Is inducibility of atrial fibrillation after radio frequency ablation really a relevant prognostic factor?

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Aims The study was intended to assess the prognostic value of inducibility of atrial fibrillation (AF) after radio frequency ablation.

Methods and results Two hundred and thirty four patients with drug-resistant paroxysmal (n = 165) or persistent AF (n = 69) underwent either Lasso-guided segmental pulmonary vein isolation (n = 83) or CARTO-guided left atrial circumferential ablation (n = 151). After ablation, two attempts to induce AF (≥1 min) by decremental coronary sinus stimulation were performed. Patients were followed for at least 6 months (median: 12.7 months). At 6 months of follow-up, 67% of patients with paroxysmal and 48% of patients with persistent AF were AF-free. Inducibility of AF was a significant predictor of AF recurrence in univariate [hazard ratio (HR) = 2.32, P < 0.001] and multivariable (HR = 2.19, P < 0.001) Cox regression analyses. The prognostic value of inducibility was present in both patients with paroxysmal (HR = 2.38, P = 0.001) and persistent AF (HR = 1.91, P = 0.034) and did not significantly differ between both ablation techniques. The sensitivity, specificity, positive, and negative predictive values of the AF induction test to predict the 6-month ablation outcome were 46.7, 75, 53.8, and 69.2%, respectively.

Conclusion Inducibility of AF after ablation is a significant predictor of recurrent AF. However, owing to the low diagnostic accuracy of the AF induction test, non-inducibility does not qualify as reliable procedural endpoint.

Introduction

Owing to the lack of a reliable electrophysiological endpoint, the role of inducibility of atrial fibrillation (AF) after radio frequency catheter ablation was examined by several authors.1-8 Accordingly, evidence exists showing a significantly higher success rate of AF ablation in non-inducible patients when compared with those with inducible AF.1-3 Non-inducibility of AF after ablation not only predicted AF-free survival in patients after AF ablation,1-3 but also in patients after ablation of isthmus-dependent right atrial flutter9 or accessory pathways,10 two arrhythmias with a high coincidence of AF. However, in these studies, the applied definitions of inducibility as well as the stimulation protocols differed widely. Furthermore, several authors examined a rather composite endpoint combining persistence and inducibility of AF after ablation1,2 and existing data are in part based on results not derived from multivariable analyses.1,2,4 Moreover, no conclusive data exist for patients with persistent AF.

The aim of the present study is to examine the prognostic value of AF induction manoeuvres after AF ablation in a multivariable approach and to assess their value for clinical decision-making. Furthermore, the present study investigated whether the prognostic value of AF induction tests is affected by the applied ablation technique or by the type of AF.

Methods

Subjects

A total of 243 patients referred for catheter ablation of AF were initially assessed for inclusion into the study. The inclusion criterion was symptomatic, drug-resistant paroxysmal or persistent AF. The type of AF was defined according to generally accepted guidelines.11 Exclusion criteria were pregnancy, ongoing infections, intracardiac thrombosis, inadequate anticoagulation prior to admission, contraindications to anticoagulation, history of myocardial infarction or cardiac surgery within the last 3 months, and refusal to give written informed consent. Five of the 243 patients were ineligible for the study because of one of the exclusion criteria. None of the patients refused to give informed consent. Consequently, 238 patients underwent the ablation procedure. Four of these patients were excluded from the analysis as the post-ablation stimulation...
test could not be carried out. The reasons were inability to achieve stable sinus rhythm despite repeat transthoracic cardioversion after ablation \((n = 3)\) or respiratory failure precluding continuation of the procedure \((n = 1)\). Finally, 234 patients with either paroxysmal \((n = 165)\) or persistent \((n = 69)\) AF were analysed. Baseline characteristics of the final study population are presented in Table 1. Patients with paroxysmal AF had a mean of 19 episodes of AF per month. The study complies with the Declaration of Helsinki and was performed according to the recommendations of the hospital’s Ethics Committee including written informed consent.

Pre-ablation treatment

Oral anticoagulation (target international normalized ratio, 2–3) or treatment with weight-adjusted low molecular heparin was given for at least 1 month before the procedure. Patients receiving antiarrhythmic drugs prior to ablation were maintained on this medication. On admission, a medical history, a physical examination, a 12-lead ECG, an X-ray, a transoesophageal echocardiogram, and standard laboratory measurements were obtained.

Electrophysiological procedure

Patients who were included between May 2002 and April 2004 underwent a Lasso catheter-guided ablation procedure\(^1\) (Lasso Catheter, Biosense Webster Inc., Diamond Bar, CA, USA). Patients included afterwards were treated by a CARTO system-guided ablation procedure\(^2\) (electroanatomical mapping system CARTO, Biosense Webster Inc.).

The procedure was performed with the patient under intravenous sedation using midazolam and fentanyl. Vascular access was obtained through the right and left femoral veins. Two 7-French deflectable catheters (Biosense Webster Inc.) were advanced into the right atrium and positioned at the atrioventricular junction and in the proximal coronary sinus (CS). The 1 mm tip quadripolar CS electrode catheter was used for pacing. Depending on the type of procedure, one or two transeptal punctures were performed using standard techniques. Subsequently, patients received heparin intravenously aiming to maintain an activated clotting time of \(\sim 300\) s.

Lasso-guided procedure

Following double transeptal puncture, a deflectable, circular venous mapping catheter (Lasso catheter, 12–25 mm) and a temperature-controlled 4 mm tip quadripolar catheter (Biosense Webster Inc.) were introduced into the left atrium. After performing selective angiograms of the pulmonary veins (PVs), the Lasso catheter was advanced sequentially into each PV and used for ostial mapping of PV potentials. Ostial sites with the earliest bipolar activation and/or the most rapid unipolar intrinsic deflection were targeted for ablation. Radio frequency energy was delivered with a maximum power output of 30 W and an upper temperature limit of 55 °C. Elimination of all ostial vein potentials and complete entrance block into PVs indicating total electrical isolation served as procedural endpoints. At the end of the procedure, angiography of the PVs was repeated in order to exclude stenosis.

CARTO-guided procedure

A temperature-controlled 8 mm tip quadripolar catheter (Navistar, Biosense Webster Inc.) was advanced into the left atrium and used for mapping and ablation. The electromagnetic mapping system CARTO was utilized for the generation of a three-dimensional electroanatomic map of the left atrium and navigation of the ablation catheter. The PVs were cannulated and tagged. Subsequently, circular ablation lines were placed around the left- and right-sided PVs, followed by an interconnecting roofline and a line from the left circle to the mitral annulus. The encircling lines were created at a distance of \(\sim 15\) mm from the PV ostia and consisted of consecutively focal lesions. Radio frequency energy was delivered at a maximum power output of 50 W and an upper temperature limit of 55 °C for 20–40 s at each ablation site. The endpoint of ablation was an 80% reduction in the amplitude of the local bipolar electrogram or a total of 40 s of energy delivery.

Patients with a history or inducibility of isthmus-dependent right atrial flutter also underwent ablation of the cavitricuspid isthmus, as previously described.\(^3\)

Post-ablation stimulation test

After completion of the ablation procedure, patients in AF were cardioverted to sinus rhythm. The standardized post-ablation stimulation test consisted of two attempts to induce AF by decremental atrial stimulation from the proximal CS. For impulse generation, a commercially available stimulator (UHS 20, Biotronik Inc., Berlin, Germany) was used. 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 cycle lengths (CLs) slightly shorter than sinus rhythm and was continued until the shortest CL with 1:1 atrial capture or until a CL of 200 ms was reached. At this final CL, pacing was maintained for 5 s. The duration of induced AF was digitally registered. AF was considered inducible if it exceeded a duration of 1 min. Patients with induction of other atrial arrhythmias were considered non-inducible. For additional statistical analyses, two alternative definitions of inducibility were used, namely, induction of AF of any duration and induction of AF exceeding a duration of 5 min (inducibility of AF \(>5\) min).

If AF \(>5\) min was inducible at the first stimulation attempt, no further stimulation attempt was performed. AF \(>5\) min was electrically cardioverted.

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. Antiarrhythmic drug medication, if present prior to ablation, and oral anticoagulation were continued for at least 3 months. Patients were discharged 2 days after the procedure. Regular follow-up visits started 6 weeks after ablation and were subsequently conducted in 3-month intervals during the first year and in 6-month intervals afterwards. All patients were followed for at least 6 months. Regular follow-up visits included a clinical evaluation, a 12-lead surface ECG, and Holter monitoring (24 or 48 h). In addition, patients were instructed to contact the outpatient clinic whenever they experienced palpitations or other symptoms suggestive of AF in order to document arrhythmias by ECG, Holter, or event monitoring. Successful ablation was defined as no recurrence of AF persisting or developing beyond a period of 2 months after ablation. Patients with documented recurrence of

### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
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<tbody>
<tr>
<td>Patients, n</td>
<td>234</td>
</tr>
<tr>
<td>Patient age (years)</td>
<td>56.7 ± 10.5</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>168 (71.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6 ± 4.1</td>
</tr>
<tr>
<td>Paroxysmal/persistent AF, n</td>
<td>165/69</td>
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<tr>
<td>Applied ablation technique</td>
<td>83/151</td>
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<tr>
<td>Failed anti-arrhythmic drugs</td>
<td>1.8 ± 0.9</td>
</tr>
<tr>
<td>AF history (years)</td>
<td>6.1 ± 4.5</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>128 (54.7)</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>52 (22.2)</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>45 ± 7</td>
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<tr>
<td>LVEF (%)</td>
<td>61.3 ± 7.4</td>
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\(^4\) Lasso catheter-guided ablation approach.

\(^5\) CARTO system-guided ablation approach.
AF were offered a repeat procedure not earlier than 3 months after the first ablation.

Study design and statistical analyses

The study was conducted as an open, prospective clinical trial. The study was powered (80% power; two-sided $\alpha = 0.05$) to detect a difference of 20% (similar to that of Haissaguerre et al.\textsuperscript{1}) in the 1-year AF-free survival rate (assumption: 50 vs. 70% survival rate in the inducible vs. non-inducible group).

Continuous data are given as mean ± standard deviation. Differences in continuous and categorical variables were evaluated by unpaired Student’s $t$-test and $\chi^2$ test, respectively. Sensitivity, specificity, predictive accuracy, and positive and negative predictive values were used to describe the diagnostic accuracy of the AF induction test to predict the 6-month ablation outcome. Cox regression analysis was performed to evaluate the univariate and multivariable influences of inducibility and other variables on recurrence rates. Twelve factors were assumed to be relevant predictive factors: age, sex, body mass index (BMI), type of AF prior to ablation (paroxysmal vs. persistent), left ventricular ejection fraction (LVEF), left atrial size, structural heart disease, antiarrhythmic drug use during follow-up (class I or III), applied ablation technique, and three definitions of inducibility as described earlier. A stepwise multivariable Cox regression analysis was performed including all factors (except the two alternative definitions of inducibility). Additionally, the interactions between inducibility and type of AF and between inducibility and the applied ablation technique were included in the full model. The rationale for the assessment of these two interaction terms is the clinical relevance of the question whether the prognostic influence of inducibility is dependent on the applied ablation technique or on the type of AF. The stepwise model selection (both directions) was based on the Akaike Information Criterion, which compares the intercept-only model and the fitted model. To investigate the stability of the stepwise selection process, the bootstrap resampling procedure was used.\textsuperscript{15} For each of 1000 bootstrap samples, the described stepwise selection was performed. The predictors that were selected in at least 50% of the models, namely, inducibility and type of AF, were retained in the final multivariable regression model.

For the evaluation of the multivariable influence of inducibility of AF >5 min, a separate multivariable model was computed. 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 SPSS 12.0 (SPSS Inc., Chicago, IL, USA). For the bootstrap resampling procedure, the software package R (freely available at http://www.r-project.org) was used.

Results

A total of 234 patients with either paroxysmal ($n = 165$) or persistent ($n = 69$) AF were analysed. Eighty-three of these patients underwent a Lasso-guided ablation procedure and 151 patients a CARTO-guided procedure. Additional ablation of the cavitricuspid isthmus was carried out in 37 patients. When compared with the CARTO-guided procedure, the Lasso approach had a significantly shorter radio frequency energy application time ($21.9 \pm 10.6$ vs. $32.4 \pm 9.6$ min, $P < 0.001$), a significantly longer fluoroscopic duration ($64.1 \pm 18.4$ vs. $46.1 \pm 18$ min, $P < 0.001$), and a significantly longer procedure duration ($172.9 \pm 45.3$ vs. $141.7 \pm 42.8$ min, $P < 0.001$). One hundred and twenty out of the 234 ablation procedures were performed during sinus rhythm and 114 during AF. In 54 of these procedures, AF terminated during ablation. In the remaining 60 procedures, sinus rhythm had to be restored by cardioversion at the end of ablation.

Follow-up and AF-free survival

The median follow-up duration was 12.7 months [95% confidence interval (CI) 11–14.4 months]. Duration of follow-up varied across patients according to time since procedure. All patients completed a follow-up of at least 6 months. Figure 1A and B displays AF-free survival curves for diverse subgroups. At 6 months of follow-up, 111 out of 165 patients (67.3%) with paroxysmal AF and 33 out of 69 patients (47.8%) with persistent AF were free of AF without ($n = 86$) or with antiarrhythmic drugs ($n = 58$) that had previously failed. Table 2 displays the 6-month ablation outcome for the entire study population and for subgroups.
Inducibility of AF was a significant predictor of recurrent AF in the Lasso group (HR = 2.36, CI 1.18–4.72, P = 0.015) as well as in the CARTO group (HR = 2.24, CI 1.37–3.66, P = 0.001) (Figure 1B). The prognostic value of inducibility did not significantly differ between either of the applied ablation techniques, as assessed by interaction terms.

**Discussion**

In the present study, inducibility of AF after ablation could be identified as a significant predictor of adverse ablation outcome in both univariate and multivariable analyses. If AF could be induced by stimulation at the end of the ablation procedure, the independent risk of recurrent AF was 2.2-fold higher than that in non-inducible patients. Its predictive value was not only restricted to patients with paroxysmal AF, but was also present in those with persistent AF.

In contrast to previous studies which showed that a composite endpoint comprising both persistence and inducibility of AF after ablation has predictive power, the present study addresses the role of inducibility of AF after ablation as a single procedural endpoint. Therefore, patients in AF at the end of the procedure were electrically cardioverted to sinus rhythm to allow testing of AF inducibility.

In previous studies on induction of AF, a multitude of different pacing protocols were used. Not only the type of stimulation, ranging from single extra-stimulus testing to burst stimulation, but also the number of induction attempts and stimulation sites differed widely. It is noteworthy that AF could be induced with aggressive stimulation in up to 100% of patients. Accordingly, data concerning inducibility of AF strongly rely on the applied stimulation protocol. In the present study, a comparably non-aggressive stimulation protocol was chosen to select individuals with high atrial vulnerability and to decrease the number of non-specific AF inductions. The standardized stimulation protocol consisting of two induction attempts from one stimulation site resulted in AF induction in 33.3% of procedures.

Secondly, the definition of inducibility of AF also differed widely in the minimum duration of induced AF considered to be significant (10 s to up to 10 min). In the present study, three definitions of inducibility were tested. Regardless of whether inducibility of AF was defined as induction of AF exceeding a duration of 1 or 5 min, inducibility turned out to be a significant independent determinant of AF recurrence. However, inducibility of AF of any duration was of no predictive value. This supports the assumption that induction of short-term AF must be regarded as a rather non-specific phenomenon.

### Value of inducibility: influence of ablation technique and type of AF

A matter of particular interest was the evaluation as to whether the prognostic power of inducibility could depend on the applied ablation technique or on the type of AF. Because a higher degree of atrial remodelling is present in patients with persistent AF, a long-term process of reverse remodelling initiated by ablation might be essential to restore and maintain sinus rhythm. Therefore, the information provided by stimulation manoeuvres carried out immediately after ablation might be misleading.

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**Table 2 Ablation outcome at 6 months of follow-up**

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Freedom from AF, n (%)</th>
</tr>
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<tbody>
<tr>
<td>Entire study population</td>
<td>234</td>
</tr>
<tr>
<td>Lasso&lt;sup&gt;a&lt;/sup&gt;</td>
<td>83</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>76</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>7</td>
</tr>
<tr>
<td>CARTO&lt;sup&gt;b&lt;/sup&gt;</td>
<td>151</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>89</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>62</td>
</tr>
</tbody>
</table>

<sup>a</sup>Lasso catheter-guided ablation approach.<br>
<sup>b</sup>CARTO system-guided ablation approach.
to some extent in this subset of patients. However, also in the persistent AF group, inducibility of AF was identified as a significant predictor of recurrent AF.

As the Lasso- and CARTO-guided ablation approaches differ in their respective endpoints, the prognostic value of the induction manoeuvres might not necessarily be the same for both types of procedures. This, however, was not confirmed by the present study. A possible explanation for the comparable value of inducibility might be that in both types of procedures, the site of energy application is similar, namely, in the vicinity of the orifice of the PVs. An alternative explanation for this finding could be that the induction test assesses AF substrate independent of both procedures.

**Inducibility: only a significant predictor or also a tool for clinical decision-making?**

Although inducibility was identified as a significant predictor of AF recurrence in the present and previous studies, the question arises whether stimulation manoeuvres can really be regarded as a clinically relevant tool capable of proving or ruling out successful ablation. Oral et al. showed in a
randomized trial that the decision to continue ablation in patients, who remained in AF or were inducible after a CARTO-guided approach, was associated with an improvement of AF-free survival. However, in the subgroup of patients of Oral et al., who were randomized to no further ablation despite persistence or inducibility of AF, also 67% of patients were event-free at the end of the follow-up period. Therefore, a continuation of ablation due to a positive stimulation test or AF persistence would have led to over treatment in a substantial proportion of patients. Furthermore, although the vast majority of patients could be rendered non-inducible by a stepwise ablation approach in a study of Jais et al., repeat procedures were needed in 31% of patients.

Focusing on the data of the present study, the diagnostic accuracy of the stimulation test to predict the 6-month ablation outcome was substantially low. Only 46.7% of the patients with recurrent AF at 6 months of follow-up were inducible in the stimulation test. If a negative stimulation test had been the basis for decision to cease the ablation procedure, ablation would have been stopped in more than half of patients with future AF recurrence. Owing to this low sensitivity, a negative result in the stimulation test is very far from ruling out future recurrence of AF. This is also mirrored by the disappointingly low negative predictive value of 69.2%, which is not much higher than the pre-test probability for ablation success of 61.5% in the present cohort.

The observed specificity of 75% implicates that one-quarter of patients with a successful ablation exhibit a positive induction test and would receive unnecessary treatment if the ablation were to be continued because of a positive stimulation test. With more aggressive stimulation, the number of AF inductions and, therefore, the sensitivity of the test could be increased. However, this would presumably be accompanied by a drop in specificity. All in all, the test could only classify correctly 64.1% of cases. In two previous studies,1,2 calculation of the diagnostic characteristics of the AF induction tests from original data yielded slightly higher values for sensitivity and slightly lower values for specificity when compared with the findings of the present trial. In view of the existing data, the predictive accuracy of AF induction tests after ablation seems to be too low to rule in or out future recurrence of AF at a satisfactorily high level of probability.

Despite this poor diagnostic accuracy, inducibility of AF was associated with a 2.2-fold higher risk of AF recurrence, compared with non-inducibility in the present study. Therefore, additional ablation for non-inducibility would increase the probability of success and probably prevent a repeat procedure. The prolongation of the procedure, however, could be associated with an increased complication rate.

The type of AF and ablation outcome
Inducibility and the type of AF independently predicted ablation outcome. The multivariable-adjusted risk to experience recurrent AF was 1.8-fold higher in patients with persistent than with paroxysmal AF. This finding is in agreement with previous studies.3,23 All other assessed factors including left atrial size, LVEF, and structural heart disease failed to significantly influence ablation outcome.

Study limitations
In numerous ablation centres, lower AF recurrence rates after ablation are described. It cannot be excluded that the present findings are only valid for centres with comparable ablation outcome. However, the ablation outcome of the present study compares well with that reported in the worldwide survey by Cappato et al.25

In the present study, antiarrhythmic medication was not discontinued prior to ablation. Therefore, antiarrhythmic drugs could have influenced the outcome of the induction test. However, the results of the induction test did not significantly differ between patients with and without antiarrhythmic drugs at the time of stimulation (data not shown).

A possible limitation of this study is that event-free follow-up included a proportion of patients continued on previously ineffective antiarrhythmic drugs reflecting a rather conservative strategy of withdrawal of antiarrhythmic drugs after ablation in our centre. To adjust for possible confounding, antiarrhythmic drug use during follow-up was included in the multivariable analysis.

Although systematic attempts to identify asymptomatic recurrence of AF were undertaken, asymptomatic episodes of AF may have been missed. As the assessment of the role of post-ablation induction manoeuvres was the primary goal of this study, baseline stimulation manoeuvres were not performed. Therefore, the rate of AF induction prior to ablation is not known. However, according to the previous published data,1 the applied stimulation protocol is likely to induce AF in the vast majority of patients prior to AF ablation.

Conclusion
In conclusion, inducibility of AF after ablation was found to be a significant independent predictor of recurrent AF. Its predictive power was present in both patients with paroxysmal and persistent AF and was not dependent on the applied ablation technique. Owing to the rather low predictive accuracy, however, the results of post-ablation stimulation test do not qualify as a reliable procedural endpoint for individual patients.

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References


