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Prognostic value of induction of atrial fibrillation before and after pulmonary vein isolation

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ABSTRACT

Background: Apart from pulmonary vein isolation, catheter ablation of atrial fibrillation (AF) lacks reliable electrophysiological endpoints. The present study investigated the prognostic value of changes in AF inducibility due to ablation.
Methods: Between 10/2006 and 10/2009 121 patients referred for catheter ablation of symptomatic, drug refractory paroxysmal AF were included. Sinus rhythm immediately before ablation was a prerequisite for study entry. Two respective attempts to induce AF (>1 min) by decremental coronary sinus stimulation before and after ablation were performed.
Results: A total of 121 patients aged 59.5 ± 10.4 years undergoing pulmonary vein isolation due to paroxysmal AF were included. The median follow-up duration was 12.1 months [quartiles: 6.5–20.3 months]. In 36 (30%) patients AF was inducible before, but not after ablation. Forty-nine (41%) patients were neither inducible before nor after the procedure, whereas 25 patients (21%) displayed unchanged inducibility. In 11 patients (9%) AF was inducible only after ablation. Patients with inducibility solely after the ablation had the highest risk of AF recurrence (HR 6.71 [95%-CI 2.76–16.30], p = 0.0005) compared to patients without inducibility before and after the procedure.
Conclusion: The results of attempted AF induction before and after ablation have significance with respect to ablation outcome. Both patient groups with either unchanged inducibility or facilitated induction after ablation had the highest recurrence rates of AF.

1. Background

Catheter ablation of paroxysmal atrial fibrillation (AF) is recommended by current guidelines for symptomatic patients with failed antiarrythmic medication or without structural heart disease [1]. However, apart from pulmonary vein isolation, catheter ablation of AF lacks reliable electrophysiological endpoints. The role of inducibility of AF after radiofrequency catheter ablation has been examined by several investigators [2–10], but the prognostic value of changes in inducibility before and after radiofrequency catheter ablation has never been scrutinized.

The aim of the present study was to investigate the prognostic value of changes in AF inducibility due to ablation.

2. Methods

2.1. Patients

Between 10/2006 and 10/2009 121 patients referred for catheter ablation of symptomatic, drug refractory paroxysmal AF, were included into the present study. Exclusion criteria were persistent AF, absence of sinus rhythm immediately before the ablation procedure, pregnancy, ongoing infections, intracardiac thrombosis, inadequate anticoagulation prior to index admission, contraindicated oral anticoagulation, previous myocardial infarction or cardiac surgery within the last 3 months, and refusal to give written informed consent. The study was approved by the ethics committee of the Medical University of Vienna and was conducted in accordance with the Declaration of Helsinki.

2.2. Treatment before catheter ablation

Oral anticoagulation with an international normalized ratio target of 2–3, or treatment with weight-adjusted low molecular weight heparin was given over a period of at least 1 month before the ablation procedure. Procedures before the ablation were performed as previously described [10].

2.3. Catheter ablation procedure

The procedures were performed applying intravenous sedation using midazolam and fentanyl. Vascular access was obtained through both femoral veins and two 7-french

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deflectable catheters (Biosense Webster) were advanced into the right atrium, positioned at the atrioventricular node and into the coronary sinus. Two transseptal punctures were performed using standard techniques. All patients were treated by initial pulmonary vein (PV) isolation using a CARTO guided ablation procedure (electroanatomical mapping system CARTO, Biosense Webster Inc.) [11] with a 3.5-mm externally irrigated-tip catheter (ThermoCool, Navistar, Biosense Webster) and a circular mapping catheter (Lasso catheter, 25 mm). Patients with a history or inducibility of isthmus-dependent right atrial flutter underwent additional ablation of the cavotricuspid isthmus. All antiarrhythmic drugs were discontinued before the procedure.

2.4. Pacing protocol for AF induction

Before the ablation procedure, patients were subjected to a standardized stimulation test consisting of two attempts to induce AF by decremental atrial stimulation (UHS 3000, Biotronik, Berlin, Germany) from the proximal coronary sinus. The electrical impulses were 2 ms in duration and delivered at twice the diastolic threshold with a maximum output of 20 mA. Stimulation was commenced at a cycle length (CL) slightly shorter than sinus rhythm and was continued until the shortest CL with 1:1 atrial capture or until reaching 200 ms. At this final CL, pacing was maintained for 5 s. The duration of induced AF was digitally registered and considered inducible if exceeding 1 min. Patients with induction of other atrial arrhythmias were considered non-inducible. If a patient was found inducible at the first stimulation attempt, no further stimulation attempt was performed.

After completion of the ablation procedure, patients in AF were cardioverted to sinus rhythm. The standardized stimulation test was repeated post-ablation. If sustained AF was induced by the post-ablation stimulation test, sinus rhythm was restored by electrical cardioversion.

2.5. Post-ablation management and follow-up

After ablation, all patients were continuously monitored and received intravenous heparin for 48 h. Oral anticoagulation was re-initiated after clinical evaluation of puncture sites. Oral anticoagulation was continued for at least 3 months. Patients were discharged 2 days after the procedure. Regular follow-up visits started 6 weeks after the ablation procedure and were conducted in 3-month intervals during the first year and in 3–6-month intervals afterwards. All patients were followed for a minimum of 6 months. Regular follow-up visits included clinical evaluation, a 12-lead surface ECG, and Holter monitoring (24 or 48 h). In addition, patients were instructed to contact the outpatient department whenever they experienced symptoms suggestive of AF for documentation by ECG, Holter, or event monitoring. Successful ablation was defined as no recurrence of AF (>30 s) persisting or developing beyond a period of 3 months after ablation.

2.6. Study design and statistical analyses

The study was conducted as a prospective, observational clinical trial. Continuous data are given as mean ± standard deviation. The reverse Kaplan–Meier method [12] was used to describe the follow-up duration. Differences in continuous variables were evaluated by unpaired Student's *t*-test. Time to recurrence of AF was depicted by the use of Kaplan–Meier estimates and compared using the log-rank test. Cox regression analysis was performed to evaluate the univariate and multivariate influences of inducibility and other variables on recurrence rates. Six factors were assumed to be relevant predictive factors: age, sex, left atrial size, structural heart disease, antiarrhythmic drug use during follow-up (class I or III) and the inducibility, comparing four groups of patients: 1.) patients without inducibility before and after the procedure, 2.) patients with inducibility only before the procedure, 3.) patients with inducibility before and after the procedure, and 4.) patients with inducibility only after the procedure. A multivariate Cox regression analysis was performed including all prognostic factors. In an additional Cox regression analysis inducibility was described by two separate prognostic factors [i.e. inducibility before the procedure (yes vs. no) and inducibility after the procedure (yes vs. no)] in order to evaluate a potential interacting effect of these two factors on the recurrence rates. Considering these two factors together with the interaction term within a Cox regression model can clarify, if the strength of the prognostic effect of the inducibility after the procedure depends on the patient's inducibility before the procedure.

All reported p-values are two-sided, and a value of less than 0.05 was considered statistically significant. Statistical analyses were carried out using the statistical software package SAS (SAS Institute Inc., 2002–2008. Cary, NC, USA).

3. Results

3.1. Patients

Of 177 patients with paroxysmal AF screened for the present study, 55 patients could not be included as they were found in AF at the beginning of the procedure. Post-ablation stimulation was not performed in one patient due to pericardial effusion. Therefore, a total of 121 patients aged 59.5 ± 10.4 years undergoing PV isolation due to paroxysmal AF, presenting in sinus rhythm just immediately before the ablation procedure, were entered. Complete PV isolation was achieved in all patients. No patients were lost to follow-up. Patients' characteristics are presented in Table 1.

3.2. Pre- and post ablation inducibility of AF

The applied stimulation protocol led to AF induction in 61 (50%) patients before and 36 (30%) patients after the ablation procedure. Focussing on the changes in inducibility, 36 patients (30%) were inducible before, but not after ablation. 49 patients (41%) were neither inducible before nor after the procedure, whereas 25 patients (21%) were always found inducible. In 11 patients (9%) AF was inducible only after ablation.

Follow-up and prognostic value of changes in AF inducibility due to ablation.

The median follow-up duration was 12.1 months [quartiles: 6.5–20.3 months].

The patterns of inducibility changes achieved by catheter ablation carried strong prognostic value ($p = 0.0003$, log-rank test). The different scenarios of inducibility are depicted in Fig. 1.

Inducibility of AF was a statistically significant predictor of AF recurrence in univariate Cox regression analyses: comparing patients with inducibility only before, before and after, or only after the procedure to patients without inducibility before and after the procedure, the Hazard Ratios (HR) were 1.62 [95%-CI 0.82–3.21], 2.09 [95%-CI 1.05–4.19] and 5.23 [95%-CI 2.30–11.90], respectively ($p = 0.001$). In multiple Cox regression analysis inducibility remained a statistically significant predictor of AF recurrence with HRs 1.66 [95%-CI 0.82–3.36], 2.06 [95%-CI 0.99–4.28] and 6.71 [95%-CI 2.76–16.30], respectively ($p = 0.0005$, Table 2).

Describing patient's inducibility by two separate prognostic factors [i.e. inducibility before the procedure (yes vs. no) and inducibility after the procedure (yes vs. no)] resulted in a statistically significant interaction effect ($p = 0.013$) in Cox regression analysis, revealing that the prognostic effect of patient's inducibility after the procedure depends on the patient's inducibility before the procedure. In order to illustrate this interacting effect, subgroup analyses were performed, evaluating the prognostic effect of inducibility after the procedure for patients inducible before the procedure and for patients non-inducible before the procedure, separately. Results of these subgroup analyses are presented in Table 3 and demonstrate that there is no effect of the inducibility after the procedure in patients inducible

Table 1
Patient characteristics (n = 121).

Patient age (years)	59.5 ± 10.4
Male, n (%)	76 (63)
BMI (kg/m^2)	27.0 ± 4.2
AF history (years)	8.3 ± 7.8
Arterial hypertension, n (%)	69 (57)
Diabetes mellitus, n (%)	5 (4)
Current smoker, n (%)	13 (11)
Structural heart disease, n (%)	36 (30)
Left atrial diameter 2D mode (mm)	52.3 ± 6.7
Left atrial diameter M mode (mm)	44.3 ± 6.9
LVEF (%)	54.2 ± 2.9
Cumulative RF energy delivered (Joule)	51867 ± 20885
Amiodarone at discharge, n (%)	19 (16)
Beta blocker at discharge, n (%)	69 (57)
Flecainide at discharge, n (%)	25 (21)
Calcium channel blocker at discharge, n (%)	10 (8)
Digoxin/digitoxin at discharge, n (%)	4 (3)

Values are presented as mean ± standard deviation or number (percent), respectively, BMI: Body mass index, AF: Atrial fibrillation, LVEF: Left ventricular ejection fraction, RF: Radiofrequency.