Modulation of atrial fibrillation
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Completely thoracoscopic pulmonary vein isolation with ganglionic plexus ablation and left atrial appendage amputation for treatment of atrial fibrillation

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Abstract

Objectives: Percutaneous catheter pulmonary vein isolation (PVI) has been the preferred choice for invasive treatment of symptomatic, drug-refractory lone atrial fibrillation (AF). Incomplete ablation lines, procedure-related morbidity and long-term success remain, however, a problem. A minimally invasive surgical approach can provide an attractive and secure alternative. Surgery offers an epicardial, bipolar approach under direct vision, but the invasiveness of surgery remains a problem. Therefore, we developed a completely thoracoscopic procedure. The objective of this study was to assess the feasibility, safety and effectiveness of a completely thoracoscopic surgical procedure to cure lone AF.

Methods: Bilateral ‘video-assisted thoracoscopy’ was performed to isolate the bilateral pairs of pulmonary veins using bipolar RF-energy, to ablate the ganglionic plexus (GP) and to amputate the left atrial appendage. Preoperative, in-hospital and follow-up data were collected for our first 30 patients.

Results: AF was paroxysmal in 63%, persistent in 27% and permanent in 10% of cases. The mean (±SD) left atrial diameter was 42.1 ± 7.4 mm and the mean duration of AF was 79.0 ± 63.9 months. Freedom from AF was obtained in 77% of the patients during a mean follow-up of 11.6 months. Forty-three percent of the patients had previously undergone a percutaneous PVI and were all free from AF during follow-up. Mean operation time was 137.4 ± 24.7 min. All patients were extubated in the operating room and left the recovery room within 12 h. The mean hospital stay was 5.1 ± 1.8 days. Two patients ultimately underwent a median sternotomy. No CVAs or pacemaker implantation were identified and none of the patients died.

Conclusions: We report our initial experience of a completely thoracoscopic PVI with GP-ablation and amputation of the left atrial appendage and demonstrate that the procedure is feasible, safe and effective for the treatment of lone AF.
Minimal invasive surgery for atrial fibrillation

Introduction
The classical Maze III procedure has been the gold standard for the treatment of symptomatic, drug-refractory atrial fibrillation (AF). Despite its high success rates, it has not been widely adopted due to many reasons. This is mainly because the procedure is technically challenging and performed through a median sternotomy with the use of extra-corporal circulation.¹

Less invasive procedures have been developed due to increasing knowledge about the pathophysiology of AF and due to the development of ablation devices, which replace the original ‘cut-and-sew’ technique for scarification.

Ectopic foci from the pulmonary veins (PVs) play an important role in the pathophysiology, especially in lone paroxysmal AF.² Therefore, both cardiologists and surgeons focus on these vessels for the cure of AF. Recent clinical and experimental studies also suggest an important role of the autonomic nervous system.³,⁴ Wolf et al. have developed an off-pump procedure in which the PVs are isolated, ganglionic plexus (GP) are ablated and the left atrial appendage is amputated through a bilateral thoracotomy.⁵ A completely thoracoscopic procedure is even less invasive and should benefit perioperative morbidity and patient discomfort.

We have recently described the operation technique for a completely thoracoscopic approach to isolate the pulmonary veins, to ablate the GP and to amputate the left atrial appendage for the treatment of AF.⁶ The present study evaluates our first 30 completely thoracoscopic procedures with a medium-term follow-up.

Material and methods
Patient selection
Completely thoracoscopic procedures for patients suffering from symptomatic, drug-refractory, (lone) AF have been performed since January 2007. Patients with drug-refractory AF, between the ages of 18 and 80 years and at least a moderate heart function, were eligible for surgery. Previous cardiac or lung surgery, very longstanding AF (more than 10 years) and a left atrium larger than 70 mm were relative contraindications. A previous unsuccessful percutaneous catheter ablation was not a contraindication for surgery. Patients were included after informed
consent.

**Operation technique (Figure 1)**

A completely bilateral video-assisted thoracoscopy (VATS) was performed as previously described by our group. briefly, the patient is placed in the supine position under general anaesthesia and double lumen tube intubation. The procedure is performed through three thoracoports on both sides. Thoracoports are inserted in the fourth and sixth intercostal space in the midaxillary line. A third port is placed about 5 cm anterior to the midaxillary line in the third or fourth intercostal space. The camera is inserted through the port which is positioned in the fourth intercostal space. The remaining two ports are used for two thoracoscopic instruments.

On the right side, the pericardium is opened a few centimetres anterior to the phrenic nerve, followed by exploration of Waterstone’s groove for optimal positioning of the ablation device later on. Before isolation of the pulmonary veins, the GP at the base of the PVs are located with the AtriCure Transpolar Pen (AtriCure, Inc., West Chester, Ohio, USA) by high-frequency pacing (1000 beats min\(^{-1}\) with a potential of 18 V). Plexus locations are identified by a high-frequency pacing-induced slowing of the heart rate, which is considered to be a vagal response. This is defined by a ventricular asystole of at least 3 s or ventricular rate slowing of more than 50% when AF is present. A positive GP location is ablated for about 20 s with the AtriCure Transpolar Pen (AtriCure, Inc., West Chester, Ohio, USA). High-frequency pacing is again performed at the same position to verify that the GP is successfully ablated. If necessary, ablation can be repeated.

Blunt dissection around the PVs is performed using the AtriCure Lumitip Dissector (AtriCure, Inc., West Chester, Ohio, USA) and isolation of the PVs is achieved by bipolar radiofrequency ablation with the AtriCure Isolator Synergy ablation clamp (AtriCure, Inc., West Chester, Ohio, USA). At least three overlapping ablation lesions are performed at the antrum of the left and right PVs. A conduction block is confirmed by the absence of PV potentials if AF is present. This is performed by bipolar mapping of the PVs just beside the ablation line. Pacing from the PVs is used to confirm conduction block when a sinus rhythm is present. An extra ablation lesion is made if necessary.

The procedure is repeated on the left side, except that the pericardium
is opened posterior to the phrenic nerve. In addition, the ligament of Marshall is dissected by electrocautery. The left atrial appendage was initially excluded by a PDS endoloop (Ethicon, Amersfoort, The Netherlands), but in later procedures, it was amputated by using an Autosuture Endo Gia stapler (Tyco Healthcare Group, North Haven, Connecticut, USA). A stapling device was used later on, because this guarantees exclusion of the cavity of the appendage. Amputation or exclusion of the left atrial appendage was performed after a thrombus was excluded by transoesophageal echocardiograph.

On completion of the procedure, the patient is extubated in the operating room and transferred to the recovery room.

Figure 1. Completely thoracoscopic pulmonary antrum isolation with GP-.ablation. Panel A: The whole procedure is performed thoracoscopically through 3 thoracoports bilaterally. The black lines with numbers indicate the intercostal spaces (ICS). The thick red line indicates the mid-axillary line. The thin red line shows the position of the thoracoport in the 6th ICS relative to the xyphoid. Panel B: This shows the bipolar RF-ablation clamp (RF-clamp) around the right set of pulmonary veins. RA, right atrium; SCV, superior cavalvein. Panel C: Controlling the electrical isolation with an EP-catheter. The arrow indicates the ablation line. Panel D: Amputation of the left atrial appendage (LAA) with a stapling device (stapler).
In-hospital post-operative management

All patients received oral anticoagulation for at least 3 months after surgery. Further, the preoperative antiarrhythmic drugs were usually continued. Sotalol was started if a patient was only on rate-control medication with a β-blocker such as verapamil or digoxin. Electrical cardioversion (ECV) was performed if a patient had symptomatic AF less than 48 h or was adequately anticoagulated (International Normalised Ratio >2.0). Patients with asymptomatic AF were often discharged without an attempt for an electrical cardioversion. In that case, the referring physician was advised to perform one later on.

Follow-up

Baseline characteristics, in-hospital and follow-up data were collected from clinical and out-patient clinic files. The referring cardiologist was sent a questionnaire for follow-up. Heart rhythm documentation was based on electrocardiograms (ECGs) and 24-h Holter-monitoring. Patients had continuous rhythm monitoring in the hospital. ECGs after discharge were performed after 1 week, 3 weeks, 3 months, 6 months and then annually. Holter-monitoring was performed at 3, 6 and 12 months for patients from our centre. Patients who were followed by a referring cardiologist and did not receive a Holter-monitoring were offered one at our centre.

The surgical procedure was considered to be unsuccessful if an episode of AF (of duration >30 s, independently of amount of episodes or symptoms) occurred after a blanking period of 3 months.

Changes in medication (withdrawal of anti-arrhythmic drugs and/or anticoagulation after a successful procedure) were an autonomous decision of the referring cardiologist.

Statistical analysis

Data are presented as mean ± standard deviation. The Fisher’s exact test was performed where appropriate.
Results

Baseline characteristics

The mean age of the patients was 55.6 ± 8.6 (range 35.9-69.8) years. The mean duration of AF was 79.0 ± 63.9 (range 36-240) months and the mean left atrial diameter was 42.1 ± 7.4 (range 35-55) mm. None of the patients had a significant mitral or tricuspid valve insufficiency. Three patients had a diminished left ventricular function with an estimated left ventricular ejection fraction of 30-40%. Eighteen patients (60%) had previously undergone a percutaneous catheter ablation(s), including left-sided ablation for AF in 13 (43%). All of them, except one, had paroxysmal AF.

In total, 19 patients (63%) suffered from paroxysmal AF, eight (27%) from persistent AF and three (10%) from permanent AF. The baseline characteristics are presented in Table 1.

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Results (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55.6 ± 8.6</td>
</tr>
<tr>
<td>Man</td>
<td>77% (23/30)</td>
</tr>
<tr>
<td>AF duration (months)</td>
<td>79.0 ± 63.9</td>
</tr>
<tr>
<td>For paroxysmal AF</td>
<td>97.3 ± 70.6</td>
</tr>
<tr>
<td>For persistent AF</td>
<td>34.5 ± 7.7</td>
</tr>
<tr>
<td>Longstanding persistent</td>
<td>40.0 ± 6.9</td>
</tr>
<tr>
<td>For permanent AF</td>
<td>88.0 ± 59.2</td>
</tr>
<tr>
<td>Type AF</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>63% (19/30)</td>
</tr>
<tr>
<td>Persistent</td>
<td>27% (8/30)</td>
</tr>
<tr>
<td>Longstanding persistent</td>
<td>10% (3/30)</td>
</tr>
<tr>
<td>Permanent</td>
<td>10% (3/30)</td>
</tr>
<tr>
<td>Preoperative LA ø (mm)</td>
<td>42.1 ± 7.4</td>
</tr>
<tr>
<td>Preoperative RA ø (mm)</td>
<td>55.8 ± 5.3</td>
</tr>
<tr>
<td>Number of failed AAD</td>
<td>4.1 ± 1.4</td>
</tr>
<tr>
<td>Including amiodaron</td>
<td>52%</td>
</tr>
<tr>
<td>Number of failed ECV</td>
<td>2.3 ± 1.9</td>
</tr>
<tr>
<td>Previous failed percutaneous catheter PVI</td>
<td>43% (13/30)</td>
</tr>
<tr>
<td>For paroxysmal AF</td>
<td>92% (12/13)</td>
</tr>
<tr>
<td>For persistent AF (none longstanding)</td>
<td>8% (1/13)</td>
</tr>
<tr>
<td>For permanent AF</td>
<td>0% (0/13)</td>
</tr>
<tr>
<td>Previous percutaneous catheter ablation (other than PVI)</td>
<td>17% (5/30)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>7% (2/30)</td>
</tr>
<tr>
<td>Preoperative CVA</td>
<td>7% (2/30)</td>
</tr>
<tr>
<td>Preoperative TIA</td>
<td>3% (1/30)</td>
</tr>
<tr>
<td>Preoperative pacemaker implantation</td>
<td>0% (0/30)</td>
</tr>
</tbody>
</table>

LA, left atrium; RA, right atrium; ø, diameter; AAD, anti-arrhythmic drugs; ECV, electrical cardioversion; PVI, pulmonary vein isolation; CVA, cerebrovascular accident; TIA, transient ischaemic attack.

1 long axis in parasternal view  2 long axis in 4-chamber view
In-hospital results
The procedure had to be converted to a median sternotomy in the third and sixth patients, one due to severe pleural adhesions and the other due to bleeding from the right lower PV. In the following 24 patients, there were no complications during surgery. In all cases, the PVs could be electrically isolated and the left atrial appendage amputated. The mean duration of surgery was just over 2 h (137.4 ± 24.7 (range 101-197) min).

All patients could leave the recovery room within 12 h and were discharged from the hospital after a mean hospitalization of 5.1 ± 1.8 (range 3-9) days. Two patients received a thoracostomy drain because of a residual pneumothorax. This was secondary to inadequate removal of the drains and not due to a pulmonary lesion. In-hospital results are presented in Table 2.

Table 2. In-hospital results.

<table>
<thead>
<tr>
<th>Results (n=30)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0% (0/30)</td>
</tr>
<tr>
<td>Conversion to sternotomy</td>
<td>7% (2/30)</td>
</tr>
<tr>
<td>Procedure time (minutes)</td>
<td>137.4 ± 24.7 (range 101 - 197)</td>
</tr>
<tr>
<td>In-hospital AF</td>
<td>60% (18/30)</td>
</tr>
<tr>
<td>Discharged with AF</td>
<td>47% (14/30)</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>5.1 ± 1.9 (range 3 - 9)</td>
</tr>
<tr>
<td>Temporary pacemaker dependency</td>
<td>0% (0/30)</td>
</tr>
</tbody>
</table>

Follow-up results
There was no peri- or post-operative mortality. The mean follow-up duration was 11.6 ± 3.9 (5.3-19.0) months. Taking a blanking period of 3 months after surgery into account, 77% of the patients did not have a ‘single’ registration of AF during follow-up. Holter-monitoring was available in 91% of the patient who were free from AF. Two patients did not want to receive a Holter-monitoring at our own hospital, but were free from complaints and had multiple ECGs with sinus rhythm. All patients who had a previously failed percutaneous left-sided catheter ablation for AF were free from AF after a mean follow-up of 9.8 ± 4.1 months.

Freedom from AF was 84%, 75% and 33% for paroxysmal, persistent and permanent AF, respectively ( p > 0.05).

Freedom from AF of the patients who had an in-hospital relapse of AF was
61% (11/18). This was 57% (8/14) for patients who were discharged while still being in AF. Six of the 23 (26%) patients, who were free from AF, had undergone an ECV during follow-up (by definition of ‘success’ within 3 months after surgery); four of them were discharged with AF.

For patients who had a successful procedure, the freedom from anti-arrhythmic drugs was 65%, freedom from coumarines 48% and freedom from both was 26%. Focussing on the first 15 patients with a longer mean follow-up of 12.8 ± 4.2 months, this was 73%, 55% and 36%, respectively.

During the follow-up period, none of the patients received a pacemaker or suffered a cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

**Discussion**

This study reports our experience of the first 30 completely thoracoscopic PV isolations with GP-ablation and amputation of the left atrial appendage with a mean follow-up of almost 1 year. It shows that a completely thoracoscopic approach is feasible and safe, although two patients needed a sternotomy because of bleeding. This complication occurred within the first six cases and the authors are convinced that this is a part of the learning curve. No complication during surgery occurred in the last 24 cases. Furthermore, the procedure is effective, even for patients with longstanding AF or who had a previously unsuccessful percutaneous catheter ablation.

Freedom from AF was 77% for the whole group after a mean follow-up of almost a year, but still, 35% were using anti-arrhythmic drugs. Comparing success rates with other groups is difficult and depends on patient selection, definition of success and duration of follow-up. The technique of isolating the PVs and ablation of the ganglionic plexus has been previously described by Wolf et al. Our results are in concordance with those of others who also adopted this technique. This procedure appears to be less successful than the more elaborate classical Maze III operation; however, the advantages of a completely thoracoscopic procedure are clear. It is an off-pump, minimal invasive procedure and has a shorter operating time, intensive care and hospital stay.

The success in patients who had a previous percutaneous catheter PVI is of special mention. All of them were free from AF during follow-up. This could be
either due to previous inadequate percutaneous endocardial ablation and now a successful addition of bipolar RF-ablation or due to the additional GP-ablation.

**Autonomic nervous system and GP-ablation**

In 1958, Alessi et al. already showed that vagal stimulation leads to non-uniform shortening of the atrial refractory period in dogs. Shortly thereafter, Moe et al. could sustain AF with vagal stimulation without a focal discharge. More recent experimental evidence comes from the group of Oklahoma. These investigators showed that conversion of a premature (pulmonary) depolarisation to AF depends on GP stimulation. They could even initiate ectopic foci from the PVs by GP stimulation alone. These experimental data question the classical ‘trigger-substrate-hypothesis’ and it is clear that the autonomic nervous system plays a key role in the initiation and maintenance of AF.

The first important clinical indication for the role of vagal denervation came from Pappone et al. They showed that patients with a vagal response during RF-ablation (hence, vagal ablation) had a higher success rate in comparison to patients without a vagal response. RF-ablation was, however, not directed against the GP. Scherlag et al. were the first to compare PVI with and without GP-ablation in a prospective study. The follow-up was short and the groups were small, but the data suggest better outcome with additional GP-ablation. Some groups have even performed only GP-ablation for AF. The reported success rates vary between 29% and 84% and the follow-up is short.

GP-ablation is, therefore, expected to contribute to the success of procedures for AF. Whether the effect of GP-ablation is persistent is a matter of debate. In dogs, autonomic innervations restore within 4 weeks and even reinnervations occur in totally denervated hearts of patients, who have undergone heart transplantation.

Detecting GP is another point of debate. From an anatomical point of view, the GP is quite large and complex. Fields of ganglia (GP) contain both sympathetic and parasympathetic neurons and form complicated networks. The clinical relevance of a vagal reaction during high-frequency stimulation of GPs is not completely understood. This reaction is not pathologic per se and due to a network of ganglia, it could well be that the site of stimulation is not the site of neurotransmitter release.

In summary, there is limited evidence that GP-ablation in combination with
a PVI leads to a higher success rate than PVI alone. There is a need for a randomised, prospective trial.

**Extended lesion set and alternative ablation devices**

In this study, we describe our first 30 completely thoracoscopic PVIs with GP-ablation. PV isolation is a well-accepted method to treat AF. However, AF was treated successfully in only one of the three patients with permanent AF. One may expect that pulmonary vein isolation alone is adequate to treat paroxysmal AF. Additional lines in the left atrium could however lead to better results and extension of the indications for surgery.\(^{21,22}\) With the recently available Coolrail (AtriCure, Inc, West Chester, Ohio, USA), totally left-sided Maze III lesion sets can be achieved relatively easy. In permanent AF and longstanding persistent AF, the efficacy of the procedure could benefit from this more extensive lesion set. The transmurality of these additional epicardial ablation lines however remains a problem. An epicardial ablation line from the pulmonary veins to the mitral valve annulus (‘left fibrous trigone line’) is especially difficult. Extensive pacing and mapping has to be performed to check whether there is a complete conduction block.

We perform a bilateral thoracoscopic procedure with the use of bipolar RF-energy for the treatment of lone AF. Other groups have performed a unilateral approach with the use of other energy sources, such as microwave, high-intensity focussed ultrasound and vacuum-assisted RF, to isolate the pulmonary veins.\(^{23-25}\) All these energy sources are capable of making transmural lesions. A unilateral approach is, however, not suitable for amputation of the left atrial appendage. Further, positioning of the ablation device is not totally performed under direct vision and could lead to loss of contact with the epicardium.

**Limitations**

We could not arrange a Holter registration for two patients, who did not have any documented relapse of AF after 3 months. These patients had, however, multiple registrations of sinus rhythm during follow-up and did not have any complaints, which could indicate a relapse of AF. Some patients experienced the procedure as a success because they had fewer and shorter episodes of AF, but by definition this was seen as failure.
The majority of our patients come from referring hospitals. There may have been differences between centres in stopping anti-arrhythmic drugs and/or anticoagulation when a patient is in sinus rhythm. This and the duration of follow-up may influence the freedom from anti-arrhythmic drugs and anticoagulation.

Verification of a conduction block requires extensive mapping and expertise. To maximise success after surgery for AF, especially in the case of additional ablation lines, we need to develop reliable and easy-to-use mapping devices. A hybrid approach with endocardial verification of electrical isolation could also be of great value.

We did not record the exact number of application of the ablation device necessary to isolate the pulmonary veins and the number of GPs and their exact location.

**Conclusion**

The present study indicates that a completely thoracoscopic procedure for drug-refractory AF is feasible, safe and effective. The advantage of the surgical procedure in comparison to a percutaneous catheter PVI is its epicardial approach under direct vision, possibility of GP-ablation and amputation of the left atrial appendage. The procedure could therefore offer an alternative for percutaneous catheter ablation and is even effective after unsuccessful ones.
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