Autonomic and surgical substrate modulation of atrial fibrillation
Krul, Sébastien

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Chapter 8

Epicardial and endocardial electrophysiological guided thoracoscopic surgery for atrial fibrillation: A multidisciplinary approach of atrial fibrillation ablation in challenging patients

SPJ Krul, L Pison, MIM La Meir, AHG Driessen, AAM Wilde, JG Maessen, BAJM de Mol, HJ Crijns and JR de Groot

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ABSTRACT

Introduction
Patients with atrial fibrillation (AF) with enlarged atria or previous pulmonary vein isolation (PVI) are challenging patients for catheter ablation. Thoracoscopic surgery is an effective treatment for these patients but comes at the cost of an increase in adverse events. Recently, electrophysiological (EP) guided approaches to thoracoscopic surgery have been described which consist of EP guidance by measurement of conduction block across ablation lines. In this study we describe the efficacy and safety of EP-guided thoracoscopic surgery for AF in patients with enlarged atria and/or prior failed catheter ablation.

Methods and Results
A total of 72 patients were included. Two different approaches to EP-guided thoracoscopic surgery were implemented: epicardial or endocardial EP-guidance at the time of surgery. Residual intraoperative conduction requiring additional ablation was detected with epicardial or endocardial mapping techniques in 50% and 11%, respectively. Additional epicardial or endocardial ablation was performed until bidirectional block was confirmed. Follow-up consisted of an ECG and a 24 h Holter at 3, 6 and 12 months after the procedure. A total of 57 patients (79%) had freedom of AF and were off antiarrhythmic drugs at one year follow-up (30 paroxysmal (83%), 27 persistent AF (75%)). Adverse events occurred in 13 patients (6 major). None of our patients died and all events were reversible.

Conclusions
EP-guidance of thoracoscopic surgery can be safely performed both epicardially and endocardially and is associated with a high rate of long-term maintenance of sinus rhythm in patients with enlarged atria and/or a previously failed ablation.
INTRODUCTION

Atrial fibrillation (AF) is a growing problem in Western society and associated with a substantial healthcare expenditure. Treatment of AF is difficult in patients who remain symptomatic despite antiarrhythmic therapy, among others hampered by side effects of antiarrhythmic drugs (AAD) and an incomplete pathophysiological understanding of the disease.

Catheter-based pulmonary vein antrum isolation (PVAI) is most effective in patients with paroxysmal AF and normally sized left atria. In patients with more advanced disease multiple catheter ablation procedures or extensive ablation within the left atrium and of other triggers of AF may be needed to achieve an acceptable success rate. Thoracoscopic pulmonary vein isolation (PVI) is an effective treatment for AF, but is more invasive than catheter ablation, and has a success rate of 69% in an unselected population. Recently, a randomized multicenter study comparing catheter ablation and thoracoscopic surgery, showed superiority of the surgical approach (65.6% vs. 36.5% arrhythmia freedom at one year) in challenging patients with remodeled atria or prior failed ablation at the cost of an increase in adverse events. Electrophysiologists with experience in AF ablation can assess bidirectional conduction block across ablation lines with EP techniques (epicardially or endocardially). The collaboration between surgeon and EP in assessment of acute conduction block in one session possibly increases the single-procedure success rate of thoracoscopic surgery, without increasing of the adverse events. In this study we investigate the single procedure efficacy and safety of EP-guidance, using two different groups with either an epicardial or endocardial guidance of thoracoscopic surgery for AF in selected patients with remodeled atria or prior failed catheter ablation. This analysis was designed as an exploration of the value of EP-guidance during two different EP-guided thoracoscopic surgery approaches in challenging patients. In both approaches, an electrophysiologist contributes actively in the surgical procedure.

METHODS

Patient population

Two centers participated in this study, the Academic Medical Center (AMC) in Amsterdam and the Maastricht University Medical Center (MUMC), Maastricht. Data were prospectively collected from consecutive patients with one year follow-up who underwent EP-guided thoracoscopic surgery for AF, all these patients had an indication for surgical ablation of
AF according to the latest guidelines. Inclusion of patients in this analysis was based on pre-procedural predictors of recurrence that identified patients that were considered less amenable to PVI and an earlier randomized study to warrant a historical comparison. Inclusion criteria were: 1) a left atrial diameter of 40–44 mm and hypertension 2) left atrial diameter of ≥45 mm or 3) previous failed PVI. Patients with incomplete follow-up, defined as absence of 6 or 12 months outpatient follow-up, or without an adequate pre-procedural echocardiogram to assess left atrial diameter were excluded. Definitions, clinical follow-up, classification of outcome and reporting of the results are according to the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society (HRS/EHRA/ECAS) consensus statement on catheter and surgical ablation.

**Thoracoscopic surgery**

Thoracoscopic surgery was employed in both centers, the different surgical procedures and mapping protocols have been described earlier in detail. Surgery was performed under general anesthesia on the beating heart. Ganglionic plexus (GP) were located anatomically and functional testing was performed with high frequency stimulation. GPs were subsequently ablated in the majority of patients until no vagal response could be elicited. Bilateral thoracoscopic PVI was performed with a radiofrequency bipolar clamp (AtriCure Isolator Transpolar Clamp, AtriCure Inc.). In patients with persistent AF or with induction of AF after the thoracoscopic PVI, additional left atrial lesions were created with a radiofrequency pen (AtriCure Isolator Bipolar Linear Pen and AtriCure Coolrail). In the epicardial EP-guided approach PV entry and exit block was tested completely epicardially with custom-made electrodes and a diagnostic decapolar EP catheter (Radia XT, Bard) as described in De Groot et al. If no entry or exit block could be confirmed additional ablation with the bipolar clamp was applied until isolation was achieved. Additional ablation lines were tested epicardially and additional touch-up ablations were delivered epicardially with radiofrequency ablation pen (AtriCure Isolator Bipolar Linear Pen) until bidirectional block was achieved. All measurements were performed and
analyzed by an electrophysiologist using a dedicated EP-workstation (Bard Labsystem PRO 2.4A, Bard).\textsuperscript{16} For the endocardially EP-guided approach patients were heparinized after the thoracoscopic lesion set was applied and a His bundle and a coronary sinus catheter were introduced through a femoral venous approach. After transseptal puncture, PVs were mapped and isolation was assessed endocardially with a circular mapping catheter (Lasso, Biosense Webster). If PVs were not isolated, endocardial touch-up ablations were delivered with a 3.5-mm-tip catheter (ThermoCool, Biosense Webster). The epicardial lesions were subsequently tested endocardially for conduction block, with endocardial completion of the mitral isthmus line and touch-up of the epicardial lesion set in the absence of bidirectional conduction block. In patients with a history of typical cavotricuspid dependent atrial flutter an additional right atrial isthmus line was created endocardially. No ablation of complex fractionated atrial electrograms was performed.

**Follow-up**

After the procedure, patients were reinstated on their pre-procedural medication, including AAD. The first three months after the procedure were blanked for the determination of absence of AF. Patients were followed at the outpatient clinic with ECGs and a 24h Holter at 3, 6 and 12 months after the procedure according to the HRS/EHRA/ECAS expert consensus statement.\textsuperscript{5} AADs were discontinued starting from the first outpatient visit, 3 months after the procedure.

**Efficacy**

The primary endpoint was freedom of AF, atrial flutter or atrial tachycardia lasting longer than 30s on any ECG or Holter monitor after the blanking period without the use of AAD after 12 months.\textsuperscript{5} A secondary outcome was defined as freedom from AF, atrial flutter or atrial tachycardia with/without the use of AAD after 12 months.\textsuperscript{5}

**Safety**

All adverse events during the peri-procedural period (within 30 days after the procedure) were monitored. Major adverse events were adverse events resulting in permanent injury or death, requiring intervention for treatment or extending hospital admission for more than 48h.\textsuperscript{5} All non-major adverse events were classified as other adverse events.

**Statistical analysis**

Data are presented as mean± standard deviation for normally distributed continuous variables or median and range for non-normal distribution. Categorical variables are presented in numbers with percentages. Differences were determined with an independent Student T-test for normally distributed data or a Mann–Whitney U test for not-normally distributed data. A Chi-square Test or Fisher’s Exact Test was used for categorical vari-
ables. A univariate analysis was performed using binary logistic regression for failure of treatment at one year follow-up. Postoperative AF-free curves were calculated using the Kaplan–Meier method and compared with the log-rank test. Statistical analyses were carried out using SPSS, version 19.0. A p-value of <0.05 was considered significant.

RESULTS

Patient characteristics

Hundred-and-two patients underwent EP-guided surgery for AF (Amsterdam n=50, Maastricht n=52) between 2008 and 2011. Seventy-seven met the inclusion criteria for this analysis and had a previous failed catheter ablation, an enlarged left atrium of ≥45 mm or hypertension and an enlarged left atrium 40–44 mm. Five patients were excluded due to insufficient follow up data (n=3) or pre-procedural echocardiogram (n=2) that precluded quantification of the left atrial diameter. In the remaining 72 patients, 31 (43%) had a previous catheter ablation, 48 (67%) had a left atrial diameter of ≥45 mm and 9 (13%) had a left atrial size of 40–44 mm with hypertension. Mean age was 59±8.7 years (range 38–78) and 57 patients were male (79%). Thirty-six patients had paroxysmal AF (50%), 32 persistent AF (44%) and 4 longstanding persistent AF (6%). Eighteen patients (25%) had one previous PVAI, 13 (18%) had two or more previous PVAI. These procedures consisted either of a PVAI (n=20) or PVAI with additional left atrial lesions (n=11). The results of patients with persistent and longstanding persistent AF are combined and reported as persistent AF. Patient characteristics are shown in Table 1.

Electrophysiological guided procedure

A total of 36 procedures with an epicardial EP-guided approach (Amsterdam) and 36 with an endocardial EP-guided approach (Maastricht) were performed. In all but one procedure (with complete PV isolation after previous catheter ablation) PVI was performed. Of the 22 patients with quantitative information available on the number of ablation in the epicardial EP-guided approach 11 (50%) patients achieved PV isolation after 3–14 initial ablations (median 6.5). Additional epicardial ablation was performed, guided by the epicardial EP measurements, until bidirectional block was attained. Four patients (11%) in the endocardial EP-guided approach needed endocardial touch-up after a total of 6 epicardial ablations. In 48 patients (67%) additional atrial lesions were created; left atrial lesions in all, and additional right atrial lesions in 13 (18%). In the epicardial EP-guided approach epicardial EP measurements revealed residual conduction across at least one additional ablation line in all patients, and further epicardial ablation was performed until bidirectional block was attained. In the endocardial EP-guided approach the left atrial lines needed additional endocardial touch-up in 2 (7%) patients. GP abla-
tion was performed in the majority of patients (n=44, 61%). LAA removal was performed in 45 patients (63%). Mean procedure time was 218±79 min and average admission duration was 6.5±3 days. Procedure characteristics are shown in Table 2.

**Efficacy**

After one year and after discontinuation of AAD 57 patients (79%) had sinus rhythm and no recurrences of AF, atrial flutter or atrial tachycardia, of whom 30 patients with paroxysmal AF (83%) and 27 with persistent AF (75%). Of note, most patients with recurrences, (AF n=6, AF and AT n=3, AT n=2, AFT n=1) presented themselves with complaints of palpitations at a physician (10/12). The majority were managed with anti-arrhythmic drugs as these patients had far less symptoms than before the procedure. A redo catheter

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**Table 1. – Patient characteristics**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All</th>
<th>Epicardial EP-guided</th>
<th>Endocardial EP-guided</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>72 (100)</td>
<td>36 (50)</td>
<td>36 (50)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>59±8.7 (38-78)</td>
<td>59±8.2 (43-77)</td>
<td>60±9.2 (38-78)</td>
<td>0.86</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>57 (79)</td>
<td>30 (83)</td>
<td>27 (75)</td>
<td>0.38</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28±3.7 (21-37)</td>
<td>29±4.3 (22-37)</td>
<td>27±3.0 (21-36)</td>
<td>0.12</td>
</tr>
<tr>
<td>CHA2DS2VASc-score,</td>
<td>1 (0-7)</td>
<td>1 (0-6)</td>
<td>1 (0-7)</td>
<td>0.63</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>3 (4)</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>30 (42)</td>
<td>14 (39)</td>
<td>16 (44)</td>
<td>0.63</td>
</tr>
<tr>
<td>Age ≥ 75, n (%)</td>
<td>3 (4)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1 (1)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Stroke/TIA/Embolus, n (%)</td>
<td>6 (8)</td>
<td>5 (14)</td>
<td>1 (3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Vascular disease, n (%)</td>
<td>7 (9)</td>
<td>2 (6)</td>
<td>5 (14)</td>
<td>0.43</td>
</tr>
<tr>
<td>Age ≥ 65, n (%)</td>
<td>15 (21)</td>
<td>10 (28)</td>
<td>12 (33)</td>
<td>0.61</td>
</tr>
<tr>
<td>History of atrial flutter, n (%)</td>
<td>13 (18)</td>
<td>1 (3)</td>
<td>12 (33)</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous atrial flutter ablation, n (%)</td>
<td>8 (11)</td>
<td>1 (3)</td>
<td>7 (19)</td>
<td>0.55</td>
</tr>
<tr>
<td>Type AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal, n (%)</td>
<td>36 (50)</td>
<td>17 (47)</td>
<td>19 (53)</td>
<td>0.64</td>
</tr>
<tr>
<td>Persistent, n (%)</td>
<td>36 (50)</td>
<td>19 (53)</td>
<td>17 (47)</td>
<td>0.64</td>
</tr>
<tr>
<td>Total duration of AF, median, range (years)</td>
<td>5.5 (1-22)</td>
<td>6 (2-22)</td>
<td>4.5 (1-13)</td>
<td>0.09</td>
</tr>
<tr>
<td>Previous catheter PVI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16 (22)</td>
<td>9 (25)</td>
<td>9 (25)</td>
<td>1.00</td>
</tr>
<tr>
<td>2≥</td>
<td>13 (18)</td>
<td>7 (19)</td>
<td>6 (17)</td>
<td>1.00</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial size*, (mm)</td>
<td>47±6.2 (32-61)</td>
<td>50±6.4 (40-61)</td>
<td>44±4.8 (32-53)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation, EP: electrophysiological, PVI: pulmonary vein isolation, TIA: transient ischemic attack

*aLeft atrial diameter measured on the parasternal long axis


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Ablation was performed in 3 patients. Two patients showed intact ablation lines endocardiably and only an additional mitral isthmus line was created. One of these patients achieved no sinus rhythm after the ablation and has subsequently been treated with rate control. The third patient had a redo-isolation of a common ostium and additional touch-up of the roof line, this patient has had no recurrences after this redo-procedure. Three patients still used AAD due to patient preference. Absence of AF at one year including these three patients was present in 60 patients (83%) in the entire cohort; in 32 (89%) and 28 (78%) patients with paroxysmal and persistent AF respectively. An overview of the outcome endpoints is shown in Table 3.

Three factors were associated with failure in univariate analysis. These were female sex (odds ratio 3.6, CI 1.014–12.467, p=0.048), presence of vascular disease (odds ratio 6.5, CI 1.281–33.451, p=0.024) and duration of AF (odds ratios 1.168, CI 1.018–1.339, p=0.022).

**Safety**

No patient died during the procedure or during follow-up. There were 6 major adverse events. Two patients received a sternotomy to control bleeding, which could not be managed thoracoscopically. The hemothorax that occurred in two other patients, re-
resulted from an intercostal artery bleeding. Careful retraction of the working port and final inspection before closure has prevented this event from occurring in all subsequent patients. One patient received a pacemaker due to a bradycardia induced torsade de pointes. One patient developed a pericardial effusion three weeks after the procedure, after drainage the patient restored without any further complications. No phrenic nerve palsies developed as the thoracoscopic approach allows very clear visualization of the phrenic nerve and the pericardium was opened N1 cm away from the nerve. There were no irreversible injuries and all bleeding complications that occurred were surgical related and did not occur during the EP measurements. An overview of the adverse events is listed in Table 4.

Table 3. Outcome

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>All</th>
<th>Epicardial EP-guided</th>
<th>Endocardial EP-guided</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRS/ESC/EHRA success, n(%)</td>
<td>57 (79)</td>
<td>27 (75)</td>
<td>30 (83)</td>
</tr>
<tr>
<td>Paroxysmal AF, n(%)</td>
<td>30 (83)</td>
<td>15 (88)</td>
<td>15 (79)</td>
</tr>
<tr>
<td>Persistent AF, n(%)</td>
<td>27 (75)</td>
<td>12 (63)</td>
<td>15 (88)</td>
</tr>
<tr>
<td>HRS/ESC/EHRA with AAD success, n(%)</td>
<td>60 (83)</td>
<td>28 (78)</td>
<td>32 (89)</td>
</tr>
<tr>
<td>Paroxysmal AF, n (%)</td>
<td>32 (89)</td>
<td>16 (94)</td>
<td>16 (84)</td>
</tr>
<tr>
<td>Persistent AF, n(%)</td>
<td>28 (78)</td>
<td>12 (63)</td>
<td>16 (94)</td>
</tr>
</tbody>
</table>

AAD: anti-arrhythmic drugs, EP: electrophysiological, AF: atrial fibrillation

Table 4. Peri-procedural complications

<table>
<thead>
<tr>
<th>Mortality and mortality</th>
<th>All</th>
<th>Epicardial EP-guided</th>
<th>Endocardial EP-guided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>All adverse events, n (%)</td>
<td>13 (18.1)</td>
<td>8 (22.2)</td>
<td>5 (13.9)</td>
</tr>
<tr>
<td>Major adverse events, n (%)</td>
<td>6 (8.3)</td>
<td>5 (13.9)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Conversion of surgery, n (%)</td>
<td>2 (2.8)</td>
<td>1 (2.8)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Pacemaker implantation, n (%)</td>
<td>1 (1.4)</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hemothorax requiring surgical intervention, n(%)</td>
<td>2 (2.8)</td>
<td>2 (5.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pericardial effusion, n (%)</td>
<td>1 (1.4)</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other adverse events, n (%)</td>
<td>7 (9.7)</td>
<td>3 (8.3)</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>Pneumonia, n (%)</td>
<td>3 (4.2)</td>
<td>2 (5.6)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Pneumothorax, n (%)</td>
<td>2 (2.8)</td>
<td>1 (2.8)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Wound problems, n (%)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>1 (2.8)</td>
</tr>
</tbody>
</table>

EP: electrophysiological
Patient population of epicardial and endocardial electrophysiological guided procedure

The patient population in both centers is similar, due to the inclusion criteria for this analysis (Table 1). Significant differences between the centers were a higher number of patients with a history of flutter in the endocardial EP-guided group (p=0.01) and larger atrial dimensions in the epicardial EP-guided group (p<0.001). Not significant, but noticeable differences include more patients with a history of stroke, TIA and/or a systemic embolus (p=0.20), a higher BMI (p=0.12), and longer duration of AF (p=0.09) in the epicardial EP-guided group. Procedure characteristics were significantly different due to the differences in the approach of the EP measurements and additional ablations (GP ablation, type of additional ablation lines, LAA removal), but did not correlate with success. Notably, procedure duration and admission duration were similar (p=0.98 and p=0.07 respectively). Between the different procedures, there were no significant dif-

Figure 1. – Freedom of AF in subgroups. Kaplan–Meier curve representing the percentage estimates of patients with freedom of AF up to one year after surgery. Panel A: freedom of AF curves for two participating centers (log-rank test p=0.45). Panel B: freedom of AF curves according to different types of AF (log-rank test p=0.70). Panel C: freedom of AF curves in left atrial diameter more or less than 45 mm (log-rank test p=0.79). Panel D: freedom of AF curves stratified according to a history of previous catheter ablation (log-rank test p=0.69).

REFERENCES in outcome, neither overall nor for subgroups (Figure 1). Finally, no significant differences were found in adverse events.

DISCUSSION

The management of AF in patients with enlarged atria or previous failed catheter ablation presents a challenge. In this study two different EP-guided surgical approaches were performed in a group consisting of challenging patients with AF. A total of 79% of patients undergoing one single EP-guided thoracoscopic procedure for AF remained free of AF during one year without the use of AAD.

**Electrophysiological guidance during thoracoscopic surgery**

Recently, a randomized multicenter study comparing catheter ablation with non-EP guided thoracoscopic surgery in a group of challenging patients reported a success rate of 36.5% versus 65.6% respectively after one year follow-up without AAD, but at the cost of more procedural adverse events: 23.0% vs. 3.2%. The patients described in our study, selected on similar inclusion criteria, are therefore not ideal candidates for catheter ablation. Half of the patients (43%) had an earlier failed ablation and 67% of the patients had a severely enlarged LA with or without hypertension, pre-procedural predictors of recurrence. In these selected patients EP-guided thoracoscopic surgery results in an increased efficacy of 79%, when compared to the published results of standalone thoracoscopic surgery in similar patient cohorts. There appears to be an addition of EP-guidance in the two different procedures, irrespective of the differences in the two approaches. These similar outcomes might be the result of the underlying philosophy of EP guidance; the enhanced resolution and ability to confirm conduction block and to detect gaps in ablation lines during thoracoscopic surgery. Our data show that in 11–50% of the procedures the PVs were not fully isolated after the initial surgical ablation attempt and that depending on the additional atrial lesion set used, all ablation lines required additional epicardial or endocardial touch-up. The difference in the integrity of PV isolation between the approaches could be partially attributed to differences in the number of applications at the initial attempt. In the epicardial EP-guided approach the duration of clamping was based on an impedance measurement during ablation, reflecting “transmurality” of the lesion. The duration of applications was about 15s in the endocardial EP-guided approach. The technical complexity in creating the trigone line could explain the frequency of incomplete block found after the first ablation attempt. Further study of these procedures is required in different populations and in prospective randomized trails against standalone surgery and catheter ablation to clarify the role and additive effect of EP-guidance in the (surgical) treatment of AF.
Patient and procedural characteristics

Both procedures had similar cornerstones with a patient tailored approach; PVI and left atrial lesions which were extensively tested with epicardial or endocardial mapping, however there were other procedural differences. The patients with an endocardial EP-guided approach received a more extensive lesion set, using a stepwise approach, with the inclusion of right atrial lesions. Potentially, right atrial lesions are necessary in patients with persistent AF or enlarged right atria to achieve a better result. On the other hand, patients with paroxysmal AF might benefit more from PVI alone. In a majority of the patients the GPs were ablated or the LAA was removed, however the success rate in these two groups was not different. This may be due to the patient selection of this analysis. In these patients the substrate of AF may be less dependent of GP function and extrapulmonary triggers may play a smaller role. It is still not univocally clear whether GP ablation during minimal invasive surgery for AF has additional benefit. Catheter ablation studies have shown, that functional localization and ablation of GP’s, with a vagal response on high frequency stimulation, are less effective than anatomical ablation. In this study a primarily anatomical approach was used, with functional confirmation. It may well be that epicardial ablation of the PVI with the use of a RF clamp interrupts the innervation of the PV’s. The success rates after one year are the same as the included groups in this study (Figure. 1). Interestingly, patients with an atrium <45 mm appear to have mostly late recurrences (after 276 days), possibly indicating a subgroup of patient with progression of underlying atrial remodeling, but the number of recurrences is low. Female sex, vascular disease and longer duration of AF were associated with recurrences in this population. While these factors could not be validated in multivariate analysis, they have been reported earlier. Patients who underwent an epicardial EP-guided procedure were heavier, had larger atria and a non-significant longer duration of AF, possibly associated with an increased recurrence risk.

Left atrial appendage exclusion

In the majority of our patients the LAA was excluded. In the remaining patients the LAA was not excluded due to anatomical restrictions or surgeon preference. LAA removal can cause bleeding, which might require conversion to sternotomy. Its effect on left atrial function and remaining thromboembolic risk is incompletely understood, and further study would be needed to clearly define the risks and benefit of surgical LAA occlusion. Moreover, removal of the LAA may contribute to the elimination of extra-pulmonary vein triggers of AF, however LAA removal was not associated with an increased success rate in our small population. This issue becomes more relevant as the possibilities of epicardial or endovascular LAA exclusion evolve and a growing patient population receives invasive treatment for AF with exclusion of the LAA. After catheter ablation stroke risk
is reduced\textsuperscript{5}, but LAA exclusion might even further decrease stroke risk in patients with a high CHA\textsubscript{2}DS\textsubscript{2}-VASc score.\textsuperscript{27,28}

**Safety of electrophysiology guided thoracoscopic surgery**

In 18\% of the patients reversible adverse events occurred. These ranged from major events, requiring additional interventions and prolonging hospital stay, to minor events, that required no intervention. The rate of adverse events is similar as reported in literature\textsuperscript{6,7,9}, but remains significant when compared to catheter ablation.\textsuperscript{4} It is important to note that these results are obtained in the first series of patients treated with EP-guided surgery for AF. The hemothorax that occurred in two consecutive patients, for instance, resulted from an intercostal artery bleeding. Careful retraction of the working port and final inspection before closure has prevented this event from occurring in all subsequent patients. Also, the rate of adverse events is expected to lie between that in catheter ablation and the Cox-Maze IV procedure.\textsuperscript{29} Some of these patients would be considered eligible for Cox-Maze IV surgery, however thoracoscopic surgery is less invasive than a Cox-Maze IV procedure. Most minor events are a direct mechanical consequence of the thoracoscopic approach. The risk of stroke is relatively low in thoracoscopic surgery and no strokes have occurred in this cohort.\textsuperscript{30} Whilst a combination of catheterization in addition to surgery has the risk of both procedures, absolute risk is not cumulative as shown in our data which show mainly surgical complications. The majority of ablation is performed epicardially. Subsequently, endocardial ablation times are severely reduced in the endocardial EP-approach reducing the likelihood of PV stenosis and atrio-oesophageal fistula. Finally, these patients represent a group with advanced disease which is often a representation of the general health and might therefore be more prone to adverse events. However, no patient characteristics correlated with the occurrence of adverse events. None of the adverse events occurred during the EP measurements, epicardial or endocardial, either of which appears a safe addition to thoracoscopic surgery for AF.

**Limitations**

This is a retrospective study, of prospectively collected data, investigating two different approaches of EP-guided surgery for AF in selected challenging patients. Of all included patients, 16 patients from the AMC and 22 from the MUMC have been previously reported in two unselected observational analyses.\textsuperscript{10,11} The 5 patients with inadequate pre-procedural data or incomplete follow-up were excluded to prevent overestimation of successful cases. The excluded patients all demonstrated sinus rhythm at one year follow-up according to the available data. No implantable loop recording was used to detect recurrences, and therefore the success rate might be an overestimation of true success.\textsuperscript{31} However, follow-up was organized to comply with the HRS/EHRA/ECAS consensus statement and reflects clinical practice in most centers. This study is a result of
pooled data of two centers with a different thoracoscopic procedure and EP approach, but with a similar philosophy in the implementation of EP measurements during surgery. These different approaches illustrate that EP measurements per se can complement stand-alone surgery for AF in this selected group of difficult patients. However, this is not a randomized study and the aim was not to compare the two approaches, or to compare EP-guided surgery with stand-alone surgery or catheter ablation.

CONCLUSIONS

EP-guided surgical ablation for AF is effective in patients with enlarged left atria or a previously failed ablation with a success rate of 79% at one year without AAD. EP guidance of the procedure can be performed safely, either using an epicardial or using an endocardial approach, and may contribute to the success rate. A heart-team approach with close cooperation between surgeons and cardiologist resulting in an EP-guided surgical ablation provides a new and promising treatment modality for these, often difficult to treat, patients. Further randomized studies are recommended to compare the added value of EP-guided surgery in the current era of invasive treatment of AF.
REFERENCES