Original Article

Prognostic Role of Subsequent Atrial Tachycardias Occurring During Ablation of Persistent Atrial Fibrillation
A Prospective Randomized Trial

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Background—The role of subsequent atrial tachycardias (AT) in the context of persistent atrial fibrillation (AF) remains undetermined. This study evaluated the prognostic role of subsequent ATs for arrhythmia recurrences after catheter ablation of persistent AF.

Methods and Results—A total of 110 patients with persistent AF (63±9 years; 22 women; 61 long-lasting persistent AF) underwent pulmonary vein isolation followed by electrogram-guided ablation. After AF terminated to AT, patients were separated by the randomization protocol to receive either direct cardioversion (group A) or further ablation of subsequent ATs to sinus rhythm (group B). After a mean follow-up of 20.1±13.3 months after the first procedure, significantly more group B patients were in sinus rhythm as compared with patients in group A (30 [57%] versus 18 [34%];  P=0.02). Moreover, recurrences of AF were significantly less frequent of group B than in group A patients (10 [19%] versus 26 [49%];  P=0.001). After the last procedure (follow-up, 34.0±6.4 months), significantly more group B patients were free of AF as compared with patients of group A (49 [92%] versus 39 [74%];  P=0.01). The proportion of AT recurrences did not differ between the 2 groups after the first and final procedures. The strongest predictor for an arrhythmia-free survival after a single procedure was randomization to the procedural end point of termination to sinus rhythm by elimination of subsequent ATs ( P=0.004).

Conclusions—Catheter ablation of subsequent ATs increases freedom from AF but not AT, suggesting a contributing role of subsequent ATs in the mechanisms of persistent AF.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01896570.

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Key Words: arrhythmias, cardiac ■ atrial fibrillation ■ catheter ablation ■ tachycardia, ectopic atrial

With an increasing complexity of catheter ablation techniques for the treatment of persistent atrial fibrillation (AF), subsequent atrial tachycardias (AT) have evolved as an important arrhythmia in terms of mechanistic cause, prognostic relevance, and treatment strategies.1-4 Although arrhythmia recurrences after pulmonary vein (PV) isolation as the sole procedural strategy predominantly consist of AF, subsequent ATs represent approximately half of all recurrences after extensive biatrial substrate ablation.1-4,7-9 Therefore, a proarrhythmogenic consequence of the ablation procedure itself by creating the basis for zones of slow conduction or enhanced electric automaticity has been proposed to cause these ATs.10 However, a cumulating body of evidence emerges, demonstrating that subsequent ATs appear as a result of a substrate transformation to the incapability to maintain fibrillatory activity and a hierarchical organization of the arrhythmia.11-13 Nevertheless, the prognostic role of subsequent ATs occurring after termination of persistent AF for the long-term outcome has not been determined thus far.

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The aim of this study was to evaluate the impact of sequential ablation of subsequent ATs occurring after termination of persistent AF on the outcome and potential consequences on the type of arrhythmia recurrences during follow-up.

Methods

Study Population
The patients were selected using the following inclusion criteria: persistent AF lasting for a minimum duration of 1 month before the procedure, a history of ≥1 attempt at electric cardioversion, AF
refractory to antiarrhythmic drug therapy, and no previous ablation procedure. Long-standing persistent AF was defined as arrhythmia duration of ≥12 months. The study was approved by the institutional review board and ethics committee. All patients provided written informed consent. Patients were enrolled at the University Heart Center Hamburg between June 25, 2009, and October 13, 2010.

**Study Design**

The patients were randomized before the procedure into one of the study arms. In all patients, a stepwise ablation procedure was performed consisting of PV isolation as the first step followed by electrogram-based ablation of the left atrium (LA), coronary sinus (CS), and the right atrium (RA) as required. The end point of electrogram-based ablation was termination of AF either with conversion to an AT or directly to sinus rhythm (SR). AT was defined as an organized atrial activity with a consistent endocardial activation sequence and monomorphic P-waves. If the patient terminated directly into SR during electrogram-based ablation, the procedure was completed without ablation of ATs. The randomization protocol was started after AF termination with conversion to AT. In group A patients, AT was electrically cardioverted without specific mapping, and ablation of AT and PV isolation were confirmed or completed if necessary during SR. No further ablation was performed. In group B patients, all subsequent ATs were targeted for ablation until SR was achieved.

**Ablation Procedures**

The following catheters were introduced via a femoral vein access: (1) A steerable decapolar catheter (Inquiry; IBI, Irvine Biomedical, Inc, Irvine, CA) was positioned within the CS; (2) a circumferential decapolar diagnostic catheter (Lasso; Biosense-Webster, Diamond Bar, CA) for mapping of the PVs; (3) a nonsteerable quadrupolar diagnostic catheter (Inquiry; IBI, Irvine Biomedical, Inc) was placed in the right atrial appendage; and (4) a 3.5-mm externally irrigated tip ablation catheter (Thermocool; Biosense-Webster). Access to LA was achieved by a single transseptal puncture with the 2 catheters placed into the LA via the same puncture. A single bolus of 50 IU/kg body weight heparin was administered after transseptal puncture. The activated clotting time was assessed every 30 minutes and maintained within a range of 250 to 350 seconds. In all study patients, the stepwise ablation approach with the desired procedural end point of AF termination was used. The ablation protocol performed as standard at our institution has been described previously in detail.\(^{2,9}\) Electric isolation of the PVs was the first step in all procedures. PV isolation was defined by elimination or dissociation of PV potentials recorded on the Lasso catheter. After complete electric PV isolation, mapping and ablation were routinely continued in the LA. For the purpose of AF cycle length (AFCL) measurement, the Lasso catheter was placed in the LA appendage. After an initial assessment of AF behavior (local AFCL, pulmonary vein isolation; and SR, sinus rhythm).

**Table 1. Patient Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±10</td>
<td>64±9</td>
<td>0.454</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>12 (22)</td>
<td>20 (36)</td>
<td>0.095</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>38 (69)</td>
<td>35 (64)</td>
<td>0.549</td>
</tr>
<tr>
<td>Diabetes mellitus (n, %)</td>
<td>5 (9)</td>
<td>5 (9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Congestive heart failure (n, %)</td>
<td>6 (11)</td>
<td>6 (11)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coronary artery disease (n, %)</td>
<td>13 (24)</td>
<td>14 (25)</td>
<td>0.829</td>
</tr>
<tr>
<td>Amiodarone treatment (n, %)</td>
<td>20 (36)</td>
<td>18 (33)</td>
<td>0.692</td>
</tr>
<tr>
<td>Left atrial size, mm</td>
<td>45±7</td>
<td>46±6</td>
<td>0.675</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>58±10</td>
<td>60±9</td>
<td>0.296</td>
</tr>
<tr>
<td>Duration of continuous AF, mo</td>
<td>12 (1–120)</td>
<td>13 (1–120)</td>
<td>0.220</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; and LVEF, left ventricular ejection fraction.

**Follow-Up**

All patients were seen regularly every 3 months in our outpatient clinic. Before visits, the patients received ≥2 separate 24-hour Holter-ECG. A detailed history of the patients’ symptoms suggestive for potential arrhythmia recurrences was taken. In case of undocumented patterns and electrogram behaviors was performed, consisting of continuous electric activity, high-frequency complex fractionated activity, locally short AFCL or intermittent local burst activity, temporal activation gradient between the distal and proximal bipolar of the roving ablation catheter, and local spreading of centrifugal activation. Ablation of the CS was performed when the LA AFCL became longer than the local AFCL in the CS. Mapping and ablation using the same criteria were continued in the RA if AF did not terminate during LA and CS ablation.

Mapping of ATs was performed using conventional techniques.\(^{6,14}\) In case of macroreentrant ATs, linear ablation was performed, and the end point of bidirectional block was assessed and confirmed by differential pacing maneuvers after restoration of SR. Focal ATs were mapped by assessing the earliest endocardial activation in relation to P-wave onset or, if P-wave onset could not be clearly identified, to a fixed intracardiac electrogram. After AT termination, no attempt at arrhythmia reinduction was performed.

Ablation was performed with a maximum power output of 30 W using an irrigation rate of 10 to 30 mL/min (0.9% saline infused with the CoolFlow Pump, Biosense-Webster) for the PVs, 35 W and an irrigation rate between 30 and 60 mL/min in the LA, and ≤30 W in the RA. RF current was applied within the CS with a maximum of 25 W and a manually adjusted irrigation rate to keep the tip-temperature <42°C.

**Figure 1. Study flowchart with numbers of patients. AF indicates atrial fibrillation; AT, atrial tachycardia; DC, direct cardioversion; PVI, pulmonary vein isolation; and SR, sinus rhythm.**

**Table 2. Comparison of Procedural Data**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline AFCL, ms</td>
<td>17±27</td>
<td>16±28</td>
<td>0.715</td>
</tr>
<tr>
<td>LAA</td>
<td>17±30</td>
<td>17±28</td>
<td>0.979</td>
</tr>
<tr>
<td>RAA</td>
<td>17±24</td>
<td>16±27</td>
<td>0.662</td>
</tr>
<tr>
<td>CS</td>
<td>195±68</td>
<td>242±65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>53±21</td>
<td>66±21</td>
<td>0.001</td>
</tr>
<tr>
<td>RF time, min</td>
<td>93±37</td>
<td>109±33</td>
<td>0.015</td>
</tr>
</tbody>
</table>

AFCL indicates atrial fibrillation cycle length; CS, coronary sinus; LAA, left atrial appendage; and RAA, right atrial appendage.
symptoms suspicious for arrhythmia recurrences, documentation by additional Tele-ECG recordings was performed. A documented symptomatic or asymptomatic arrhythmia episode lasting >30 seconds was defined as recurrence.

An initial blanking period of 3 months was accepted. During the blanking period, antiarrhythmic drug treatment was continued at the discretion of the operator. All antiarrhythmic drugs (excluding β-blocker for the treatment of hypertension) were ceased after the blanking period. Patients with an arrhythmia recurrence after the blanking period were offered and scheduled for a redo procedure.

Ablation Approach of Repeat Procedures
As the first step, electric conduction of the PVs were assessed using a circumferential mapping catheter, and reisolation was performed. If AF persisted, electrogram-guided ablation was performed with the same techniques as described for the index procedure. Mapping and ablation of AT were also performed using the techniques described above. The end point was termination of all occurring arrhythmias with procedural achievement of SR in all patients regardless of the initial randomization protocol.

Statistical Analysis
All continuous variables are reported as means±SD and medians with ranges, whereas categorical variables were summarized as proportions. Categorical variables were compared using the χ² test. Comparison between groups was performed with either Student t test or the χ² test. For non-normally distributed variables, the Mann–Whitney U test was used. A P value of <0.05 was considered to indicate a statistically significant difference. On the basis of our clinical experience, we assumed a P value of 0.05 for α error and a P value of 0.15 for β error (β−1=0.85). With an expected rate of the arrhythmia-free survival of 0.6 (group B) and 0.3 (group A), we calculated a sample size of 100 patients. On the assumption of an overall rate of loss to follow-up of 10%, we included a total number of 110 patients in both groups. Time to arrhythmia recurrence was estimated using the Kaplan–Meier method and compared by the log-rank test. Multivariate analysis by means of a logistic regression model and stepwise backward selection was performed to identify significant and independent predictors of arrhythmia recurrence. Independent variables were chosen when a P<0.10 emerged on univariate analysis. Variables in the initial model for arrhythmia recurrence included the procedural end point (randomization group), age, male sex, history of hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, amiodarone treatment, LA diameter, and left ventricular ejection fraction, time of continuous AF and baseline AFCL in left atrial appendage, right atrial appendage and CS, respectively. The 95% confidence limits of correlation coefficients were determined by Fisher r-to-z transformation. Statistical analysis was performed with a statistical software package (version 21; SPSS, IBM, Armonk, NY).

Results
Patient Characteristics
A total number of 110 patients with persistent (N=49; 45%) and long-standing persistent (N=61; 55%) AF were included. The mean age was 63±9 years, and 22 patients were female. The patients were in continuous persistent AF for 25±30 months (median, 12; range, 1–120). Fifty-five patients were randomized to a procedural end point of cardioversion after AF termination with conversion to AT (group A), and 55 patients were randomly assigned to group B where the targeted end point was achievement of SR by ablation of all subsequent ATs. The baseline characteristics of patients in both groups are demonstrated in Table 1. One third of patients were on amiodarone (N=38; 35%), 8 (7%) on flecainide or propafenone, and 2 patients...
(2%) on dronedarone. Overall, 36 (33%) patients received β-blocker for either ventricular rate control or treatment of hypertension.

### Procedural Results

In all patients, the procedure was started in spontaneous AF. The first step of ablation, PV isolation, resulted in AF termination in 8 (7%) patients (3 in group A and 5 in group B). Termination of AF occurred with a mean of 3.4±0.7 PVs isolated and with conversion directly into SR in all of these patients. The remaining 102 patients underwent electrogram-based ablation of the atrial substrate. In 11 (10%) patients, AF terminated during ablation directly into SR (7 during LA ablation and 4 during RA ablation). Sites of AF termination were located in the LA, CS, and RA in 72%, 8%, and 19%, respectively. Termination of AF was not achieved by PVI and biatrial defragmentation in 22 (20%) patients, and electric cardioversion was required to restore SR (Figure 1).

In group A patients, SR was achieved in all patients by electric cardioversion. In patients of group B, a total number of 83 AT occurred after AF termination (2.3±0.8 ATs per patient). Seventy-four (89%) ATs were successfully terminated to SR by ablation. In 2 patients, the mechanism of the first AT occurring after AF termination could not be identified, and the patients were cardioverted. In another 5 patients, the procedure was not continued after elimination of ≥2 subsequent ATs because of prolonged procedure durations, and the final AT was terminated by cardioversion. Procedural data of patients in both groups are demonstrated in Table 2.

### Clinical Outcome After Ablation

A total of 106 patients were eligible for outcome analysis. Three patients were lost to follow-up, and 1 patient died 16 months after ablation because of malignancy. All remaining patients completed a follow-up of ≥24 months after study inclusion.

#### Rhythm Outcome After First Ablation

After a mean follow-up of 20.1±13.3 months after the first ablation procedure, significantly more group B patients were in SR as compared with patients in group A (30 [57%] versus 18 [34%; \( P=0.02 \)). Moreover, recurrences of AF were significantly less frequent in group B patients than those in group A patients (10 [19%] versus 26 [49%; \( P=0.001 \)). The exact numbers of rhythm outcomes after a single procedure are demonstrated in Figures 2 and 3. The Kaplan–Meier arrhythmia-free survival estimation showed a trend toward a better outcome in group B patients as compared with patients of group A without reaching statistical significance (Figure 4A). However, freedom from AF survival estimation revealed a significantly better outcome in patients of group B than in group A patients (\( P=0.005 \); Figure 4B).

#### Rhythm Outcome After Last Ablation

The mean follow-up time for patients with multiple procedures was 34.0±6.4 months. The mean number of procedures was similar in group A and B patients (1.7±0.7 versus 1.8±0.7;...
Ultimately, significantly more group B patients were free of AF after the last procedure as compared with patients of group A (49 [92%] versus 39 [74%]; \(P = 0.01\); Figure 5). The arrhythmia-free survival estimation after the last procedure again revealed a more favorable outcome in group B patients, however failing to achieve statistical significance (Figure 6A). Nevertheless, freedom from AF was significantly higher in group B as compared with that in group A patients (\(P = 0.016\); Figure 6B).

**Predictors for Procedural Success**

Patient characteristics as presented in Table 1, and baseline AFCL were evaluated in univariate and multivariate regression analyses. Even after adjustment for higher left ventricular ejection fraction and a longer baseline AFCL in the RA, randomization to group B remained a strong predictor of arrhythmia-free survival (Table 3).

**Adverse Events**

In the study patients, no major complications occurred including cardiac tamponade, phrenic nerve injury, stroke, or atrioesophageal fistula. In 3 patients, groin hematoma occurred after the ablation procedure, 1 of them requiring blood transfusion.

**Discussion**

**Main Findings**

This prospective randomized study revealed the following data on the prognostic role of subsequent ATs occurring after AF termination: First, the elimination of subsequent ATs is associated with a significant decrease in recurrences of AF but not ATs. Second, subsequent ATs can be successfully ablated in the majority of patients with an acceptable procedural investment. Third, the strongest predictor for an arrhythmia-free survival after a single stepwise ablation procedure was the targeted procedural end point of termination to SR by ablation of subsequent ATs. Thus, these data support the hypothesis of the contributing role of subsequent ATs in the mechanisms of persistent AF.

**AT Substrates in AF**

Procedural AF termination is most commonly associated with conversion to AT with the majority of them underlying a macroreentrant mechanism. Conversion of AF to AT characteristically occurs after an arrhythmia organization, which is represented by a continuous increase of the AFCL up to a critical level \(\approx 200\) ms. The mechanisms and antiarrhythmic processes by which electrogram-guided ablation of AF results in arrhythmia organization yet are still not completely clear and are a critical matters of discussion. Recently, 2 different new computational mapping techniques have been introduced to map and ablate more specifically the arrhythmia-perpetuating atrial substrate of persistent AF. The focal impulse and rotor modulation approach is based on multispline contact mapping of rate-dependent repolarization to assess the shortest successive activation times and rate-dependent conduction slowing to identify propagation paths that are depicted in a computational color-coded map. In contrast, panoramic mapping is based on noninvasively acquired cardiac surface potentials and unipolar electrograms using a 252-electrode vest placed on the patients’ torso. Although these 2 different mapping techniques revealed divergent data in terms of spatiotemporal stability of AF sources, both studies demonstrated multiple (\(\geq 2\)) rotors or focal activity.

**Table 3. Univariate and Multivariate Regression Analyses for Predictors of Arrhythmia-Free Survival After First Ablation**

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>(P) Value</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization to group B</td>
<td>0.033</td>
<td>0.426</td>
<td>0.194–0.933</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.029</td>
<td>0.933</td>
<td>0.878–0.993</td>
</tr>
<tr>
<td>Baseline RAA AFCL</td>
<td>0.049</td>
<td>0.969</td>
<td>0.939–1.000</td>
</tr>
<tr>
<td>Randomization to group B</td>
<td>0.004</td>
<td>0.191</td>
<td>0.063–0.581</td>
</tr>
</tbody>
</table>

AFCL indicates atrial fibrillation cycle length; LVEF, left ventricular ejection fraction; and RAA, right atrial appendage.
maintaining the atria in AF.\textsuperscript{20,21} Interestingly, a hierarchical order of simultaneously existing sources seems to define the dynamics and dominance of each element in the perpetuation of AF.\textsuperscript{20} Considering that an arrhythmia organizing effect has also been described for left atrial linear ablation,\textsuperscript{2} the following mechanisms may explain the antifibrillatory effect of subsequent AT ablation: (1) the focal, rotor, or macroreentrant activity of a subsequent AT may have had an arrhythmogenic role in the persistent AF processes, and its elimination potentially decreases the number of residual AF sources. (2) Linear lesions for the treatment of macroreentrant ATs may constrain dominant or preferred wavefront propagation paths of meandering sources of AF with the potential to restrict their spatiotemporal propagation. (3) Contiguous lesions for the treatment of multiple subsequent ATs in addition to linear lesions create electric boundaries in the atria (eg, inferior LA-CS, left atrial appendage-anterior wall, interatrial septum) with the result of a substrate compartmentalization that prevents AF sources to sustain.

**Improving Outcomes of Persistent AF Ablation**

The best end point for persistent AF ablation critical to arrhythmia-free survival remains contested. Broadly, the spectrum of instruments consists of PV isolation alone,\textsuperscript{2,4} electrogram-guided ablation,\textsuperscript{2} and linear ablation.\textsuperscript{22} The stepwise ablation approach combines these techniques, importantly however, with the end point of procedural AF termination.\textsuperscript{16} The predictive value of AF termination seems to depend on the rate AF termination. Although studies with a low or moderate AF termination rate (<35%) did not show a correlation to long-term success,\textsuperscript{21,22} AF termination rates >50% revealed a significant association to a favorable outcome when the procedural end point was achieved.\textsuperscript{9,15,16,25} We think our study is the first to demonstrate a significant reduction in AF recurrence after a single procedure when the end point of ablation of all subsequent ATs to SR is sought from the outset of persistent AF ablation. With the focal impulse and rotor modulation ablation approach, AF terminated by a limited amount of RF (mean, =15 minutes) with conversion to AT in one third of the patients.\textsuperscript{21} Certainly, these more individualized and patient-tailored approaches will enhance our understanding of the mechanisms of persistent AF. However, the impact of subsequent ATs on AF recurrences after such a specified computational-guided mapping approach needs clarity. A similar result as shown in this trial will further substantiate the theory of an important contributory role of subsequent ATs in AF mechanisms.

**Limitations**

In the present study, no significant difference between both groups was observed in terms of recurrences of any atrial tachyarrhythmia after both the first and last ablation procedures. The study may have been underpowered to detect a statistically significant difference in outcomes between the 2 groups.

**Conclusions**

Subsequent ATs are the predominant arrhythmia remnants after AF termination. Further ablation aiming at elimination of all subsequent ATs significantly reduces recurrences of AF but not AT. Thus, the results of this study corroborate the hypothesis that subsequent ATs have the potential to contribute to the multifaceted mechanisms of persistent AF.

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**Disclosures**

None.

**References**


Procedural atrial fibrillation (AF) termination is predominantly associated with the occurrence of regularized atrial tachycardias (AT) requiring further mapping and ablation to achieve conversion into sinus rhythm. However, the prognostic role of subsequent ATs occurring after AF termination for the long-term outcome remains undetermined. In this prospective randomized trial, we compared the single procedure and overall outcome of patients undergoing ablation of subsequent ATs versus those who did receive electric cardioversion once AF has terminated into regularized AT. After the first procedure, significantly more patients with ablation of subsequent ATs were in sinus rhythm as compared with those without. Moreover, both after the first and the last ablation procedures, the proportion of patients free of AF recurrences was significantly greater in the group of patients who underwent ablation of subsequent ATs. Recurrences of ATs were equally prevalent in both groups. The strongest predictor for a successful single-procedure outcome was the ablation of subsequent ATs. The data of the present study demonstrate that ablation of subsequent regularized ATs increases freedom from AF. Thus, termination to sinus rhythm by elimination of subsequent ATs should be considered a prognostic importantly and therefore integral part of persistent AF ablation. Ablation of subsequent ATs decreased recurrence rates of AF but not AT. Therefore, these data further corroborate a potentially contributing role of subsequent ATs in the mechanisms perpetuating persistent AF.
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