Recurrence of paroxysmal atrial fibrillation after pulmonary vein isolation: is repeat pulmonary vein isolation enough? A prospective, randomized trial

Stephanie Fichtner1,*, Korbinian Sparn2, Tilko Reents2, Sonia Ammar2, Verena Semmler2, Roger Dillier2, Alexandra Buiatti2, Susanne Kathan2, Gabriele Hessling2, and Isabel Deisenhofer2

1Medizinische Klinik I, Klinikum der Universität München, Marchioninistr. 15, Munich 81377, Germany; and 2Deutsches Herzzentrum München, Lazarettstr. 36, Munich 80636, Germany

Received 20 October 2014; accepted after revision 10 December 2014; online publish-ahead-of-print 18 February 2015

Aims
In patients with paroxysmal atrial fibrillation (pAF), pulmonary vein isolation (PVI) has become an accepted treatment option with single procedure success rates of 60–80%. A repeat ablation is performed in ~30% of patients because of arrhythmia recurrence. The strategy for this repeat procedure is not defined.

Methods and results
Patients with pAF recurrence after PVI were prospectively randomized and underwent a second ablation procedure with either PVI of all reconnected veins or PVI with an additional left atrial anterior line. Follow-up in our arrhythmia clinic was every 3 months up to 12 months including 7 day Holter monitoring. A total of 77 patients (mean age 63 ± 9 years, 69% males) were included in the analysis. A repeat PVI was performed in 41 patients, PVI + anterior line in 36 patients. After a follow-up of 12 months, 26 of 41 (63%) patients after repeat PVI and 18 of 36 (50%) patients with PVI + anterior line were in stable sinus rhythm off antiarrhythmic medication (P = 0.26). In most patients (12 of 15 patients with PVI and 14 of 18 patients with PVI + anterior line) with an arrhythmia recurrence after the second procedure, the recurring arrhythmia was paroxysmal AF. In 2 of 15 patients of the PVI group and in 4 of 18 patients of the PVI + anterior line group atypical flutter was the reoccurring arrhythmia (P = NS).

Conclusion
In this prospective randomized trial, patients with a recurrence of paroxysmal AF had no better outcome after repeat PVI + one left atrial line compared with patients with repeat PVI only.

Keywords
Atrial fibrillation • Relapse • Pulmonary vein isolation • Anterior line • PVI

Introduction
Pulmonary vein isolation (PVI) has become a widely used and accepted treatment option in patients with paroxysmal atrial fibrillation (AF) with single procedure success rates of 60–80%.1–3 Although treatment expertise and technical equipment improve, about 30% of patients undergo a repeat ablation procedure because of arrhythmia recurrence.2,4

Pulmonary vein (PV) reconnection (detected in the majority of PVs during the repeat ablation) is suggested to be the main cause of arrhythmia recurrence.4–9 Another hypothesis is a progression of the atrial substrate and/or a higher percentage of extra PV foci in patients with AF recurrence. From experience with the surgical maze procedure, the addition of linear lesions to PVI has been suggested to modify the substrate for AF and improve clinical outcomes.9–10 Therefore, the question arises whether patients would profit from a more extensive ablation approach during the repeat procedure.

As up to now no prospective randomized trial has dealt with the optimal treatment strategy for the repeat ablation procedure in patients with recurrent paroxysmal AF after PVI, we compared a repeat PVI with a PVI and a left atrial line (AL).

Methods
Patients
This single-centre prospective randomized trial was performed at the German Heart Center in Munich, Germany, and was accepted by the
local ethic committee (clinical trial.gov identifier: NCT01229306). Patients were eligible if they had a documented relapse of paroxysmal AF and had previously undergone PVI for paroxysmal AF. Patients with persistent AF or atrial tachycardia were excluded. All patients were randomized using randomization envelopes either to the repeat PVI group or to the group with repeat PVI plus an additional left AL. Patients were recruited from July 2010 until October 2012.

Primary endpoint: Freedom from atrial arrhythmias after 12 months off antiarrhythmic medication
Secondary endpoint: reconnected PVs, type of arrhythmia recurrence after repeat procedure, adverse events.

Procedure
Patients were kept on continuous oral anticoagulation with intra-procedural INR levels of 2.0–2.7 or continued taking Dabigatran. Ablation procedures were performed under conscious sedation using a three-dimensional mapping system for anatomy and catheter visualization (Carto 3, Biosense-Webster or Ensite Navx, St. Jude Medical). The individual left atrial anatomy as segmented from the previous computed tomographic scan was displayed during the procedure and fused with the reconstructed anatomy in the three-dimensional mapping system if felt appropriate. An 8 polar catheter was placed in the coronary sinus (CS; XPT, C.R. Bard) and the left atrium (LA) was accessed by single or double transseptal puncture or via an open foramen ovale. Preablation and postablation angiograms of all PVs were performed. After placement of electrode catheters within the LA, heparin was given to maintain an activated clotting time at ≥270 s.

Reisolation of all reconnected pulmonary veins
Pulmonary vein isolation was performed using a circular steerable mapping catheter (Lasso™, Biosense-Webster or Orbiter PV™, C.R. Bard) and an irrigated tip ablation catheter (Celsius Thermocool™, Biosense Webster, or Therapy Cool Path™, St. Jude). If PVs showed reconnection, a complete circumferential approach isolating all reconnected PVs was used (see Figure 1), even if only a single gap was seen. The circular mapping catheter was positioned as close to the pulmonary vein ostium as possible. Circular mapping was performed by obtaining 10 bipolar electrograms (1 to 2, 2 to 3, up to 10 to 1 electrode pairs) from the circularly arranged electrodes. Pulmonary vein isolation was performed by applying radiofrequency (RF) current at the antral sites. At the end of the procedure, entry and exit block of all PVs was documented.

Reisolation of all reconnected pulmonary veins plus additional anterior line
Initially all reconnected PVs were circumferentially re-isolated. In addition, a left AL from the anterior mitral annulus to the left superior pulmonary vein was drawn as described earlier (see Figure 1). This was performed under continuous pacing from the left atrial appendage. Bidirectional block was tested using differential pacing criteria and the line was tested for double potentials (for further information see ref11).

Follow-up after ablation
Patients were scheduled for visits at the arrhythmia clinic 3, 6, and 12 months after the procedure. At each visit, intensive questioning for arrhythmia-related symptoms was done and in all patients 7 day Holter electrocardiogram was performed at each visit. A blanking period of 6 weeks was used and any documented atrial arrhythmia occurring after the blanking period and lasting >30 s were counted as arrhythmia recurrence. If no AF recurrence was detected within the first 6 months and the CHA2DS2 Vasc score was ≤2, oral anticoagulation was discontinued. No antiarrhythmic medication besides beta blockers was prescribed after the ablation procedure.

Statistical analysis
All values are presented as mean ± SD. Student’s t-test, Fisher’s exact test, Wilcoxon’s test, and χ2 test were applied for comparisons. A probability value of P < 0.05 was considered statistically significant.

Results
Patient characteristics
A total of 77 patients with relapse of paroxysmal atrial fibrillation were included in the study; 41 patients in the PVI group, 36 in the
PVI + AL group. Baseline characteristics in both groups were comparable (see Table 1). Patients’ age was 64 ± 9 years (PVI group) and 62 ± 8 years (PVI + AL group). Paroxysmal AF was present since 74.5 ± 76 (PVI) and 97.3 ± 80 (PVI + AL) months, respectively. The initial PVI procedure had taken place 21.5 ± 27.6 (PVI) and 17.3 ± 24.7 (PVI + AL) months before the repeat procedure. The cardiovascular risk factors were equally distributed in both groups (see Table 1).

**Procedural results**

In all patients repeat PVI was performed successfully and 100% of reconnected PVs were isolated. In all patients of the PVI + AL group, the AL was successfully applied and bidirectional block confirmed. Reconnected atrio-PV conduction was present in 3.7 ± 0.9 of PVs in the PVI group and 3.3 ± 0.9 in the PVI + AL group (P = 0.02). Procedure time was comparable with 106.6 min in the PVI group and 117.9 min in the PVI + AL group (P = 0.3). Radiofrequency time was significantly higher in the PVI + AL group compared with the PVI group (44.7 ± 19 vs. 33.5 ± 18, P = 0.01). Fluoroscopic time and dose showed no significant differences (fluoroscopic time 21.8 ± 14 (PVI) vs. 16.9 ± 13.5 (PVI + AL) and fluoroscopic dose 1818 ± 1219 (PVI) vs. 1557 ± 1203 (PVI + AL)) (Table 2).

No serious adverse events were observed. A groin pseudoaneurysm in the PVI group was managed without surgical intervention.

**Primary endpoint outcome**

After 12 months follow-up, stable sinus rhythm off antiarrhythmic medication was present in 63% of patients in the PVI group and 50% of patients in the PVI + AL group (P = 0.26) (Figure 2).

Patients with arrhythmia recurrence after the repeat ablation procedure had paroxysmal AF in most cases in both groups (75% vs. 78%). Atypical atrial flutter occurred in four patients in the PVI + AL group and in two patients in the PVI group (see Table 3). In two of the four patients with atypical flutter of the PVI + AL group perimtral flutter was the reason and could be terminated by closing the gap in the ablation line.

### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>PVI (n = 41)</th>
<th>PVI + anterior line (n = 36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64 ± 9</td>
<td>62 ± 8</td>
<td>0.33</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>68%</td>
<td>69%</td>
<td>1.0</td>
</tr>
<tr>
<td>Duration of atrial fibrillation (months)</td>
<td>74.5 ± 76</td>
<td>97.3 ± 80</td>
<td>0.25</td>
</tr>
<tr>
<td>Time since initial PVI (months)</td>
<td>21.5 ± 27.6</td>
<td>17.3 ± 24.7</td>
<td>0.5</td>
</tr>
<tr>
<td>CHADS² VASc score</td>
<td>2.3 ± 1.7</td>
<td>2.1 ± 1.8</td>
<td>0.62</td>
</tr>
<tr>
<td>Art. hypertension</td>
<td>71%</td>
<td>61%</td>
<td>0.47</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>39%</td>
<td>61%</td>
<td>0.07</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>14.6%</td>
<td>8.3%</td>
<td>0.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12%</td>
<td>8.3%</td>
<td>0.7</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>7.3%</td>
<td>16.7%</td>
<td>0.3</td>
</tr>
<tr>
<td>Size of left atrium</td>
<td>44 ± 6.2</td>
<td>43.7 ± 5</td>
<td>0.85</td>
</tr>
</tbody>
</table>

### Table 2 Procedural data

<table>
<thead>
<tr>
<th></th>
<th>PVI</th>
<th>PVI + anterior line</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconnected PV per patient</td>
<td>3.7 ± 0.9</td>
<td>3.3 ± 0.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>106.6 ± 42</td>
<td>117.9 ± 52</td>
<td>0.3</td>
</tr>
<tr>
<td>RF time (min)</td>
<td>33.5 ± 18</td>
<td>44.7 ± 19</td>
<td>0.01</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>21.8 ± 14</td>
<td>16.9 ± 13.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Fluoroscopy dose (cGy)</td>
<td>1818 ± 1219</td>
<td>1557 ± 1203</td>
<td>0.35</td>
</tr>
<tr>
<td>Tamponade</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Procedural stroke</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Groin pseudoaneurysm</td>
<td>1</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### Table 3 Type of arrhythmia recurrence after repeat procedure

<table>
<thead>
<tr>
<th></th>
<th>PVI (N = 16)</th>
<th>PVI + anterior line (N = 18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal AF</td>
<td>75%</td>
<td>78%</td>
<td>0.4</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>12.5%</td>
<td>0%</td>
<td>0.0</td>
</tr>
<tr>
<td>Atypical flutter</td>
<td>12.5%</td>
<td>22%</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**Figure 2** After a follow-up of 12 months 63% in the PVI only group and 50% in the PVI + anterior line group were in stable sinus rhythm off antiarrhythmic medication.
Discussion

Main findings
In this prospective randomized trial, patients with recurrent paroxysmal AF after PVI did not profit from a more extensive reablation approach including PVI and a left anterior line compared with patients who underwent repeat PVI only.

Pulmonary vein isolation and substrate modification in patients with paroxysmal atrial fibrillation
There are reports that in patients with paroxysmal AF, a substrate modification ablating complex atrial fractionated electrograms (CFAEs) showed no additional benefit to PVI only. However, in patients with persistent AF, adding CFAE ablation to PVI improved the success rates significantly. Additional isolation of the vena cava superior and the coronary sinus in patients with paroxysmal AF and PVI did also not show a significant improvement compared with PVI alone. In another study, patients with paroxysmal AF were randomized to PVI alone or PVI plus roof line and mitral isthmus line during the initial ablation. No significant difference was found after 16 months of follow-up with regard to sinus rhythm after antarrhythmic medication. However, patients in the PVI plus line group showed significantly more often left atrial atypical flutter as reoccurring arrhythmia. Another study could also show no additional benefit in patients with initially PVI plus lines. However, patients treated with lines according to the maze procedure had an improved outcome compared with patients with single PVI regardless of the type of AF.

To our knowledge, no study investigated patients with paroxysmal AF relapse after PVI adding substrate modification to the repeat PVI. It is well known that about 30% of patients after PVI need a repeat procedure because of arrhythmia recurrence. From these studies, the assumption arises that atrio-PV reconnection is the main cause of arrhythmia recurrence. However, in patients with persistent AF, PVI alone leads to worse success compared with PVI plus substrate modification. It might be speculated that at least a part of patients with paroxysmal AF relapse after PVI already have a more advanced level of atrial disease and might benefit from substrate modification and as could be shown in multiple maze studies lines do alter the substrate. This could not be demonstrated in our study. The rate of reconnected PVs was high in both groups and the additional AL from the mitral annulus to the left superior pulmonary vein did not improve outcome which emphasizes the role of reconnected PVs as the leading cause of arrhythmia recurrence.

Success after repeat ablation procedure
To our knowledge, there is only one prospective clinical trial that only included patients with arrhythmia recurrence after PVI using cryoballon. In this trial, patients with arrhythmia relapse were randomized to repeat PVI using cryoballon vs. repeat PVI using RF. In the group using RF for repeat PVI a higher rate of freedom from AF was observed (58% vs. 43%, P = 0.06). In our study, stable sinus rhythm after 12 months off antarrhythmic medication was reached in 63% vs. 50% of patients leading to the assumption that patients who need a repeat procedure are more difficult to treat.

Type of arrhythmia recurrence after the repeat ablation
Patients who had arrhythmia relapse after the repeat ablation procedure presented with paroxysmal AF in the majority of cases; only a minority of patients developed atypical atrial flutter in both groups. In the study by Sawhney et al., significant more atypical flutter was detected in patients with an additional AL; however, in this study two AL s (mitral isthmus line and roof line) were done that might lead to a higher risk of gaps in the lines.

Limitations
This is a single-centre study only with a limited number of patients; therefore significant differences might have been missed.

Conclusion
In this prospective randomized trial, patients with recurrent paroxysmal AF after PVI had no better outcome (sinus rhythm off antarrhythmic medication) after a repeat PVI + one left AL compared with patients who underwent a repeat PVI only.

Conflict of interest: none declared.

Funding
No external funding was received, only through the German heart center.

References


