Quantification of Left Atrial Fibrosis in Patients After Pulmonary Vein Isolation Using the Second-Generation Cryoballoon

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Summary

Left atrial (LA) fibrosis is associated with a poor outcome after atrial fibrillation (AF) ablation. This study examined the extent of low-voltage areas in patients with recurrence of atrial tachyarrhythmia (ATA) after CB-based pulmonary vein isolation (PVI).

Sixty patients (mean age 67 ± 10 years, n = 32 female; n = 34 paroxysmal AF) who received radiofrequency redo-procedure due to recurrence of ATA within 6 months after CB-based PVI were included. A point-by-point 3D-map was performed, and low-voltage sites were delineated based on bipolar voltage < 0.5 mV. The extent of fibrosis was categorized as stage A (0-10% of the LA wall), stage B (10-30%), stage C (30-50%), and stage D (> 50%).

The median area of LA low-voltage sites was 28.9 (9; 50.3) cm², corresponding to 17.4 (6; 30.6) % of the LA wall surface. 17/60 (28.3%) patients were categorized as fibrosis stage A, 21/60 (35%) as stage B, 18/60 (30%) as stage C, and 4/60 (6.7%) as stage D. Patient age and LA diameter were associated with more pronounced LA fibrosis; the extent of LA fibrosis was significantly higher in patients with LA tachycardia (LAT) during redo-procedures (P < 0.01), and ablation of linear lesions was more often performed (P < 0.01).

In patients after CB2-based PVI, expanded LA tissue fibrosis was associated with the occurrence of LAT and more extensive LA ablation during redo-procedures.

Key words: Atrial fibrillation, AF ablation, LA fibrosis, Clinical outcome

Atrial fibrillation (AF) is the most common arrhythmia and is associated with an increased risk for ischemic stroke and cardiovascular mortality. Catheter ablation is an established treatment option for patients with symptomatic, drug-refractory AF.1 Cryoballoon-based pulmonary vein isolation (PVI) has been shown to be comparable to radiofrequency (RF)-based PVI2 in particular for patients with paroxysmal AF (PAF). (FIRE and ICE) The pulmonary veins (PVs) are an important trigger site for AF3 and electrical reconduction of previously isolated PVs is the major determinant for recurrence of atrial tachyarrhythmia (aTa) after PVI.4 Novel mapping and ablation tools are being developed aiming for higher durability of PVI.5

Currently, local voltage abnormalities are additionally used as a surrogate for diseased cardiac tissue such as fibrosis. Recently, to predict poor outcome after AF ablation, extensive left atrial (LA) tissue fibrosis has been used.6 Additional ablation strategies have been developed to improve clinical outcomes such as ablation of linear lesions and complex fractionated atrial electrograms (CFAE).7,8

However, data regarding LA fibrosis in patients with AF recurrence after second-generation cryoballoon (CB2) based PVI are lacking. Therefore, this study thought to evaluate the incidence of LA fibrosis in patients selected for cryoballoon ablation as well as its association to patients’ baseline characteristics and procedural parameters.

Methods

Study design and patient cohort: Consecutive patients who received RF based repeat ablation procedure due to recurrence of ATA within 6 months after second-generation cryoballoon (CB2, Arctic Front Advance, Medtronic Inc., Minneapolis, USA) based PVI were retrospec...
tively analyzed. Index CB-based procedures were performed from 08/2012 until 08/2017.

All clinical, imaging, and procedural data were recorded. Exclusion criteria for PVI were contraindications to post-interventional oral anticoagulation, severe valvular heart disease at the time of ablation, and prior LA surgery or surgical catheter ablation.Written informed consent was obtained from each patient prior to the procedure, and all patient information was anonymized. This study conforms to the guiding principles of Helsinki of 2014 and was approved by the local ethics committee (WF-44/18).

**First procedure - CB2-based PVI:** CB2-based ablation was performed by highly experienced operators trained in the usage of the CB2. In all procedures, the 28 mm CB2 was used. The ablation procedure was performed according to our routine approach as previously described. In brief, single transeptal puncture was performed using a modified Brockenbrough technique and an 8.5 Fr transeptal sheath (SL1, St. Jude Medical, St. Paul, MN). The transeptal sheath was exchanged over a wire for a 12 Fr steerable transeptal sheath (Flexcath Advance, Medtronic). After transeptal puncture, heparin bolus were administered targeting an activated clotting time > 300 seconds. To identify the individual PV ostia, selective PV angiographies were performed. A temperature probe (Sentitherm, St. Jude Medical; or Circa S-Cath, Circa Scientific, Englewood, CO, USA) was placed within the esophagus to monitor esophageal temperatures during freeze cycles. During CB2 applications along the septal PVs, continuous pacing of the phrenic nerve (PN) was performed via a diagnostic catheter positioned within the superior vena cava (7 Fr, Webster, Biosense Webster, Diamond Bar, CA). Pacing was set at maximum output and pulse width and a cycle length of 700 ms. Monitoring of PN was based on tactile feedback of diaphragmatic conduction gaps were targeted using a 3.5 mm irrigated tip catheter (Biosense Webster, Navi-Star™, ThermoCool™). The procedural endpoint was complete electrical isolation of previously ineffective antiarrhythmic drug therapy and/or deployment of linear lesion sets dependent on the AT mechanism.

**Classification of LA fibrosis:** The area of fibrosis was measured via the CARTO analyzing software in the respective CARTO map and then analyzed in proportion to the total area. Low-voltage sites were delineated based on bipolar voltage measurements of <0.5 mV in all patients according to previous studies. These sites were measured as absolute and relative (related to complete LA volume) extent of fibrosis and categorized as stage A (0-10% of the LA wall), stage B (10-30%), stage C (30-50%), and stage D (> 50%).

**Postprocedural care:** Following the ablation procedure, to rule out pericardial effusion, all patients received transthoracic echocardiography. A thoracic x-ray was taken whenever subclavian vein access was attempted to rule out pneumothorax. All patients were treated with proton-pump inhibitors for 6 weeks. Anticoagulation was continued for at least 3 months post ablation and then based on the individual CHA2DS2-VASc score. Anticoagulation was continued for at least 3 months post ablation and then based on the individual CHA2DS2-VASc score. Continuation of previously ineffective antiarrhythmic drug therapy was recommended to be continued for 3 months.

**Statistical analysis:** Continuous data are described as mean and standard deviation or as median plus first and third quartile. Categorical data are presented as absolute and relative frequencies.

Logistic regression models were used to associate fibrosis to AT (compared to other recurrence types) as well as SR during mapping (with regard to all other rhythm status). Logistic regression models were also performed to detect risk factors for LA fibrosis. In addition to the patient’s baseline characteristics (given in the Table), the minimal balloon temperature and total freezing time was performed. In patients on vitamin K antagonists, ablation was performed under therapeutic INR values of 2-3. Direct oral anticoagulants were stopped the day before the procedure and continued 6 hours post ablation.

**Electroanatomical mapping and RF reablation procedure:** Three-dimensional reconstruction of the LA was conducted using an electroanatomical mapping system (CARTO, Biosense Webster, Diamond Bar, CA). LA low voltage was defined as areas with bipolar voltage < 0.5 mV. To ensure highest accuracy of electrogram criteria, a minimal number of 70 mapping points were acquired per map.

The PV ostia were tagged according to the selective PV angiographies and local electrical signals. A spiral mapping catheter (LASSO® NAV, Biosense Webster) was placed at the ostium of each PV to record electrical PV potentials. The presence/absence of electrical PV conduction was analyzed using a standard mapping catheter. Re-conduction gaps were targeted using a 3.5 mm irrigated tip catheter (Biosense Webster, Navi-Star™, ThermoCool™). The procedural endpoint was complete electrical PVI. In patients with persistent isolation of all PVs admitted in SR, ostial potentials along previously performed ablation lines were identified and ablated, and/or linear lesions were applied. In patients admitted in AF/AT persistent isolation of all PVs, ostial potentials were identified and ablated followed by additional CFAE-ablation and/or deployment of linear lesion sets dependent on the AT mechanism.

**Preprocedural setup:** Prior to the procedure, transthoracic and transesophageal echocardiography was performed to rule out intracardiac thrombi and to assess the LA diameter. No additional preprocedural imaging was performed. In patients on vitamin K antagonists, ablation was performed under therapeutic INR values of 2-3. Direct oral anticoagulants were stopped the day before the procedure and continued 6 hours post ablation.
analyzed. Effects of fibrosis on procedural and rhythm data were presented with P-values. All P-values were two-sided, and a P-value < 0.05 was considered significant. All calculations were performed with the statistical analysis software R (R Core Team, 2018).

Results

Study population: A total number of 60 patients were included in this analysis. AF at baseline was paroxysmal in 34 (56.7%) patients and persistent in 26/60 (43.3%) patients. Mean patient age was 67 ± 10 years, and mean LA diameter was 42.5 ± 10 mm; 32/60 (53.3%) patients were female. Detailed patient data are given in the Table. Patients' age and LA diameter were detected as risk factors for LA fibrosis (P < 0.01, P = 0.04).

CB-based PVI: Index CB-based procedures were performed from 08/2012 until 08/2017.

In 45/60 (75%) patients, a time-to-effect based cryoaolation protocol was used. In 13/60 (22%), a fixed freeze cycle of 180 seconds was applied. In only 2/60 (3%) patients, a bonus-freeze was applied after verification of pulmonary vein isolation.

Procedural data - repeat ablation procedure: Repeat RF catheter ablation procedure due to symptomatic recurrence of AT was performed at a median of 104 (57; 135.5) days after the index procedure. Mean total procedure time was 105 (± 39.8) minutes, and mean fluoroscopy time was 20 (± 7.7) minutes.

43/60 (71.7%) patients presented with recurrence of AF. In 17/60 (28.3%) patients, LAT was documented as the clinical arrhythmia recurrence. In 40/60 (66.7%) patients, PV-reisolation and/or ablation of CFAEs was performed during the redo-procedure. In 3/60 (5%) patients, additional ablation of the cavotricuspid isthmus was performed. In 17/60 (28.3%) patients, ablation of linear lesions within the LA (n = 12 anterior line, n = 5 mitral isthmus line) was conducted.

Mapping results-extent of LA low-voltage: The LA voltage map was created during sinus rhythm in 34/60 (57%) patients, during AF in 16/60 (27%), and during atrial tachycardia in 10/60 (17%). In total, the analyzed maps consisted of a mean of 121 (± 43.4) mapping points.

The mean total LA wall surface was 138.3 ± 29.1 cm², according to the CARTO area surface measurement tool. The median total area of LA tissue fibrosis was 28.9 (9; 50.3) cm², which corresponded to 17.4 (6; 30.6) % of the overall LA wall surface (Figure 1).

In general, 17/60 (28.3%) patients were categorized into fibrosis stage A, 21/60 (35%) into stage B, 18/60 (30%) into stage C, and 4/60 (6.7%) into stage D. 13/34 (38.2%) patients with paroxysmal and 4/26 (15.4%) patients with persistent AF were categorized into stage A, 15/34 (44.1%) versus 6/26 (23.1%) patients into stage B, 4/34 (11.8%) versus 14/26 (53.9%) patients into stage C, and 2/34 (5.9%) versus 2/26 (7.7%) patients into highest level D (Figure 2). Next, a higher degree of fibrosis (stage C and B) was more commonly seen in patients with persistent AF (15/22, 68.2%). The patients' ages and LA diameters were found as predictors for LA wall fibrosis.

Type of arrhythmia recurrence in correlation to LA wall fibrosis: In 5/17 (29.4%) patients presenting with left AT for re-procedure, LA fibrosis was categorized into class A or B and in 12/17 (70.6%) patients into class C or D before. A statistically significant correlation was found between the presence of atrial tachycardia and the extent of LA wall fibrosis (P < 0.01; Figure 3). In addition, in patients with extended LA tissue fibrosis, ablation of linear lesions was more often performed (P < 0.01).

Periprocedural complications: Major complications occurred in 3/60 (5%) patients, including one stroke, one groin complication requiring surgery, and one pericardial tamponade after transseptal puncture requiring pericardiocentesis. Furthermore, one groin hematoma (1/60, 1.7%) as a minor complication occurred, and it was managed by conservative treatment only.

Discussion

Main findings: To the best of our knowledge, this is the first study reporting on the impact of LA fibrosis in patients with AF recurrence after CB2-based PVI. In our study, consecutive patients who received RF based repeat ablation procedure due to recurrence of AT within 6 months after CB2-based AF-ablation were retrospectively analyzed.

The main findings of the present study are as follows: 1) Tissue fibrosis of the LA wall is common in patients with recurrence of AT and after initial CB2-based PVI; 2) Expanded LA tissue fibrosis was associated with the occurrence of atrial tachycardia as the index procedure in redo-procedures; and 3) in the patients with a higher extent of LA wall fibrosis, more extensive ablation was performed during redo-procedures. 4) Age and LA diameter were found as predictors for LA wall fibrosis.

Predictors for LA wall fibrosis: In the current literature, several parameters have been identified as risk factors for the occurrence of LA wall fibrosis, such as LA size and arterial hypertension.

Table. Baseline Patient Data

| Parameter                  | Value   |
|----------------------------|---------|
| Female                     | 32 (53.3%) |
| Age, years                 | 67 (± 10) |
| Type of atrial fibrillation|         |
| Paroxysmal                 | 34 (56.7%) |
| Persistent                 | 26 (43.3%) |
| Left atrial diameter, mm   | 42.5 (± 10) |
| Ejection fraction, %       | 55 (± 4) |
| Arterial hypertension      | 34 (56.7%) |
| Diabetes mellitus          | 6 (10%) |
| Antithrombotic drugs at baseline |     |
| β-blocker                  | 49 (81.7%) |
| Class IC                   | 30 (50%) |
| Class III                  | 13 (21.7%) |
| Oral anticoagulation at baseline |    |
| Vitamin K antagonist       | 14 (23.3%) |
| Novel oral anticoagulant (NOAC) | 46 (76.7%) |

Continuous data are summarized as means ± standard deviations or as medians [25th and 75th percentiles]. Categorical data are presented as n (%).
Figure 1. Example of a left atrial voltage map acquired using Carto-guided point-by-point mapping as our clinical routine approach in a posterior-anterior and left-lateral view. Bipolar voltage reference interval was set as < 0.5 mV. A and D according to the extent of low-voltage areas as previously described.

Figure 2. Extent of LA wall fibrosis according to type of atrial fibrillation (AF).
In our analysis, LA low-voltage areas after CB-based PVI were detected in particular in patients with pre-existing persistent AF, although this finding did not reach statistical significance. The distribution of LA wall low-voltage areas in patients with PAF and persistent AF is shown in Figure 1. In addition, our analysis confirmed that patients’ age as well as LA diameter are risk factors for LA fibrosis, which is in line with previous studies. Knowledge about predictors of tissue fibrosis might help to optimize patient selection for CB2-based AF-ablation.

**Persistent AF and LA wall fibrosis:** Cryoballoon ablation emerged as an effective treatment option for symptomatic AF with encouraging clinical results, in particular in patients with paroxysmal AF. In addition, CB ablation has been shown to be non-inferior to radiofrequency (RF) ablation with regards to efficacy and overall safety in patients with drug-refractory paroxysmal AF in the large prospective and randomized FIRE and ICE trial. Recently, CB-based PVI has been applied also in patients with persistent AF with encouraging clinical outcome data reported in some smaller studies. However, local voltage abnormalities are used as a surrogate for diseased cardiac tissue such as fibrosis and recently, extensive LA tissue fibrosis, which often occurs in patients with persistent AF, has been used to predict poor outcome after AF ablation. This means that, in particular, those patients with persistent AF are required to be carefully selected.

LA tachycardia is more often seen in patients with persistent AF and in patients with more extensive LA wall fibrosis. LAT is common in patients after PVI and is reported to be up to 20%. To the best of our knowledge, this is the first report giving insights into the extent of LA wall fibrosis in patients after cryoballoon-based PVI and recurrence of aTa. Due to some overlap of the balloon with the posterior LA wall, cryoballoon ablation results not only in PVI but also in substrate modification. However, LA tachycardias often result from LA wall fibrosis leading to perimital or anterior wall/roof dependent LAT. This is also reflected by the findings of our study where the majority of patients with LAT as the index tachycardia in redo-procedures were treated with ablation of an anterior line (12/17, 70%). Although the star AF trial has not shown clinical benefit after additional ablation of LA lines as compared to PVI only, ablation of LA wall scar in the index procedure might be useful in patients with extensive scarring, to prevent the occurrence of LAT in these patients. This highlights the importance of the findings of the present study.

**LA fibrosis in consequence of CB2-based AF ablation:** The fact that isolation of the PVs is the key element of CB-technology could potentially limit clinical long-term outcome after CB-based PVI in patients. Conversely, recent studies also showed that the area of the posterior LA wall ablation with the CB2-catheter is wide and antral, and the resulting posterior LA wall debulking could be a part of the cryoballoon efficacy beyond PVI.

**Prospect:** As previously discussed, local voltage abnormalities are being used more and more often as a surrogate for diseased cardiac tissue such as fibrosis. Recently, extensive LA tissue fibrosis has been used to predict poor outcome after AF ablation. In our analysis, patients with extended LA fibrosis presented more often with AT as clinical aTa recurrence. In these patients, more extensive ablation - especially ablation of linear lesions - was performed more frequently. These results support the assumption that, PVI only, which is the key element of cryoablation, might not be sufficient in several patients with persistent AF. Knowledge about the incidence and extent of tissue fibrosis might help to optimize patient selection for cryoballoon ablation and help to optimize clinical outcome in this patient population. Additionally, it might be helpful to assess
pre-interventional imaging with cardiac MRI in patients with persistent AF planned for cryoballoon ablation to optimize patient selection.

Limitations: The current observational study is a retrospective single-center experience with a limited number of patients. High-density mapping might have resulted in more detailed 3D maps; however, all mapping points in the present study were taken manually and were therefore, carefully selected and controlled point by point to guarantee highest mapping quality and prevent misinterpretation of the data.

Conclusion

Low-voltage of the LA wall was a common finding in patients with recurrence of ATA after CB2-based PVI. Age and LA diameter were predictors for the extent for LA wall fibrosis. Extensive LA wall fibrosis has been mainly seen in patients with initial persistent AF. Extended low-voltage areas of the LA wall were associated with the occurrence of atrial tachycardia and in the corresponding patients more extensive ablation was performed during redo-procedures.

Disclosure

Conflicts of interest: Karl-Heinz Kuck reports research contracts/grants from Biosense Webster, Medtronic, Abbott Vascular, and Boston Scientific and consulting fees from Abbott Vascular. Tilman Maurer received travel grants from Biosense Webster and Abbott EP. Andreas Metzner received speaker’s honoraria and travel grants from Medtronic, Biosense Webster, Bayer, Boehringer Ingelheim, EPD Solutions/Philips and Cardiofocus. Andreas Rillig received travel grants from Biosense, Medtronic, St. Jude Medical, Cardiofocus, EP Solutions, Ablamap and EPD Solutions/Philips and lecture and consultant fees from St. Jude Medical, Medtronic, Biosense, Cardiofocus, Novartis and Boehringer Ingelheim. Bruno Reissmann received speaker’s honoraria and travel grants from Medtronic.

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