INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia with increasing incidence and prevalence. AF is associated with considerable morbidity and mortality and has an important impact on healthcare costs.\(^1,2\) Pulmonary vein isolation (PVI) has become a cornerstone therapy in the treatment of AF. In 2016 the cryoballoon (CB) ablation of AF was shown to be non-inferior compared to radiofrequency (RF) current catheter ablation.\(^3\) When performing PVI, a crucial step is an approach to the left atrium (LA) by transseptal puncture (TSP). Hazardous complications may occur like pericardial effusion (PE) or even tamponade or puncture of the aorta.\(^4,5\) Various methods have been established to minimize the risk of fatal complications while performing TSP. Some operators use transesophageal echocardiography (TOE) or intracardiac echocardiography (ICE).\(^6\) In Europe, merely use of pressure monitoring in addition to fluoroscopy is used

Transesophageal echocardiography guided transseptal puncture and nadir temperatures in cryoballoon pulmonary vein isolation

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Abstract

Introduction: Cryoballoon (CB) guided pulmonary vein isolation (PVI) is an established procedure in the treatment of atrial fibrillation (AF). Transseptal access is an indispensable step during PVI and may be associated with severe complications. For specific interventions, specific puncture sites of the fossa ovalis are advantageous. Here, we analyzed the potential impact of a transesophageal echocardiography (TOE) guided transseptal puncture on nadir temperatures in CB PVI.

Methods and Results: We retrospectively analyzed 209 patients undergoing CB PVI in our hospital. The use of TOE had been at the operator’s discretion. No TOE-related complications such as perforation of the pharynx or esophagus or loss of teeth were noted. Concerning the applied freezes, we found significantly lower nadir temperatures in all PVs in the TOE group than in the non-TOE group. Procedure time and fluoroscopy time and complications were similar in both groups.

Conclusion: TOE-guided TSP in CB PVI is safe and feasible. Our study found significantly lower nadir temperatures of CB freezes after TOE-guided TSP which potentially underscores the value of a more infero-anterior puncture site.

KEYWORDS
atrial fibrillation, cryoballoon, fossa ovalis, pulmonary vein isolation, transseptal puncture
to gain LA access. Depending on the intervention, specific puncture sites of the fossa ovalis (FO) are recommended. In CB PVI a more infero-anterior puncture site is advised to facilitate the rotation of the balloon in the LA and therefore achieve a better occlusion of the vein. When using a TOE for TSP the operator is enabled to choose the puncture site of FO more precisely.

The aim of the present retrospective study was to compare the impact of TOE-guided TSP with pressure monitoring guided TSP on the safety of the procedure and on procedural parameters.

2 MATERIAL AND METHODS

We retrospectively analyzed 209 consecutive patients who underwent CB PVI in 2019. The baseline characteristics are shown in Table 1. All patients were anticoagulated for a minimum of 4 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 just for one dosage in the morning. All patients underwent TOE to exclude intracardiac thrombus, especially within the left atrial appendage. Written form of informed consent was obtained from all patients before the procedure. All PVIs were performed by experienced investigators (>100 PVIs per year). The use of TOE-guided TSP was at the operator’s discretion. Both approaches of transseptal access have been practiced in our clinic before.

PVI was conducted under deep sedation using midazolam and propofol. In case of TOE-guided TSP, we used a GE vivid S5 ultrasound machine with a TOE probe (General Electric Company). The probe was inserted orally with the patient in supine and the neck and head in straight position when sedation was adequate. If required, the neck was reclined to facilitate insertion. Furthermore, a laryngoscope was held available. TSP was performed with a fixed, 8F sheath (SL1; SJM) using a BRK-1 XS needle (SJM) under fluoroscopy and pressure monitoring. Afterward, a stiff wire (Amplatz super stiff; Boston Scientific) 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) over the wire and the 28 mm second generation CB (Arctic front advance, Medtronic) was inserted in the LA targeting the PVs with a spiral catheter (achieve, Medtronic). In this study, we used the second generation CB in all cases. After inflation, the correct occlusion of the targeted vein was proved by dye injection. The freeze duration protocol was 240 s per freeze which has been reported to potentially create increased lesion durability compared to 180 s. Shortening of the freeze was required when the temperature of the esophagus decreased under 15–17°C or when the stimulation of the phrenic nerve was disturbed. The temperature of the esophagus was monitored with a temperature probe (Sensitherm; St. Jude Medical). The phrenic nerve was monitored by stimulation and simultaneous palpation during the freezes of the right pulmonary veins.

In TOE-guided TSP tenting of the FO was observed in bicaval and short-axis views before puncture with the aim of an inferior and slightly anterior puncture site. If necessary, the sheath and the needle were relocated under echocardiographic and fluoroscopic view. After successful TSP the TOE probe was removed. Patients

| TABLE 1 Baseline characteristics of the two patients’ groups (non-TOE and TOE) |
|---------------------------------|-----------------|-----------------|-----------------|
| Age (years) | 60.4 ± 10 | 61.6 ± 9.1 | .407 |
| Sex (male) | 104 (72.7%) | 42 (63.6%) | .197 |
| BMI | 27.4 ± 4.2 | 28 ± 4.2 | .344 |
| CHA2DS2VASC Score | 1.8 ± 1.4 | 1.9 ± 1.5 | .815 |
| LA Diameter (mm) | 46 ± 7.3 | 40.7 ± 4.3 | <.001 |
| Paroxysmal AF | 100 (69%) | 47 (71.2%) | .872 |
| Persistent AF | 43 (30.1%) | 19 (28.8%) | .872 |
| Grade of mitral valve regurgitation (0 = none; 3 = severe) | 0.925 ± 0.53 | 0.9 ± 0.49 | .829 |
| EHRA Score 2, 3, 4 | 57 (39.9%), 66 (46.2%), 20 (14%) | 23 (34.8%), 32 (48.5%), 11 (16.7%) | .742 |
| ATH | 63 (44.1%) | 34 (51.5%) | .371 |
| DM II | 14 (9.8%) | 10 (15.2%) | .255 |
| CAD | 22 (15.4%) | 7 (10.6%) | .398 |
| Dyslipidemia | 27 (18.9%) | 16 (24.2%) | .365 |
| Betablocker | 112 (78.3) | 42 (63.6%) | .029 |
| Class Ic AA | 30 (21.0%) | 13 (19.7%) | 1.000 |
| Class III AA | 12 (8.4%) | 9 (13.6%) | .321 |
| Phenprocoumon | 15 (10.5%) | 1 (1.5%) | .024 |
| NOAC | 128 (89.5%) | 65 (98.5%) | .024 |
with sustained AF where mostly cardioverted before the first freeze application. The time to isolation (TTI) was defined as the time of last documentation of a PV potential before isolation of the vein.

Isolation of the PV was proven in sinus rhythm by entrance block and exit block, the latter verified by pacing from the spiral catheter. Adenosine was not used. The procedure time was counted from groin puncture till the removal of all sheaths at the end of the procedure.

Directly after the procedure PE was excluded and the patient was monitored by telemetry for 24 h. DOACs were re-administered the day of the procedure the same as phenprocoumon. Before discharge pericardial effusion was excluded again. Anticoagulation was continued for at least 3 months post-ablation afterward depending on the CHA2DS2VASC score. Patients were advised to present to their cardiologists after 1, 3, 6, and 12 months for follow-up.

In all 209 PVIs, the transseptal access was successful and the PVI was performed. Isolation of all veins was achieved. In 19 cases (9.1%), we found a common ostium of the left PVs (cLPV), a common ostium of the right pulmonary veins was not seen. The introduction of the TOE probe was achieved in all 66 cases with the patient in supine position either straightaway without difficulties or by repositioning of the patient’s neck. Only in one case, a laryngoscope was used.

The two groups (non-TOE vs. TOE) showed no significant differences concerning sex (72.7% vs. 63.6% male, p = 0.197), age (60.4 ± 10 vs. 61.6 ± 9.1 years, p = 0.407), BMI (27.4 ± 4.2 vs. 28.0 ± 4.2, p = 0.344), CHA2DS2-VASC score (1.8 ± 1.4 vs. 1.9 ± 1.5, p = 0.815), type of AF (69% vs. 71.2% paroxysmal AF, p = 0.872), comorbidities or symptoms (Table 1). In the TOE group patients took significantly less often betablockers (63.6% vs. 78.3%, p = 0.029), more often DOAC than phenprocoumon (98.5% vs. 89.5%, p = 0.024) and had a significantly smaller LA diameter (40.7 ± 4.3 mm vs. 46.0 ± 7.3 mm, p < 0.001).

A total of five minor complications occurred. In the non-TOE group 2 patients suffered from pseudoaneurysms, one with a hematoma; in both cases, no operation was needed. A third patient suffered from a phrenic nerve palsy which recovered by the end of the procedure.

In the TOE group, one patient suffered from a pseudoaneurysm without the need of surgical intervention and one patient had phrenic nerve palsy, which recovered till discharge from the hospital. In summary, the complications in both groups showed no significant difference (p = 0.652, Table 2).

In both groups, no major complications like PE, stroke, or need for surgical interventions occurred. Of note, no TOE-related complications such as perforation of the pharynx or esophagus or loss of teeth were noted. A few patients complained of hoarseness recovering till discharge from the hospital. Furthermore, no sedation related complications like aspiration were observed.

All PVs were isolated at the end of the procedure. In the TOE group, we found significantly lower nadir temperatures in all PVs than in the non-TOE group (procedural characteristics shown in Table 2). The LSPV showed a mean minimal temperature of −52.9 ± 4.9 °C vs. −47.5 ± 5.2 °C (p < 0.001), LIPV −48.5 ± 4.8 °C vs. −44.6 ± 4.9 °C (p < 0.001), cLPV −58.8 ± 4.1 °C vs. −52.1 ± 5.4 °C (p = 0.02), RSPV −53.4 ± 5.6 °C vs. −50.2 ± 5.7 °C (p = 0.001) and the RIPV −51.4 ± 5.5 °C vs. −47.5 ± 6.6 °C (p < 0.001).

The number of freezing attempts was significantly higher in the TOE group for the LIPV (1.32 ± 0.57 vs. 1.14 ± 0.41, p = 0.023) and showed a trend for the RIPv (1.23 ± 0.46 vs. 1.1 ± 0.33, p = 0.054). TTI was significantly lower in the TOE group for the LSPV (39.45 ± 15.02 vs. 53.9 ± 16.59 s, p = 0.001) and showed a trend to be shorter in the cLPV (34.2 ± 4.49 vs. 45.6 ± 17.86 s, p = 0.122), the RSPV (40.98 ± 25.69 vs. 50 ± 27.35, p = 0.087) and the RIPV (39.5 ± 18.91 vs. 46.84 ± 24.65 s, p = 0.116).

Premature termination of a freeze application due to loss of phrenic nerve capture (in the RPVs) or due to low esophageal temperature (in any PV) showed no significant differences, only a trend toward more terminations for the LIPV in the TOE group (18.03% vs. 7.1 min in the TOE group (p = 0.080). The fluoroscopy time was also equal with 18.1 ± 7.1 min in the non-TOE group vs. 17.0 ± 7.3 min in the TOE group (p = 0.255).
DISCUSSION

TSP, first described in 1959, is an indispensable step during PVI for patients with AF.9 But even in experienced hands, TSP may be associated with major complications like PE or unintended puncture of the aorta. Chun et al. reported in their study from a high-volume center a total of 32 PEs in 3000 consecutive ablations (1.1%). De Ponti et al.10 reported in their large Italian study of 5520 TSP an overall incidence of 0.79% in 2003 and 0.74% the years before. Bayrak et al.11 showed in their study that 16% of all TSP conducted by an unexperienced operator needed a so-called major catheter repositioning under TOE guidance to avoid major complications. Several techniques to prevent complications during TSP have been established. A puncture under echocardiographic view can be done guided by TOE or by ICE. The first is mostly available and cost-efficient but presumes a deeper sedation with the potential risk of pharyngeal or esophageal perforation. The latter is considerably more expensive, needs a period of training and an additional femoral venous access. Nevertheless, ICE has become a broadly used imaging tool especially in the US.6 In an editorial, Kautzner refers to unpublished data of 1692 TSP with ICE without any puncture associated complications.12 Furthermore Su et al. "highly recommend" ICE in their practice guide for CB ablation.13

In our study, we compared the impact of TOE on the safety and efficacy of PVI but also on its potential impact on procedural parameters like nadir temperatures. TOE-guided TSP had no effect on the rate of PE in our study population of 209 patients. However, in PIVs with TOE-guided TSP we found significantly lower nadir temperatures of the applied freezes in all PVs. Furthermore, we found significant lower TTI values for the LSPV and trends to lower TTI for the cLPV, the RSPV, and the RIPV without affecting the need for premature termination of the applied freeze due to loss of phrenic nerve capture or low esophageal temperature. The fact of a shorter TTI may possibly explained by achieving not only deeper nadir temperatures but also by achieving deeper temperatures earlier after starting the application. We also found in the TOE group significantly more attempts for the LIPV and a trend for the RIPV; we think that this fact may be due to the smaller sample size of the TOE cohort. Another explanation might be, that in the TOE cohort more patients showed...
atypical or different branches of PVs requiring more attempts before a good occlusion, but this is speculative. Depending on the planned intervention TSP may be conducted at specific sites of the FO (Figure 1). In mitral valve interventions for example the operator aims for a superior and posterior puncture site. In RF PVI the infero-posterior aspect is targeted as the PVs are located posteriorly.\textsuperscript{14,15} In CB PVI in contrast the preferable site is located infero-anterior to allow the balloon to rotate better to the veins, especially toward the RIPV.\textsuperscript{7,13,16} Chierchia et al.\textsuperscript{17} found no differences concerning clinical outcome in CB PVI when comparing anterior, medial, or posterior transseptal access, thus in different horizontal axis. In our experience with the help of TOE visualization, we frequently tend to relocate the fluoroscopically focused puncture site toward a slightly more inferior and slightly more anterior position. Of note, these slight movements were not undertaken to avoid an unfavorable puncture site (e.g. puncture of the aorta). As described, they rather served for a better, especially more inferior positioning of the puncture site. Here, the CB has more potential to rotate especially toward the RIPV but also to the other veins leading to a better occlusion as illustrated in Figure 2.

| PV            | Estimated effect (95% CL) | p-value |
|---------------|---------------------------|---------|
| Temp LSPV     |                           |         |
| M1            | -5.4 (-7.0; -3.9)         | <.001   |
| M2            | -5.4 (-7.1; -3.8)         | <.001   |
| M3            | -5.5 (-7.6; -3.3)         | <.001   |
| Temp LIPV     |                           |         |
| M1            | -3.9 (-5.4; -2.5)         | <.001   |
| M2            | -3.9 (-5.4; -2.3)         | <.001   |
| M3            | -3.7 (-5.2; -2.3)         | <.001   |
| Temp cLPV     |                           |         |
| M1            | -6.7 (-11.6; -1.9)        | .009    |
| M2            | -6.8 (-12.9; -0.8)        | .029    |
| M3            | -8.1 (-15.6; -0.5)        | .036    |
| Temp RSPV     |                           |         |
| M1            | -3.2 (-4.9; -1.6)         | <.001   |
| M2            | -3.1 (-5.0; -1.3)         | .001    |
| M3            | -2.4 (-4.4; -0.5)         | .013    |
| Temp RIPV     |                           |         |
| M1            | -3.9 (-5.7; -2.2)         | <.001   |
| M2            | -3.5 (-5.4; -1.7)         | <.001   |
| M3            | -3.1 (-5.2; -1.0)         | .004    |

Note: M1: Simple linear regression; M2: Linear regression adjusted for LA diameter; M3: Propensity-score matching estimator using LA diameter.

Abbreviations: AA, antiarrhythmic drug; AF, atrial fibrillation; ATH, arterial hypertension; BMI, body mass index; CAD, coronary artery disease; cLPV, common os left pulmonary vein; DM, diabetes mellitus; DOAC, direct oral anticoagulant; FT, fluoroscopy time; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PT, procedure time; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

FIGURE 1 Fossa ovalis (FO) with recommended puncture site for radiofrequency pulmonary vein isolation (PVI) (yellow), cryoballoon PVI (green), left atrial appendage occluder (blue) and mitral valve intervention (red), adopted from\textsuperscript{7}

FIGURE 2 Illustration of (A) medial transseptal access and (B) infero-anterior transseptal access with scheme of a cryoballoon, targeting the right inferior pulmonary vein (view from the left atrium
Worth mentioning, in the TOE group patients had a significantly smaller LA diameter (40.7 ± 4.3 vs. 46.0 ± 7.3 mm). It is known that the diameters of PV and LA may enlarge in patients with AF and that this effect is reversible after PVI.\textsuperscript{18} In addition, the size of LA and PV may influence the grade of occlusion during CB PVI. In their study on 130 consecutive patients, Watanabe et al. found no correlation of the PV ostial diameter with the nadir temperatures except for the RSPV which interestingly showed a negative correlation with the nadir point.\textsuperscript{19} In addition, Kajiyama et al.\textsuperscript{20} reported on 110 patients undergoing CB PVI with pre-procedural cardiac computed tomography to identify anatomic parameters predicting procedural temperatures and procedural difficulties with the 2nd generation CB. For all veins, the PV diameter was not found to be a negative predictor. However, we performed a linear regression model and a propensity-score matching (PSM) with adjustment for LA diameter (Table 3). For both analyses, we found the same significantly different nadir temperatures for all PVs. Thus, the differences in LA diameter seem not to bias the findings of our study. The procedure time tended to be longer in the TOE group (p = 0.080). It is debatable if this difference would be significant in a larger cohort due to the extra time spent for insertion of the TOE probe.

### 4.1 Limitations

This study has several notable limitations due to its retrospective character. Furthermore, it is a single-center and non-randomized study and the patient cohort is rather small. We do not have prospective data as many patients do their follow-up at outpatient’s clinics or walk-in centers. Hence, we cannot prove that the lower nadir temperatures may potentially go along with reduced AF recurrence. We cannot provide data of the PV occlusion grade for all patients which may be described in a semiquantitative way (e.g., A = complete occlusion, C = bad occlusion). The mentioned relocation of the transseptal needle to change the puncture site has not been recorded, thus we cannot provide fluoroscopy or TOE frames showing the movement before/after relocation. In all cases, we used the 2nd generation CB. We used a fix 240 s freeze protocol although studies have introduced and evaluated TTI protocols with newer CB generations showing equal efficacy with shorter procedure time and comparable complications.

### 5 Conclusion

TOE-guided TSP in CB guided PVI is safe and feasible. In our study, no TOE-related complications occurred. Our study showed significantly lower nadir temperatures in all isolated PVs when using TOE potentially explained by a more infero-anterior puncture site during TSP. Even though our findings are mostly hypothesis generating, they underscore the need and value of a specific TSP puncture site in CB PVI.

### CONFLICT OF INTEREST

None for all authors.

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