorical data are presented as n (%). AF= atrial fibrillation, TIA= transient ischemic attack

4.2 Procedural characteristics

When compared with the AFA group, the POLARx group had significantly longer procedure times (POLARx: 80 [60, 105] min vs. AFA: 62 [42, 80] min, p<0.001) and longer fluoroscopy times (POLARx: 17 [13, 22] min vs. AFA: 11 [7, 16] min, p<0.001). The amount of contrast dye used was higher in the POLARx group (POLARx: 70 [45, 85] ml vs. 60 [40, 69] ml, p=0.015). Detailed procedural characteristics are given in **Table 2**.

Table 2 Procedural characteristics

	POLARx (n=50)	**AFA** (n=50)	p-value
Initial rhythm AF, n (%)	27 (54)	24 (48)	0.613
Total procedure time, min	80 [60, 105]	62 [42.25, 80]	**<0.001**
Total fluoroscopy time, min	17 [13, 22]	11 [7, 16]	**<0.001**
Cumulative radiation dose, cGycm2	528 [341.9, 844.5]	422 [269.35, 622.25]	0.054
Contrast dye, ml	70 [47, 85]	60 [40, 68.75]	**0.015**

Continuous data are summarized as median (25^{th} and 75^{th} percentiles). AF= atrial fibrillation

4.3 Acute procedural outcome and biophysical characteristics

A total of 393 PVs (POLARx: 197 PVs, AFA 196 PVs) were targeted. Complete PVI confirmed by entrance block with the circumferential multipolar catheter was achieved in 196/197 PVs with the POLARx and in 196/196 PVs with the AFA (p=1.00). In one patient of the POLARx group the right inferior PV was not accessible and no freezing cycle was employed. Procedures conducted with the POLARx system required more freeze cycles than procedures conducted with the AFA system (POLARx 5 [4, 6] vs 4.5 [4, 5], p= 0.002). This difference was mainly driven by more freezing cycles delivered in the right superior PV (POLARx 1.6 ± 0.9, AFA 1.1 ± 0.3, p= 0.001). Complete isolation of all PVs with one freeze cycle per PV (first-pass) was not significantly different between both groups (POLARx: 28%, AFA: 48% p= 0.064). Acute success rates per individual freeze cycle are shown in **Table 3**.

Table 3 Acute success rates per individual freeze cycle

	POLARx (n=50)					**AFA** (n=50)				
	LSPV (n=47)	LIPV (n=47)	LCV (n=3)	RIPV (n=50)	RSPV (n=50)	LSPV (n=46)	LIPV (n=46)	LCV (n=4)	RIPV (n=50)	RSPV (n=50)
Isolation of pulmonary vein (%)	**100**	**100**	**100**	**98**	**100**	**100**	**100**	**100**	**100**	**100**
Isolation with 1st freeze (%)	70	83	33	56	64	85	83	75	82	88
Isolation with 2nd freezes (%)	26	15	0	36	20	13	13	25	14	12
Isolation with 3rd or more freezes (%)	4	2	67	6	16	2	4	0	4	0

LSPV= left superior pulmonary vein, LIPV= left inferior pulmonary vein, LCV= left common vein**,** RSPV= right superior pulmonary vein, RIPV= right inferior pulmonary vein

While time to isolation (TTI) was similar in both groups (POLARx 35 [27, 48] sec, AFA 30 [21, 43] sec, p = 0.165), the POLARx was associated with a lower balloon temperature at TTI (POLARx -44 [-48, -27] °C, AFA -31 [-38, -21] °C, p<0.001) and lower nadir temperature (POLARx -60 [-65, -55] °C, AFA -48 [-54, -45] °C, p<0.001), in line with the lower target temperatures set for the POLARx system. The rate of real-time recordings was similar in both groups (POLARx 55,8%, AFA 52,6%, p=0.378). Cryoablation procedural details per PV is presented in **Table 4**.

Table 4 Cryoablation procedural details for pulmonary veins

		POLARx	AFA	p-value
LSPV		47	46	
	Freeze cycles (min;max)	1.4 ± 0.6 (1;4)	1.2 ± 0.4 (1;3)	0.103
	Occlusion grade 4, n	30	32	0.987
	Live signals (%)	31 (66)	32 (70)	0.881
	Time to isolation, sec	41 [29, 52]	32 [24, 45]	0.116
	Temperature at isolation (°C)	-46 [-54, -39]	-35 [-40, -30]	**0.001**
	Total freezing duration, sec	180 [180, 240]	180 [180, 195]	0.240
	Minimal temperature (min; max)	-62 [-66, -58]	-49 [-55, -47]	**<0.001**
	Min. esophageal temp (°C)	34 [31, 35]	34 [32, 35]	0.256
LIPV		47	46	
	Freeze cycles (min;max)	1.2 ± 0.5 (1;3)	1.2 ± 0.5 (1;3)	0.796
	Occlusion grade 4, n	29	31	1.00
	Live signals (%)	33 (70)	25 (54)	0.172
	Time to isolation, sec	31 [23, 47]	25 [18, 31]	0.125
	Temperature at isolation (°C)	-40 [-48, -28]	-27 [-30, -14]	**<0.001**
	Total freezing duration, sec	180 [180, 204]	180 [180, 180]	0.769
	Minimal temperature (min; max)	-58 [-62, -55]	-46 [-50, -43]	<**0.001**
	Min. esophageal temperature (°C)	32[24, 35]	34 [21, 35]	0.295
LCV		3	4	
	Freeze cycles (min;max)	2.7 ± 1.5 (1;4)	1.25 ± 0.5 (1;2)	0.135
	Occlusion grade 4, n	3	4	n/a
	Live signals (%)	2 (67)	3 (75)	1.00
	Time to isolation, sec	81 [66, 96]	35 [28, 37]	0.083
	Temperature at isolation (°C)	-53 [-58, -47]	-36 [-37, -28]	0.083
	Total freezing duration, sec	436 [338, 554]	180 [168, 225]	0.074
	Minimal temperature (min; max)	-60 [-60, -63]	-55 [-58, -51]	0.108
	Min. esophageal temperature (°C)	24 [22, 28]	33 [32, 33]	0.077
RSPV		50	50	
	Freeze cycles (min;max)	1.6 ± 0.9 (1;4)	1.1 ± 0.3 (1;2)	**0.001**
	Occlusion grade 4, n	34	31	0.958
	Live signals (%)	23 (46)	29 (58)	0.230
	Time to isolation, sec	29 [24, 35]	30 [20, 53]	0.849
	Temperature at isolation (°C)	-42 [-50, -34]	31 [-41, -24]	**0.015**
	Total freezing duration, sec	180 [180, 247]	180 [160, 180]	0.125
	Minimal temperature (min; max)	-62 [-65, -55]	53 [-56, -48]	**<0.001**
	Min. esophageal temperature (°C)	34 [34, 35]	34 [34, 35]	0.234
RIPV		50	50	
	Freeze cycles (min;max)	1.5 ± 0.6 (1;3)	1.3 ± 0.66 (1;4)	0.130
	Occlusion grade 4, n	29	35	1.00
	Live signals (%)	22 (44)	14 (28)	0.124
	Time to isolation, sec	42 [34, 48]	38 [24, 61]	0.479
	Temperature at isolation (°C)	-49 [-50, -45]	-33 [-37, -27]	**0.001**
	Total freezing duration, sec	180 [180, 242]	180 [180, 180]	0.162
	Minimal temperature (min; max)	-60 [-67, -56]	-47 [-52, -45]	**<0.001**
	Min. esophageal temperature (°C)	34 [29, 35]	35 [33, 35]	0.123

Continuous data are summarized as means ± standard deviations or as medians (25^{th} and 75^{th} percentiles). Categorical data are presented as n (%). LSPV= left sup pulmonary vein, LIPV= left inf pulmonary vein, LCV=

left common vein**.** RSPV= right superior pulmonary vein, RIPV= right inferior pulmonary vein, LCV= left common vein**.**

Four patients in both cohorts had early recurrence of AF and underwent cardioversion before hospital discharge. All patients were discharged in sinus rhythm.

4.4 Procedure-related complications

In two patients within the POLARx group (4%) a cerebral ischemic event occurred, with demarcation of infarct areas in computed tomography (CT) and magnetic resonance imaging (MRI). PN palsy occurred in two patients in the POLARx group (4%) and in two patients in the AFA group (4%), in both groups during energy delivery targeting the right superior PV. No cardiac tamponade, atrioesophageal fistula or death occurred in both groups. Procedure-related complications are shown in **Table 5.**

Table 5 Procedure-related complications

	POLARx (n=50)	**AFA** (n=50)	p-value
Life-threatening complications			
Oesophageal perforation/fistula	0 (0)	0 (0)	n/a
Periprocedural thromboembolic event	2 (4)	0 (0)	0.159
Cardiac tamponade	0 (0)	0 (0)	n/a
Severe complications			
Persistent phrenic nerve palsy	2 (4)	2 (4)	1.00
Vascular complications	0 (0)	0 (0)	n/a
Moderate or minor complications			
Various	0 (0)	0 (0)	n/a

Ablation-related complications classified according to the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation[1]

5 Discussion (Diskussion)

Our main findings are:

(1) The POLARx is as effective for acute PVI as the AFA with very high acute efficacy and similar TTI.
(2) Procedure duration and fluoroscopy times were longer in patients treated with the POLARx.
(3) The number of freeze cycles was higher in the POLARx cohort, mainly due to more freezes needed in the right superior pulmonary vein.
(4) The nadir CB temperature and the temperature at time of isolation was significantly lower in the POLARx group.
(5) The rate of complications in the POLARx group is numerically higher when compared to the AFA group.

CB-ablation for PVI, with the AFA-CB being by far the most frequently used balloon device, has an established track record of both safety and efficacy. Particularly the incidence of cardiac tamponade is significantly lower in balloon procedures as compared to RF-based procedures.[12] The novel POLARx CB has been designed as another ablation balloon system.

In our study, the rate of complications was statistically not significantly different between the groups. However, in two patients (4%) treated with the POLARx, a thrombo-embolic event occurred. Symptoms occurred directly after the procedure and the diagnosis of a periprocedural stroke was confirmed by CT and MRI. In both cases, the complication was procedure related – whether it was also directly device related cannot be answered. Yap et al. report of one patient (1.8%), experiencing a transient left sided hemiparesis due to a transient ischemic attack after the procedure with the POLARx. CT and MRI imaging showed no demarcation of infarct

areas.[7] In the POLARx cohort by Tilz et al. a transient ST-elevation for <10 min was observed in one of 25 patients (4%). Due to the shortness of the ST-elevation, an air embolism was presumed.[8] The reported stroke rate in larger cohorts using AFA is 0.5%.[5] The sheath of the Boston cryoablation system (POLARSHEATH) is slightly larger in diameter (15.9 F compared to 15F Medtronic Flexcath Advance), which might potentially increase the risk for air embolism. However, current data is too limited to draw a final conclusion.

The rate of phrenic nerve palsy was similar between the two groups (two patients in each group, p= 1.00). This is comparable with the incidence of phrenic nerve palsy reported in the literature.[12] Phrenic nerve capture was monitored by tactile feedback of diaphragm contraction during pacing using a diagnostic catheter in the superior vena cava and assessment of the right diaphragmatic CMAP. The Boston system offers a novel diaphragmatic movement sensor (DMS), which is based on an accelerometer technology and is placed on an electrode below the right-sided costal cartilage. DMS can only assess diaphragm movement adequately, when palpation of phrenic nerve capture is not performed on the chest or abdomen. As some of the operators relied on tactile feedback by placing the hand on the abdomen, DMS was not routinely used to monitor PN function. The rate of PN palsy reported by Tilz et al. and Yap et al. was similar, despite using the DMS. (POLARx 4%, AFA 4% p=0.999 and POLARx 3.5%, AFA 3,7%, p=1.00). A potential benefit of this additional tool might be shown in future studies.

We also systematically measured intraluminal esophageal temperatures during cryoablation. Cryoablation was stopped when intraluminal esophageal temperature reached the predefined 15°C cutoff.[13] There was no difference between the luminal esophageal temperature despite significantly lower balloon temperatures with the POLARx.

There are several key differences in the balloon and sheath design of the POLARx with the intent to improve experience in the ablation procedure. The POLARx has lower inner balloon pressure and it does not increase in size during cryoablation. Moreover, the POLARSHEATH is softer and more flexible when being compared to the Medtronic Flexcath sheath. This difference in design and materials results in a slightly different approach for balloon positioning at the PV ostium. Optimal coaxial alignment and less push is needed to achieve adequate balloon-to-tissue contact. In our study, the grade of PV occlusion and the rate of PVI was similar between the groups. One right inferior PV in the POLARx group could not be reached and therefore was not isolated.

The AFA shows a high rate of acute PVI after the first freeze. First pass isolation of left common PVs was only 33% when using the POLARx and thus is considerably low in this patient cohort. A potential explanation could be less mechanical stability provided by the POLARSHEATH. However, larger patient numbers will be mandatory before final conclusions regarding this aspect can be drawn. Differences between both technologies as well as less experience with the PolarX system as compared to that with the AFA might have influenced our results.

There is a significant difference of the biophysical parameters during cryoablation with the two technologies. The mean nadir balloon temperature reached with the POLARx was significantly lower than that with the AFA, however, this was not translated to lower minimal intraluminal esophagus temperatures or a difference in TTI. This finding might be explained by a slightly different position of the temperature probe within the POLARx, different materials or differences in pressure within the balloon. This actual tissue temperature seems not to be significantly different. The rate of real time recording, as it is commonly utilized for time-to-effect-based dosing strategy, was not different between the groups. The unique biophysical parameters raise the need for further investigation to optimize dosing.

5.1 Study limitations

This cohort study has inherent limitations. As such, no randomization has been performed. The POLARx group had a higher proportion of male patients when compared to the AFA group. Anatomical differences between the male and female patients have been reported and as such may influence the outcome. To prevent selection bias consecutive patients were included and the procedure was done by the same experienced operators. However, the level of experience with both technologies was different: while all operators had vast experience with the AFA, they just started collecting first experiences with the POLARx. Although the basic principals of both systems are similar, a certain learning curve cannot be excluded and might have influenced the reported results. The thawing time as a potential predictor for durable PVI has not been investigated. Furthermore, due to the recent launch of the system, only acute procedural efficacy and safety data in a relatively limited number of patients are reported. Evaluation of durable PVI with the POLARx cryoablation system as well as clinical outcome data needs further investigation.

5.2 Conclusion

Both systems enable effective isolation of the pulmonary veins. The POLARx required longer procedure and fluoroscopy times. Larger, prospective and randomized studies are needed to assess long-term efficacy and safety of this technology.

6 Abstract (Zusammenfassung)

6.1 English Abstract

Introduction: Cryoballoon ablation for pulmonary vein isolation is an effective treatment of atrial fibrillation (AF). Recently, a novel cryoablation system was introduced. The aim of the study was to compare the safety, efficacy and biophysical characteristics of a novel cryoablation system (POLARx™, Boston Scientific) to a commonly used and clinically well characterized system (Arctic Front Advance Pro™, AFA, Medtronic).

Methods and Results: Fifty consecutive patients with symptomatic AF, who underwent cryoballoon-based ablation with the POLARx were compared to 50 consecutive patients treated with the AFA. Acute pulmonary vein isolation was achieved in 99.8% (POLARx 99.5%, AFA 100%, p=1.00). Time to isolation (TTI) was comparable in both groups (POLARx 35 [27, 48] sec, AFA 30 [21, 43] sec, p=0.165). The POLARx showed a lower balloon temperature at TTI (POLARx -44 [-50, -36] °C, AFA -31 [-38, -21] °C, p<0.001) and lower nadir temperature (POLARx -60 [-65, -55] °C, AFA -48 [-54, -45] °C, p<0.001). Procedure time (POLARx 80 [60, 105] min, AFA 62 [42, 80] min, p<0.001), fluoroscopy time (POLARx 17 [13, 22] min, AFA 11 [7, 16] min, p<0.001) and freeze cycles per patient (POLARx 5 [4, 6], AFA 4.5 [4, 5], p=0.002) were higher in the POLARx group. Two cerebral ischemic events occurred in the POLARx group, two patients in each group had phrenic nerve injury.

Conclusion: Both systems enable effective isolation of pulmonary veins. The POLARx required longer procedure and fluoroscopy times. Larger, prospective and randomized studies are needed to assess long-term efficacy and safety of this technology.

6.2 German Abstract

Einleitung: Die Kryoballonablation zur Pulmonalvenenisolation ist eine effektive Therapie von Vorhofflimmern. Vor kurzem wurde ein neues Kryoablationssystem vorgestellt. Ziel der Studie war es, die Sicherheit, Wirksamkeit und biophysikalischen Eigenschaften dieses neuen Kryoablationssystems (POLARxTM, Boston Scientific) mit einem gängigen und gut charakterisierten System (Arctic Front Advance ProTM, AFA, Medtronic) zu vergleichen.

Methoden und Ergebnisse: 50 konsekutive Patienten mit symptomatischem Vorhofflimmern, die sich einer Kryoballon-basierten Ablation mit dem POLARx unterzogen, wurden mit 50 konsekutiven Patienten verglichen, die mit dem AFA behandelt wurden. Eine akute Pulmonalvenenisolation wurde bei 99,8 % erreicht (POLARx 99,5 %, AFA 100 %, p=1,00). Die Zeit bis zur Isolation war in beiden Gruppen vergleichbar (POLARx 35 [27, 48] Sekunden, AFA 30 [21, 43] Sekunden, p=0,165). Der POLARx zeigte eine niedrigere Ballontemperatur zum Zeitpunkt der Isolation (POLARx -44 [-50, -36] °C, AFA -31 [-38, -21] °C, p<0,001) und eine niedrigere Minimaltemperatur (POLARx -60 [- 65, -55] °C, AFA -48 [-54, -45] °C, p<0,001). Prozedurzeit (POLARx 80 [60, 105] Minuten, AFA 62 [42, 80] Minuten, p<0,001) und Durchleuchtungszeit (POLARx 17 [13, 22] Minuten, AFA 11 [7, 16] Minuten, p<0,001) waren in der POLARx-Gruppe länger, die Anzahl an Kryoapplikationen pro Patient (POLARx 5 [4, 6], AFA 4,5 [4, 5], p=0,002) war in der POLARx-Gruppe höher. In der POLARx-Gruppe kam es zu zwei zerebralen ischämischen Ereignissen, bei zwei Patienten in jeder Gruppe trat eine Phrenikusparese auf.

Schlussfolgerung: Beide Systeme ermöglichen eine effektive Isolation der Lungenvenen. Der POLARx erforderte eine längere Prozedur- und Durchleuchtungszeit. Größere, prospektive und randomisierte Studien sind erforderlich, um die langfristige Wirksamkeit und Sicherheit dieser Technologie zu prüfen.

7 Abbreviations (Abkürzungsverzeichnis)

AF	Atrial fibrillation
AFA	Arctic Front Advance™ cryoballoon
CB	Cryoballoon
CMAP	Compound motor action potential
CT	Computed tomography
DMS	Diaphragmatic movement sensor
LA	Left atrium
MRI	Magnetic resonance imaging
NOACs	Novel oral anticoagulants
PN	Phrenic nerve
POLARSHEATH	Boston Scientific cryoablation sheath
POLARx	Boston Scientific cryoablation system (POLARx™)
PVI	Pulmonary vein isolation
PV	Pulmonary vein
RF	Radiofrequency
SEC	Seconds
TTI	Time to isolation

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9 Extended abstract (Zusammenfassende Darstellung der Publikation)

Vorhofflimmern ist die häufigste Herzrhythmusstörung mit einer Prävalenz von 2-4%. (1)
Die mit Vorhofflimmern assoziierten Herausforderungen bestehen weltweit und werden in den kommenden Jahren weiter zunehmen. (2,3) Die Risiken sind dabei erheblich. Vorhofflimmern ist sowohl mit einer erhöhten Morbidität als auch Mortalität assoziiert. Die EAST - AFNET 4 Studie konnte zeigen, dass eine frühe rhythmuserhaltende Therapie einer bis dahin als Standard geltenden frequenzregulierenden Therapie überlegen ist und schwere Komplikationen wie kardiovaskulärer Tod, Schlaganfall, Herzinfarkt oder eine Krankenhauseinweisung aufgrund einer Herzschwäche signifikant verringern kann. (4)
Die Pulmonalvenenisolation als rhythmuserhaltende Therapie hat sich in den letzten Jahren als sicheres und effektives Therapieverfahren in der Behandlung von Patienten mit symptomatischem Vorhofflimmern etabliert und ist hinsichtlich der Rhythmusstabilität einer medikamentösen, antiarrhythmischen Therapie überlegen. (5) Sie scheint zudem die Progression vom paroxysmalen zum persistierenden Vorhofflimmern im Vergleich zu einer medikamentösen antiarrhythmischen Therapie aufzuhalten bzw. zu verzögern. (6) Die Katheterablation mittels Radiofrequenzstrom galt initial als alleiniger Goldstandard zur Pulmonalvenenisolation. Im Rahmen der großen randomisierten Vergleichsstudie, der „Fire and Ice Study“, erwies sich die Pulmonalvenenisolation mittels Kryoballon der Radiofrequenzstrom-basierten Ablation hinsichtlich Effektivität und Sicherheit als nicht unterlegen. (7) Aufgrund der kürzeren Prozedurzeiten und steileren Lernkurve werden sogenannte „single shot devices“, wie der Kryoballon, zunehmend im Rahmen der Erstablation eingesetzt.

In den letzten 15 Jahren konnte viel Erfahrung mit dem Kryoballon-Sytem Arctic Front Advance von Medtronic gesammelt werden. Dabei erfuhr das System im Laufe der Jahre wiederholt Anpassungen mit Verbesserung der Kühleigenschaften und Elektrogram-Visualisierung. Derzeit befindet sich das System in der vierten Generation. (8)

Vor kurzem wurde ein neues Kryoablationssystem, der POLARx Cryoballon von Boston Scientific (Marlborough, MA, USA), vorgestellt. Erste Erfahrungen zeigen eine ähnliche Sicherheit und Wirksamkeit mit unterschiedlichen biophysikalischen Eigenschaften im Vergleich zum etablierten System von Medtronic. (9,10) Ziel der im Rahmen der Promotionspublikation verfassten und im *Journal of Cardiovascular Electrophysiology* erschienen Originalarbeit war es, die Effektivität und periprozedurale Sicherheit des POLARx direkt mit dem etablierten System zu vergleichen und die Unterschiede der biophysikalischen Eigenschaften zu erfassen. (11)

Im Rahmen der Kohortenstudie wurden dabei die klinischen Merkmale und Behandlungsergebnisse von 50 konsekutiven Patienten mit paroxysmalem oder persistierendem Vorhofflimmern, bei denen das neue POLARx-System angewendet wurde (POLARx-Gruppe), mit 50 Patienten, die sich vor Einführung des neuen Systems einer Kryoballon-basierten Pulmonalvenenisolation unterzogen haben (AFA-Gruppe), verglichen. Die Katheterablation beider Gruppen wurde von denselben erfahrenen Ärzten durchgeführt und die Standards für die Kryoballon-basierte Ablation änderten sich während des Studienzeitraums nicht.

Vor dem Eingriff wurde eine transösophageale Echokardiographie durchgeführt, um linksatriale Thromben auszuschließen. Es wurde keine zusätzliche präprozedurale Bildgebung durchgeführt. Die Ablation wurde unter ununterbrochener oraler Antikoagulation mit einem

Vitamin-K-Antikoagulation und einem Ziel-INR von 2,0–3,0 am Tag des Eingriffs durchgeführt. Bei Patienten, die eines der neuen oralen Antikoagulanzien (NOAKs) erhielten, wurde die Antikoagulation für 12 Stunden vor dem Eingriff unterbrochen. Der Eingriff wurde unter tiefer Anlagosedierung mit Midazolam, Fentanyl und Propofol oder Vollnarkose durchgeführt. Eine Temperatursonde wurde in der Speiseröhre platziert, um die Temperatur während der Kälteapplikationen in der Speiseröhre zu überwachen. Nach Punktion der Vena femoralis rechts erfolgte die Platzierung eines multipolaren Katheters im Koronarvenensinus sowie eine transseptale Punktion unter fluoroskopischer Kontrolle. Nach transseptaler Punktion wurde intravenös Heparin mit einer angestrebten aktivierten Gerinnungszeit (ACT-Wert) von ≥ 300 Sekunden verabreicht. Eine selektive Angiographie der Pulmonalvenen diente zur Identifizierung der einzelnen PV-Ostien. Der Kryoballon mit 28 mm Durchmesser (Medtronic AFA-Pro™ 8-mm-Spitze, Boston Scientific POLARx™ 5-mm- oder 12-mm-Spitze) wurde mittels steuerbarer Schleuse (Medtronic 15-F FlexCath Advance™; Boston Scientific 15,9-F POLARSHEATH™) in den linken Vorhof vorgeführt. Ein zirkulärer Katheter (Medtronic Achieve Advance™; Boston Scientific POLARMAP™) wurde in der jeweiligen Pulmonalvene ostiumnah positioniert, um die Pulmonalvenenisolation während bzw. nach der Kälteapplikation zu prüfen. Mittels Kontrastinjektionen über das zentrale Lumen des Kryoballons konnte die Okklusion des Ballons am Pulmonalvenen-Ostium beurteilt werden. Im Rahmen des sogenannten. „Time-to-Isolation“ (TTI) - basiertem Ablationsprotokolls führte man die Kryoapplikation für weitere 120 Sekunden ab Zeitpunkt der Isolation fort. Wenn die Isolation nicht innerhalb von 60 Sekunden erreicht wurde, wurde die Kryoapplikation gestoppt, um gegebenenfalls eine bessere Ballonposition bzw. Okklusion anzustreben. Konnte der Zeitpunkt der Isolation aufgrund von fehlenden Pulmonalvenen-Signalen nicht festgehalten werden, erfolgte eine Standardapplikation von 180 Sekunden Dauer. Die Kryoablation wurde vorzeitig beendet, wenn die minimale vordefinierte Ballontemperatur (-60 °C für den AFA, -70 °C für den POLARx) erreicht war, eine verringerte Zwerchfellexkursion festgestellt wurde

oder die intraluminale Ösophagustemperatur unter 15°C fiel. Während der Kryoablation der rechten PVs erfolgte die Stimulation des N. phrenicus zur Beurteilung der Zwerchfellekontraktion.

Die POLARx-Gruppe hatte im Vergleich zur AFA-Gruppe einen höheren Anteil männlicher Patienten (82 % vs. 62 %, p = 0,045). Alle weiteren erhobenen Patientencharakteristika unterschieden sich nicht zwischen den Gruppen.

Im Vergleich zur AFA-Gruppe hatte die POLARx-Gruppe signifikant längere Prozedurzeiten (POLARx: 80 [60, 105] min vs. AFA: 62 [42, 80] min, p < 0,001) und längere Durchleuchtungszeiten (POLARx: 17 [13, 22] min vs. AFA: 11 [7, 16] min, p < 0,001). Die eingesetzte Kontrastmittelmenge war in der POLARx-Gruppe höher (POLARx: 70 [45, 85] ml vs. 60 [40, 69] ml, p=0,015).

Eine elektrische Isolation der Pulmonalvenen, konnte bei 196/197 Pulmonalvenen mit dem POLARx und bei 196/196 Pulmonalvenen mit dem AFA erzielt werden. Bei einem Patienten der POLARx-Gruppe war die rechte untere Pulmonalvene (RIPV) nicht zu sondieren und es wurde keine Kälteapplikation abgegeben. Prozeduren, die mit dem POLARx-System durchgeführt wurden, erforderten mehr Kälteapplikationen als Prozeduren, die mit dem AFA-System durchgeführt wurden (POLARx 5 [4, 6] vs. 4,5 [4, 5], p = 0,002). Dieser Unterschied war bedingt durch die höhere Anzahl an Kälteapplikationen der rechten oberen Pulmonalvene (POLARx 1,6 ± 0,9, AFA 1,1 ± 0,3, p = 0,001). Die vollständige Isolierung aller Pulmonalvenen mit jeweils einer Kälteapplikation pro Vene (First-Pass) unterschied sich zwischen beiden Gruppen nicht (POLARx: 28 %, AFA: 48 %, p = 0,064).

Die Zeit bis zur Isolation (TTI) in beiden Gruppen war ähnlich (POLARx 35 [27, 48] Sek., AFA 30 [21, 43] Sek., p = 0,165), der POLARx erreichte niedrigere Ballontemperaturen zum Zeitpunkt der Isolation (POLARx - 44 [-48, -27] °C, AFA -31 [-38, -21] °C, p<0,001) sowie eine niedrigere Minimaltemperatur (POLARx -60 [-65, -55] °C, AFA -48 [-54, -45] °C, p < 0,001). Der Anteil an der Elektrogrammvisualisierung während der Applikation war in beiden Gruppen ähnlich (POLARx 55,8 %, AFA 52,6 %, p=0,378).

Bei zwei Patienten in der POLARx-Gruppe (4 %) kam es zu einem zerebralen, ischämischen Ereignis mit Nachweis eines Infarktareals in der Computertomographie sowie Magnetresonanztomographie. Eine Phrenicusparese trat bei zwei Patienten in der POLARx-Gruppe (4 %) und bei zwei Patienten in der AFA-Gruppe (4 %) auf. Zu einer Herzbeuteltamponade, atrioösophagealen Fistel oder Todesfällen kam es während des Krankenhausaufenthaltes nicht

Größere, multizentrische Studien wie die ANTARCTICA Studie konnten die im Rahmen der Publikationspromotion erhobenen und publizierten Ergebnisse bestätigten. (12) Dabei wurden insgesamt 317 Patienten mit paroxysmalem oder persistierendem Vorhofflimmern in sechs europäischen Zentren eingeschlossen, die eine Kryoballon-basierte Pulmonalvenenisolation mit dem POLARx erhielten. Bei 317 Patienten [Mittleres Alter: 64 ± 12 Jahre, 209/317 (66 %) paroxysmales VHF] wurden insgesamt 1256 Pulmonalvenen identifiziert und 1252 (99,7 %) Pulmonalvenen erfolgreich isoliert. Die mittlere minimale Kryoballon-Temperatur betrug –57,9 ± 7°C. Der Anteil an der Elektrogrammvisualisierung während der Applikation lag bei 72%. Die Rate schwerwiegender unerwünschter Ereignisse betrug 6,0 % und war nach einer Lernkurve von 25 Fällen signifikant reduziert (9,3 % vs. 3,0 %, P = 0,018).

Eine Nachbeobachtung des im Rahmen der Promotionspublikation untersuchten Patientenkollektivs steht zum derzeitigen Zeitpunkt noch aus. Erste publizierte Erfahrungen zeigen keinen Unterschied in der Erfolgs- bzw. Komplikationsrate nach sechs Monaten bzw. einem Jahr. (13,14) Größere Studien sowie längere Nachbeobachtungszeiten werden in naher Zukunft weitere Erkenntnisse liefern, ob ein System überlegen ist.

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10 Author contribution statement (Erklärung des Eigenanteils)

Der überwiegende Anteil der Publikation wurde von dem Doktoranden geleistet. Unter der Supervision von Prof. Andreas Metzner erfolgte die Planung und Gestaltung des Projekts durch den Doktoranden. Die Datenerhebung mit Erfassung der Patientencharakteristika sowie der prozeduralen Charakteristika mit Erhebung der Kryoballon-spezifischen Messwerte (von den jeweiligen Kryo-Konsolen, den Röntgenanlagen sowie der Prozedurdatenblättern erfasst) und die Nachbeobachtung während des stationären Aufenthaltes erfolgten ausschließlich durch den Doktoranden. Des Weiteren erfolgte die statistische Datenanalyse mit Interpretation der Daten und Erstellen der Tabellen sowie das Schreiben des Manuskripts ausschließlich durch den Doktoranden und ist somit eine dem Doktoranden eindeutig zuzuordnende Leistung. Dieser vom Doktoranden geleistete Beitrag ermöglichte das Zustandekommen der Publikation.

Die Ko-Autoren haben als Teil der Arbeitsgruppe Elektrophysiologie vom elektrophysiologischen Labor des Universitären Herz- und Gefäßzentrum Hamburg Eppendorf unter der Leitung von Prof. Andreas Metzner aktiv an den Prozeduren teilgenommen, diese teilweise durchgeführt oder den jeweiligen Untersucher bei der Prozedur unterstützt und somit zur Generierung der Daten mit beigetragen.

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12 Curriculum vitae (Lebenslauf)

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13 Statutory declaration (Eidesstattliche Erklärung)

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: