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Time-to-isolation guided titration of freeze duration in 3rd generation short-tip cryoballoon pulmonary vein isolation – Comparable clinical outcome and shorter procedure duration

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ABSTRACT

Background: The optimal freeze duration in cryoballoon pulmonary vein isolation (PVI) is unknown. The 3rd generation cryoballoon facilitates observation of the time-to-isolation (TTI) and thereby enables individualized cryoenergy titration. To evaluate the efficacy of an individualized freeze duration we compared the clinical outcome of patients treated with a TTI-guided ablation protocol to the outcome of patients treated with a fixed ablation protocol.

Methods: We compared 100 patients treated with the 3rd generation cryoballoon applying a TTI-based protocol (TTI group) to 100 patients treated by a fixed freeze protocol (fixed group). In the fixed group a 240 s freeze cycle was followed by a 240 s bonus freeze after acute PV isolation. In the TTI group freeze duration was 180 s if TTI was ≥30 s and reduced to only 120 s, if TTI was <30 s. In case of a TTI >60 s a 180 s bonus freeze was applied.

Results: Freedom from atrial arrhythmia recurrence off class I/III antiarrhythmic drugs after one year was not different between the TTI group (73.6%) and the fixed group (75.7%; $p = 0.75$). Mean procedure duration was 85.8 ± 27.3 min in the TTI group compared to 115.7 ± 27.1 min in the fixed group ($p < 0.001$). Mean fluoroscopy time was 17.5 ± 6.6 min in the TTI group and 22.5 ± 9.8 min in the fixed group ($p < 0.001$).

Conclusions: TTI-guided cryoenergy titration leads to reduced procedure duration and fluoroscopy time and appears to be as effective as a fixed ablation strategy. A single 2-minute freeze seems to be sufficient in case of short TTI.

1. Introduction

Cryoballoon pulmonary vein isolation (PVI) has emerged as an effective therapy to treat symptomatic atrial fibrillation [1–3]. Advantages of the cryoballon to achieve PVI include shorter procedure duration compared to radiofrequency (RF) catheter ablation, but on the contrary fluoroscopy time is longer in cryoballoon procedures as compared to RF PVI [1].

The optimal cryoenergy dosage, i.e. freeze cycle duration and number of freezes, is not known. The advantage of a limitation of cryoenergy might be even shorter procedure duration, reduction of fluoroscopy, and reduction of off-target side effects, especially extracardiac complications, such as phrenic nerve palsy and thermal esophageal lesions. In contrast, one can expect a minimal cryoenergy dosage threshold below which the efficacy and durability of PVI will be compromised. Initially, a freeze cycle duration of 240 s followed by a bonus freeze after acute PVI has been recommended after introduction of the 2nd generation cryoballoon (Arctic Front Advance, AFA) [4–6]. Several different protocols aiming at a reduction of freeze duration have since been proposed. Omission of a bonus freeze showed comparable results to the initial bonus freeze approach [7,8]. In another study reduction of the freeze cycle from 240 s to 180 s did not lead to increased arrhythmia recurrence rates [9]. Even reduction of the freeze cycle to 180 s and omission of a bonus freeze did not lead to decreased overall efficacy [10].

Introduction of a spiral mapping catheter through the inner lumen of the cryoballoon catheter into the pulmonary vein enables real-time monitoring of pulmonary vein isolation. The time-to-isolation (TTI) has been established as a valuable biophysical surrogate marker to estimate the quality of an ablation lesion. While a short time-to-isolation seems to be predictive of a durable isolation, a long time-to-isolation is associated with an increased risk of PV reconnection [11–13]. A freeze protocol that omitted a bonus freeze depending on the observed TTI (<75 s) has led to low recurrence rates in a recent randomized trial [14].

The 3rd generation cryoballoon (Arctic Front Advance ST, AFA-ST) facilitates real-time registration of PV isolation due to a shorter distal tip, thus enabling the implementation of TTI-based freeze protocols

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[15–18]. We have developed a cryoballon PVI freeze protocol with a standard 180 s freeze cycle until PVI, based on the finding that a single 180 s freeze results in equal overall efficacy compared to two 240 s freezes [10]. Taking TTI into account, we even further reduced the freeze cycle to only 120 s, if PV isolation was achieved in less than 30 s. On the other hand, since a TTI >60 s has been shown to be linked to higher recurrence rates, we conducted a bonus freeze only if documented TTI was ≥60 s [12]. To evaluate the efficacy of this cryoballon PVI protocol, we here compared the clinical outcome of patients treated with this TTI-guided ablation protocol to the outcome of patients treated with the fixed ablation protocol.

2. Methods

2.1. Study population

200 consecutive patients that underwent PVI for the treatment of symptomatic paroxysmal or persistent atrial fibrillation at Ulm University Medical Center between June 2014 and September 2016 were included into the study. The first 100 patients were treated with the 2nd generation cryoballoon (Medtronic Arctic Front Advance, 28 mm, Medtronic, Minneapolis, MN) and a fixed dosing regimen (fixed group). The last 100 patients were treated with the 3rd generation cryoballoon (Arctic Front Advance ST, 28 mm, Medtronic, Minneapolis, MN) and an individualized TTI-dependent freeze protocol (TTI group). Patients were not randomized. Patients with a left common trunk were excluded from analysis. Further exclusion criteria were long standing persistent atrial fibrillation, moderate or severe reduction of left ventricular ejection fraction (LVEF <45%), moderate to severe mitral regurgitation and left atrial diameter >55 mm. The study was approved by the local ethics committee.

2.2. Aim of the study

The aim of the study was to assess overall freedom from atrial arrhythmia recurrence 12 months after the index procedure off class I or class III antiarrhythmic drugs (AAD) in patients treated with the TTI-based ablation protocol compared to the fixed ablation protocol.

2.3. Preprocedural management and cryoballoon ablation procedure

Left atrial thrombus was ruled out by transesophageal echocardiography in all patients prior to PVI. The cryoballoon procedure was guided by fluoroscopy only, including pulmonary vein angiography after transseptal puncture and before introduction of the cryoballoon, no additional pre-procedural or intra-procedural imaging such as CT, MRI or intracardiac echocardiography was applied. Vitamin K antagonists (VKA) were administered uninterruptedly to a target INR of 2.0–3.0 at the time of the procedure. Patients treated with non-VKA oral anticoagulants (NOACs) were advised to hold their anticoagulant 24 h prior to the ablation procedure.

The cryoballoon ablation procedure has been described in detail before [17,19]. Briefly, under deep sedation a 10-polar diagnostic catheter was placed in the coronary sinus (cs). The cryoballoon was advanced to the LA via a 12F steerable sheeth (Flexcath Advance, Medtronic, Minneapolis, MN) after single transseptal puncture and inflated at the PV ostia. Instead of a guidewire an 8-polar spiral mapping catheter (20 mm Achieve, Medtronic, Minneapolis, MN) was advanced through the balloon inner lumen and positioned in the PV at the closest achievable proximity to the cryoballoon in order to record real-time PV potentials during PV isolation. PV occlusion was documented by injection of contrast medium. During PV isolation the potentials from the PV were recorded. The TTI was defined as the time of the last recording of a PV potential before sustained isolation.

2.4. Cryoenergy dosing protocols

In the fixed group freeze cycles of 240 s were administered at each PV until acute PVI could be documented by entrance- and exitblock. A single 240 s bonus freeze was applied at each PV thereafter. TTI was recorded but was not used to modify freeze duration or bonus freezes. In the TTI group freeze duration was modified depending on the observed TTI: In case of a TTI <30 s the total freeze cycle duration was decreased to 120 s and no bonus freeze was applied. If TTI was between 30 s and 60 s a single 180 s freeze cycle was applied. If TTI was >60 s a 180 s freeze cycle followed by a 180 s bonus freeze was applied. If no TTI could be documented, but isolation was achieved, a single 180 s freeze cycle was applied. In case of unsuccessful PV isolation or acute PV reconnection during or immediately after the applied freeze cycle additional freeze cycles were added with the identical freeze protocol until PV isolation was achieved (Fig. 1). Isolation of all PVs was reassessed at the end of the procedure by documentation of entrance- and exit-block in the TTI-group.

Esophageal temperature was monitored by a transnasally introduced temperature probe (Sensitherm; St. Jude Medical Inc., St Paul, MN or Circa; Circa Scientific Inc., Englewood, CO) in all patients. Cryoablation was prematurely terminated if luminal esophageal temperature (LET) decreased below 15 °C. Phrenic nerve function was monitored by phrenic nerve stimulation via the diagnostic catheter placed in the superior vena cava and palpation of the right-sided diaphragm and with additional recording of compound motor action potentials (CMAP) of the right sided diaphragm by surface ECG [20,21]. A decrease in CMAP potentials or weakening of palpable diaphragm contractions led to immediate termination of the freeze cycle. Other reasons for premature termination of the freeze cycle included drop of balloon temperature below −60 °C, or dislodgement of the cryoballoon.

2.5. Postprocedural management and clinical follow-up

Echocardiography was performed in every patient immediately after the procedure and before hospital discharge to rule out pericardial tamponade or pericardial effusion. Oral anticoagulation was resumed on the day of the ablation procedure. AADs were held immediately after the procedure and in select cases with highly symptomatic recurrences during the blanking period given until the end of the blanking phase. Patients were scheduled for outpatient clinic visits including clinical assessment, echocardiography, 12 lead rest-ECG, and 7-day-Holter-monitoring at 1, 3, and 6 months after the procedure and thereafter every 6 months. Any documented sustained atrial arrhythmia on 12 lead rest-ECG or any atrial arrhythmia of ≥30 s on Holter ECG was counted as primary endpoint. Initiation of AADs or failure to hold them after the 3-months blanking period was also counted as a primary endpoint.

2.6. Statistical analysis

Significance of differences of numeric values between the two groups was calculated by *t*-test if normal distribution with equal variance was given. Normal distribution was determined by Shapiro-Wilk test and equal variance by Brown-Forsythe test. Numeric variables that were not normally distributed were analyzed by Mann-Whitney rank sum test. Categorical variables were analyzed by Chi square test or Fisher's exact test. A p-value <0.05 was considered significant. Statistical assessment was performed with Excel (Version 2016, Microsoft Inc., Redmond, WA) or XLStat software (V 2016.02.28430, Addinsoft, New York, NY).

3. Results

3.1. Patients

In the 200 enrolled patients – 100 in the fixed group and 100 in the TTI group – we identified a total of 800 PVs with 400 PVs in each group. Baseline characteristics are not significantly different between both groups concerning age, sex, body-mass-index (BMI), EHRA classification and comorbidities (Table 1).

3.2. Cryoballoon ablation procedure

PVI with the cryoballoon was successful at all 800 PVs (100%) targeted. No additional ablations were necessary in any patient to achieve complete PV isolation. No ablations targeting non-PV foci or any type of substrate modification was performed in any patient.

In the TTI group the overall real-time registration of PV isolation was much more common (n = 326; 81.5%) compared to the fixed group (n = 171; 42.8%; p < 0.001). In contrast, the mean TTI was not different between both groups (44.3 ± 25.4 s vs. 42.2 ± 22.2 s; p = 0.55). No difference in the distribution of the observed TTI intervals (<30 s, 30–60 s, >60 s) was noted between the TTI group and the fixed group: a TTI <30 s occurred in 59 PVs (34.5%) in the fixed group and in 111 PVs (34.0%) in the TTI group (p = 0.9), a TTI between 30 s and 60 s was observed in 83 PVs (48.5%) in the fixed group and in 155 PVs (47.5%) in the TTI group (p = 0.8), and a TTI >60 s was documented in 29 PVs (17.0%) in the fixed group and in 60 PVs (18.4%) in the TTI group (p = 0.7). The TTI based cryoenergy dosing (Fig. 1) led to a much shorter total cryoenergy delivery time (14.2 ± 5.1 min vs. 33.5 ± 4.4 min, p < 0.001), and a significant reduction of freeze cycles applied per patient (5.4 ± 1.8 vs. 8.7 ± 2.2; p < 0.001) and per vein (1.4 ± 0.5 vs. 2.2 ± 0.6; p < 0.001). Abortion of freeze cycles due to cryoballoon temperature below −60 °C occurred only in the fixed group (0.9% vs. 0%, p = 0.03, Supplementary Table 1). PV isolation with the first freeze occurred more commonly in the TTI group (87.3%) compared to the fixed group (76.3%; p < 0.001). The mean nadir temperature was less low in the TTI group (−45.0 ± 5.9 °C) compared to the fixed group (−48.8 ± 2.3 °C; p < 0.001). Ultimately, the TTI-guided ablation protocol led to a reduction in procedure duration in the TTI group (85.8 ± 27.3 min) compared to the fixed group