Minimally invasive surgical management of atrial fibrillation

The role of ganglionated plexuses

Driessen, A.H.G.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Minimally Invasive Surgical Management of Atrial Fibrillation,
The Role of Ganglionated Plexuses

Antoine Driessen
Minimally Invasive Surgical Management of Atrial Fibrillation,
The Role of Ganglionated Plexuses

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel

op vrijdag 16 maart 2018, te 10:00 uur

door Antonius Henricus Gertrudis Driessen

geboren te Tegelen
Promotiecommissie:

Promotores: prof. mr. dr. B.A.J.M. de Mol AMC-UvA
            prof. dr. J.R. de Groot AMC-UvA

Overige leden: prof. dr. W.J. Morshuis Radboud Universiteit
               prof. dr. M.I.M. La Meir Vrije Universiteit Brussel
               prof. dr. L.V.A. Boersma AMC-UvA
               prof. dr. R. Balm AMC-UvA
               prof. dr. B. Preckel AMC-UvA
               dr. R. Coronel AMC-UvA
               prof. dr. A.A.M. Wilde AMC-UvA

Faculteit der Geneeskunde
CONTENTS

CHAPTER 1  7
GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

PART 1

CHAPTER 2  23
NAVIGATING THE MINI-MAZE: SYSTEMATIC REVIEW OF THE FIRST RESULTS AND
PROGRESS OF MINIMALLY-INVASIVE SURGERY IN THE TREATMENT OF ATRIAL FIBRILLATION

CHAPTER 3  45
THORACOSCOPIC VIDEO-ASSISTED PULMONARY VEIN ANTRUM ISOLATION,
GANGLIONATED PLEXUS ABLATION, AND PERIPROCEDURAL CONFIRMATION OF
ABLATION LESIONS

CHAPTER 4  63
EPICARDIAL CONFIRMATION OF CONDUCTION BLOCK DURING THORACOSCOPIC
SURGERY FOR ATRIAL FIBRILLATION - A HYBRID SURGICAL-ELECTROPHYSIOLOGICAL
APPROACH

CHAPTER 5  79
ELECTROPHYSIOLOGICAL EVALUATION OF THORACOSCOPIC PULMONARY VEIN ISOLATION

PART 2

CHAPTER 6  103
GANGLION PLEXUS ABLATION IN ADVANCED ATRIAL FIBRILLATION
THE AFACT STUDY.

CHAPTER 7  125
ELECTROPHYSIOLOGICALLY GUIDED THORACOSCOPIC SURGERY FOR ADVANCED
ATRIAL FIBRILLATION 5-YEAR FOLLOW-UP

CHAPTER 8  141
QUALITY OF LIFE IMPROVES AFTER THORACOSCOPIC SURGICAL ABLATION OF ADVANCED
ATRIAL FIBRILLATION
PART 3

Chapter 9
Second Chance for a Totally Thoracoscopic Video-Assisted Pulmonary Vein Isolation for Atrial Fibrillation

Chapter 10
Previous Cardiac Surgery does not Preclude Thoracoscopic Ablation of Advanced Atrial Fibrillation.

Chapter 11
General discussion and future perspectives

Summary
Nederlandse Samenvatting
Co-Authors
Abbreviations
About the Author
Publications
Dankwoord
CHAPTER 1

General Introduction and Outline of the Thesis
Atrial fibrillation as a health care problem

Atrial fibrillation is the most common arrhythmia in man, affecting approximately 300,000 patients in the Netherlands and more than 6 million in the European Union.\(^1\)\(^2\) Almost half of patients suffering from paroxysms of AF develop permanent AF.\(^5\) In these patients the arrhythmia is accepted and medical treatment is aimed at controlling ventricular rate, as sustained tachycardia (i.e. a too high heart rate) can eventually result in heart failure, referred to as tachycardiomyopathy.

Irrespective of the type of AF, AF patients have a five-fold increased risk of developing a stroke.\(^2\) Oral anticoagulation with vitamin K antagonists or non-vitamin K oral anticoagulants decrease that risk by approximately 2/3.\(^4\) However, in the presence of risk factors as assessed by the CHA\(_2\)DS\(_2\)-VASC score, anticoagulation should be continued lifelong, even after successful restoration of sinus rhythm.\(^2\) Similarly, patients with atrial fibrillation have a two-fold increased mortality, although it is unknown whether this is caused by the arrhythmia itself or AF is merely a consequence of the interplay between other risk factors such as hypertension, heart failure and vascular disease.

Due to demographic changes, it is expected that the prevalence of AF will further increase and even double over the forthcoming decades.\(^1\) The prevalence varies in life from 0,12-0,16% under 50 to over 10% in individuals over 80 years of age.\(^5\) It is expected that in Europe, the number of patients will reach between 14-17 million in 2030.\(^1\)\(^6\) With an average cost of $640 per patient per month in a chronic phase of AF treatment, the cumulative costs may be projected to rise over 100 billion euros per year in Europe alone.\(^7\)

Treatment of Atrial Fibrillation

The main pillars of AF treatment are the prevention of thromboembolic complications by the use of oral anticoagulant medication and the regulation of ventricular heart rate to prevent tachycardiomyopathy. For the subset of patients who remain symptomatic, a strategy aimed at restoring sinus rhythm is advised. Therefore, after prevention of adverse events, the main strategies with regard to the rhythm disturbance are 1) ventricular rate control (aimed at preventing tachycardia without attempting to restore sinus rhythm) and 2) rhythm control (aimed at maintaining or restoring sinus rhythm with antiarrhythmic drugs, cardioversion or ablation strategies).\(^2\)

Two important randomized trials from earlier this century tested the hypothesis that rate controls was similar to rhythm control.\(^9\)\(^10\) These studies concluded that there was no difference in mortality between either of these therapeutic strategies, which has led to the current dogma.
that rate control is similar to rhythm control. A few points of discussion have to be mentioned
to properly interpret these studies. First, the common belief in those days was that the presence
of sinus rhythm would allow safe discontinuation of anticoagulant therapy. Also, the risk
estimation schemes that are currently used, were not globally implemented then. Finally, there
are long-term follow up data from the AFFIRM trial that suggest that the mortality curves are
drifting apart after 4 years after randomization, and that there is indeed a mortality benefit for
rhythm control.\(^{(11)}\)

There is a continuing debate on which precautions should be taken to prevent thromboembolic
stroke. There is evidence that closure of the left atrial appendage would confer the same
degree of protection as oral anticoagulation.\(^{(12,13)}\) However, the comparator in these studies was
warfarin, a vitamin-K antagonist which primary action depends on how well the patient is in
therapeutic range. Several non-vitamin K antagonists nowadays have shown to be at least as
effective as warfarin, but associated with significantly less bleeding events, intracranial bleeds
in particular.\(^{(14-17)}\) Whether or not the efficacy and safety of left atrial appendage occlusion
devises holds true against novel anticoagulants has yet to be determined. The guidelines of the
European Society of Cardiology recommend continuation of anticoagulation, despite (presumed)
correction of the heart rhythm with medication or following successful ablation.\(^{(2)}\) Furthermore,
at this moment, closing of the left atrial appendage is not a substitute for anticoagulation.

### Rhythm control and invasive treatment of Atrial Fibrillation

For patients remaining symptomatic despite adequate regulation of the ventricular rate, a
rhythm control strategy is indicated. Generally, rhythm control consists of (a combination of)
class 1 or 3 antiarrhythmic drugs, electrical or chemical cardioversion and/or ablation of the
arrhythmogenic substrate with endocardial catheters or via a surgical approach.

Several surgical approaches have been pursued to treat atrial fibrillation. Driven by the
notion that a critical mass of atrial tissue is necessary to sustain atrial fibrillation, approaches
to reduce the mass of atrial tissue whilst preserving the connecting the sinus node and the
atrioventricular node were undertaken. Guirandon et al described the sinus node-atrioventricular
node isolation, or corridor operation, where a corridor, connecting the sinus and atrioventricular
node, was isolated from the remaining (fibrillating) right and left atrium.\(^{(18)}\) The operation
was infrequently used because of modest effectiveness and a pacemaker implantation rate close
to 50%. In 1987, James Cox reported the third iteration of his Maze procedure, in which the
atrium was compartmentalized (cut-and-sew technique) to prevent macroreentrant activations,
but also to reduced the mass of fibrillating atrial myocardium.\(^{(19)}\) This procedure, still
considered the gold standard for atrial fibrillation interventions, was initially reported to have
a success rate of over 95%.\(^{(20)}\) Recently, and employing more contemporary rhythm monitoring
techniques, it was shown that after 2 years 82% of patients were in sinus rhythm and not using antiarrhythmic drugs. Procedural complications included mortality of 2% and a pacemaker implantation rate between 7 and 9%, dependent on whether the Cox Maze 3 or Cox Maze 4 was performed (where conduction block was achieved with radiofrequency energy, instead of cut-and-sew).\[^{21,22}\] Due to its surgical complexity and invasiveness, the Cox Maze procedure was never carried out on a large scale, and the main body of evidence that is available comes from few high volume centers.\[^{21,23,24}\] Also, recently it was demonstrated in a large randomized trial that the initial efficacy rates of concomitant Maze surgery (that is, atrial fibrillation ablation on top of other cardiothoracic surgery) could not be reproduced.\[^{25}\]

Attempts to reproduce the Cox Maze lesion pattern with ablation catheters were unsuccessful, but in 1998 Michel Haissaguere and colleagues reported that the triggers that set off atrial fibrillation arise from the pulmonary veins, and that these triggers can be ablated.\[^{26}\] This gave rise to an enormous expansion of invasive therapy for AF. Catheter ablation proved superior to antiarrhythmic drugs and quality of life was consistently higher in patients after ablation.\[^{27-29}\] Later it was shown that similar efficacy can be derived using cryotherapy instead of radiofrequency.\[^{30,31}\] However, the long-term results of catheter ablation were reported from two of the most experienced centers in the world, and can be considered modest at best: 20-29% absence of AF after a single procedure, raising to 45-67% after up to seven procedures.\[^{32-34}\] Similarly, in the real world, the complication rate of catheter ablation for atrial fibrillation, albeit low compared to surgical approaches, cannot be neglected.\[^{35}\]

**Minimally invasive surgery for Atrial Fibrillation**

In an attempt to combine the high reported efficacy of the Cox Maze procedure with a less invasive approach, Wolf et al described a bilateral mini-thoracotomy to allow clamping and radiofrequency ablation of the pulmonary veins.\[^{36}\] Consequently, Van Boven and Yilmaz modified this procedure into a totally thoracoscopic procedure.\[^{37}\] Several small studies demonstrated efficacy and safety of this approach.\[^{38,39}\] Initially high recurrence rate due to atrial tachycardia were reported.\[^{40,41}\] This urged investigators to design hybrid approaches where surgeons join forces with electrophysiologists to assess conduction block across their ablation lesions and to perform additional (endocardial) ablation when needed. Hybrid approaches, with either endocardial or epicardial mapping, appear more efficacious than stand-alone surgery, although direct comparisons have never been performed.\[^{42}\] Subsequently, operators started employing a staged hybrid approach, where the catheter part of the procedure is carried out several weeks to months after the surgical part.\[^{43}\] Two randomized trials comparing thoracoscopic surgery for AF with catheter ablation in patients who had failed catheter ablation earlier, or who had a severely enlarged left atrium
Chapter 1

showed approximately twice as many patients with AF freedom, at the cost of more procedural complications.\textsuperscript{(44,45)}

**Role of additional ablation targets: the autonomic nervous system**

Aside from isolation of the pulmonary veins, and particularly in patients with persistent AF, additional modification of the atrial substrate may be needed to achieve an acceptable outcome of the ablation procedure.\textsuperscript{(8)} One of the potential targets for additional ablation is the autonomic nervous system.

The atria and the ventricles of the heart are innervated by an intricate network of sympathetic and parasympathetic nerves, supplied by extrinsic nerve pathways. The extrinsic sympathetic innervation is mediated via cervical, stellate and thoracic ganglia, whereas the extrinsic parasympathetic system is routed via the vagus nerve. The extrinsic nervous system branches out and interconnects to epicardial subplexuses.\textsuperscript{(46)} Ganglionated plexi are epicardially located conglomerates of ganglia, derived from these different subplexuses.\textsuperscript{(46,47)} The anatomy of the autonomic nervous system, as well as the function and modulation in arrhythmias, have been reviewed extensively before.\textsuperscript{(46-48)} There is extensive evidence that stimulation of the GPs triggers atrial fibrillation by triggering ectopy from the pulmonary veins in animals and humans.\textsuperscript{(49-51)} The parasympathetic stimulation results in activation of the acetylcholine activated potassium current, which results in shortening of the action potentials. Subsequently, sympathetic stimulation increases calcium release from the sarcoplasmic reticulum.\textsuperscript{(52)} GP stimulation also directly affects conduction velocity in the atrium in a proarrhythmic way, mainly mediated by a parasympathetic effect.\textsuperscript{(53,54)}

When the connection between extrinsic and intrinsic autonomous nervous system is interrupted, hyperactivity of the GPs, shortening of the action potential and increased burden of AF was observed in dogs.\textsuperscript{(55)} Hence, taking away the inhibitory action of the extrinsic nervous system by ablating GP, would decrease the burden of AF as GP causes proarrhythmic GP hyperactivity. It forms the rationale for ablation of the GPs.

Clinically, the balance of sympathetic and parasympathetic nerves changes in persistent atrial fibrillation compared to healthy subjects.\textsuperscript{(56)} There are reports that occurrence of a vagal response during AF ablation is related to a beneficial outcome.\textsuperscript{(57)} Although a vagal response is no prerequisite for localization of the GPs, as ablation based on anatomical landmarks is more effective.\textsuperscript{(58)} Katritsis et al performed a randomized trial where patients with paroxysmal AF were randomized to catheter ablation of the GPs, pulmonary vein isolation or both treatments combined.\textsuperscript{(59)} The absence of AF was higher in patients receiving both treatments, compared to any of the treatments alone. Of note, the amount of radiofrequency ablation was also higher
in the group receiving both pulmonary vein isolation and GP ablation. This is the logical consequence of ablation of an epicardial structure with an endocardial catheter, but precludes conclusions on whether the more rigorous PV isolation or the autonomic denervation was responsible for the effect.

Based on these findings, surgeons added ablation of the GPs to their minimally invasive ablation lesion set, but the findings provoked performing a randomized clinical trial, directly testing the efficacy and safety of this approach (chapter 6).(60-62)

**How to combine what we know into better surgical treatment?**

Contemporary strategies in minimally invasive surgical treatment of atrial fibrillation move towards some degree of a hybrid approach. The concept of an ablation platform with a higher efficacy in creating transmural lesions, in combination with the more precise mapping of residual conduction across ablation lines with catheter (or dedicated epicardial) mapping techniques is appealing, but has not been tested head-to-head against surgical ablation alone. (42) Also, the role of exclusion of the left atrial appendage in the prevention of stroke has yet to be determined. The ongoing LAAOS-3 trial will provide answers to this issue. (63) Nevertheless, removal of the left atrial appendix is conceived an advantage of the surgical treatment.

What remains a great difficulty is comparing all the different ablation strategies for atrial fibrillation with respect to efficacy and safety. Not only is the patient selection often ill-defined, which has considerable consequences for the interpretation of the results, also follow-up strategies differ markedly. The HRS/EHRA/ECAS consensus document provides guidelines on how recurrences should be defined, and which amount of rhythm monitoring is considered minimal. However, most of the available data are derived from studies employing alternative follow-up strategies, sometimes not even including electrocardiograms. Therefore, caution should be taken when comparing different studies. Novel concepts of outcome, consisting of reductions in burden of AF and changes in health related quality of life may be important to better guide treatment. Until then, comparison of therapies, the success rate, the adverse effects and the effect on arrhythmia burden, remains a challenge.

Of note, novel therapy will be adopted by motivated operators, and may be feared by more conservative professionals. To reliably introduce novel therapy, a thorough analysis of failures and complications is imminent. Particularly when considering that novel therapy will usually be introduced in sicker patient groups, with larger atria, longer persistent AF and more comorbidities. These are the patients that do not respond well to conventional therapy, and this notion has to be taken into consideration when judging a novel approach.
Outline of the Thesis

Part 1 An epicardial hybrid approach toward surgical ablation of atrial fibrillation

The first part of this thesis focus on the technique in evaluating a novel, epicardially guided hybrid approach. In chapter 2 we present a review efficacy and safety of minimally invasive surgery for atrial fibrillation. The efficacy of the therapy, defined as absence of AF after one year without the use of antiarrhythmic drugs was 69%. The complication rate in this early era of minimally invasive surgery was relatively high. Chapter 3 describes the outcome of the first 31 patients treated with the epicardial hybrid approach. After one year and after a single procedure, 86% of patients did not have AF recurrence, demonstrated by repetitive Holter monitoring, and without the use of antiarrhythmic drugs. Follow-up was organized conforming to the recommendations of the HRS/EHRA/ECAS consensus document [8]. In chapter 4, focus is laid on explaining the potential benefit of a hybrid setup and explaining our techniques for confirmation of conduction block using a custom made epicardial mapping electrode during thoracoscopic surgery for AF. Chapter 5 describes in detail our electrophysiological evaluation of surgical ablation lesions together with a review of existing mapping methods.

Part 2 Clinical studies of thoracoscopic surgery for Atrial Fibrillation

Chapter 6 describes the results of the randomized AFACt trial in which we compared ablation of the ganglion plexus on top of an epicardial ablation lesion set versus that same epicardial ablation set without ablation of the GPs in 240 patients. AFACt showed that additional ablation of the ganglion plexus did not confer a benefit in terms of AF absence. However, ablation of the GPs was associated with a significant increase in adverse effects, bleeding and pacemaker implantation in particular. In Chapter 7 we describe the long-term results of thoracoscopic AF surgery in the first 66 patients that underwent this procedure in our institution. We show that of these patients, 33 or 50% were free of AF during the entire 5-year follow-up period without AAD use. Interestingly, at the 5-year visit 88% of patients were in SR, and 91% had no or less than 3 AF recurrences/year during the follow-up period. Hence, only 9% had frequent recurrences of AF or permanent AF. Chapter 8 describes a sub analysis of AFACt with regard to health related quality of life. Overall, quality of life improved after thoracoscopic AF ablation in the AFACt population. Patients with no or only one AF recurrence improved to the standardized Dutch population. Multiple recurrences of AF and irreversible procedural complications were associated with persistently lower QoL.
Part 3 Surgical consideration of thoracoscopic ablation of Atrial Fibrillation

In this part of the thesis we explore the limits of what can be done with thoracoscopic surgery. Chapter 9 describes two patients in which a bleeding that occurred at the initial procedure resulting in abortion of the procedure to prevent escalation of the bleeding. In both patients a conversion to full sternotomy could be prevented. We show that during a second procedure, weeks after the index procedure, the operation could be finished successfully. Chapter 10 reports on 6 patients in which previous open heart surgery (12-49 years before), or an aborted terminated thoracoscopic operation for AF (because of bleeding), more than 1 year before was performed. In all subjects, the thoracoscopic operation could be completed successfully. After more than one year, 3 out of 4 patients were in sinus rhythm, although only 1 was without any AF recurrences.

Chapter 11 provides a general discussion of the thesis.

A summary of the thesis in English and Dutch are provided thereafter.
Chapter 1

References


Chapter 1


General Introduction and Outline of the Thesis


Chapter 1


PART 1
CHAPTER 2

Navigating the mini-maze:
Systematic review of the first results and progress of minimally-invasive surgery in the treatment of atrial fibrillation

Sébastien P.J. Krul
Antoine H.G. Driessen
Aeilko H. Zwinderman
Wim J. van Boven
Arthur A.M. Wilde
Jacques M.T. de Bakker
Joris R. de Groot

International Journal of Cardiology 166 (2013) 132–140
Navigating the mini-maze: Systematic review

Abstract

Background:
In this paper we present a systematic literature overview and analysis of the first results and progress made with minimally-invasive surgery using RF energy in the treatment of AF. The minimally-invasive treatment for atrial fibrillation (AF) tries to combine the success rate of surgical treatment with a less invasive approach to surgery. It has the additional potential advantage of ganglion plexus (GP) ablation and left atrial appendage exclusion. Furthermore, additional left atrial ablation lines (ALAL) can be created in non-paroxysmal AF patients.

Methods:
For the search query multiple databases were used. Exclusion and inclusion criteria were applied to select the publications to be screened. All remaining articles were critically appraised and only relevant and valid articles were included in our results.

Results:
Twenty-three studies were included. In 15 studies GPs around the pulmonary veins were ablated. In four studies ALAL were performed. Single procedure success rate was 69% (95% CI, range 58%–78%) without antiarrhythmic drugs (AAD) and 79% (95% CI, range 71%–85%) with AAD at one-year follow-up. Mortality was 0.4%, and various complications were reported (3.2% surgical, 3.2% post-surgical, 2.6% cardiac, 2.1% pulmonary, 1.7% other).

Conclusions:
Twenty-three studies of minimally-invasive surgery for AF have been reviewed with success rates between that of the standard maze procedure and catheter ablation. These first combined results show promise; however, minimally-invasive surgery is still evolving, for instance by the recent inclusion of electrophysiological endpoints. Furthermore, the type of ALAL and the additional value of GP ablation have to be elucidated.
Introduction

Treatment of AF, worldwide the most common supraventricular arrhythmia, is a challenge for the cardiologist, despite increasing pharmalogical and technological options. Some patients experience no or few complaints during AF while others are adequately managed with pharmacologic rate or rhythm control. Unfortunately, there is a group of patients with AF who have debilitating symptoms during AF that cannot sufficiently be treated with AAD. The Cox–Maze procedure described by Cox et al. was the first invasive surgical procedure for the treatment of AF.\(^{(1,2)}\) It has a success rate of 75\%--95\% after up to 15 years of follow up. In 1998 Haïssaguerre et al. published a landmark paper in which an endovascular approach was described to target pulmonary vein triggers.\(^{(3)}\) Catheter based interventions have a lower single procedure success rate of 57\% (95% CI, range 50\%--64\%) off AAD after a mean follow up of 14 months, but are less invasive than the Cox–Maze-III procedure, which requires open heart surgery. Indeed, a single procedure is not always enough to prevent AF recurrences and most patients require multiple procedures to achieve a success rate of 71\% (95% CI, 65\%--77\%) off AAD.\(^{(4)}\) In 2005 Wolf et al. described the first results of 21 patients treated with a minimally-invasive surgical approach to PVI.\(^{(5)}\) The minimally-invasive procedure tries to combine the success rate of surgical treatment with a less invasive intervention for the patient akin to catheter ablation. Since the first publications, experience with the minimally-invasive procedure has increased, but the technique has not yet been established as a regular treatment option of AF. A potential advantage of the epicardial approach is the possibility of GP ablation, which may modulate the substrate for AF-induction.\(^{(6)}\) Furthermore, ALAL can be created to prevent AF recurrence and AT in patients requiring more extensive ablation. The risk of embolic events might be reduced through the possibility of excluding the LAA during surgery. Multiple energy sources have been investigated, including microwave\(^{(7-9)}\) or high frequency ultrasound,\(^{(10)}\) but application of these energy sources results in a lower success rate than RF energy. In this paper we present an analysis of the first results and progress made with minimally-invasive surgery, using RF energy only, in the treatment of AF. Additionally, we discuss the recent developments and the place of minimally-invasive surgery in the therapeutic options of AF-treatment.

Methods

Search query

For the search query the following databases were used: PubMed and Embase on 07/07/2011. The search query is shown in Table 1. We have added the results of Pison et al. (Pison et al., submitted) to the analysis.
Navigating the mini-maze: Systematic review

<table>
<thead>
<tr>
<th>Database</th>
<th>Search query</th>
<th>Search results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embase</td>
<td>(“atrial fibrillation”:ti,ab OR “AF”:ti,ab) AND (“epicardial ablation”:ti,ab OR “endoscopic”:ti,ab OR “thoracoscopic”:ti,ab OR “videothoracoscopy”:ti,ab OR “surgical ablation”:ti,ab OR “minimal invasive”:ti,ab OR “minimally invasive”:ti,ab OR “mini-maze”:ti,ab OR “VATS”:ti,ab OR “epicardial pulmonary vein isolation”:ti,ab OR “surgical pulmonary vein isolation”:ti,ab)</td>
<td>Total: 632 Exclusion: 43 Inclusion: 23</td>
</tr>
</tbody>
</table>

The search was performed on 07-07-2011.
Exclusion criteria: Animal studies, reviews, case reports, concomitant surgery, not atrial fibrillation, not minimally-invasive surgery, not English, no full-text availability.
Inclusion criteria: Studies with > 10 patients, follow-up of > 3 months, use of radio frequent energy, off-pump cardiac surgery.

**Search strategy**
The exclusion criteria were chosen to make a selection based on title and/or abstract, hereby selecting the papers needed to screen. Inclusion criteria were applied on the full text of the selected articles. Exclusion and inclusion criteria are listed in Table 1. Studies using RF-energy were selected as this method of ablations shows superior results compared with other energy sources like high intensity focused ultrasound and microwave ablation. Doubles were filtered manually and all remaining articles were combined. All included full texts were screened on references.

**Statistical analysis**
Forest-plots to present an overview of the studies have been made using Meta-Analyst Beta 3.13 (Tufts Medical Center, Boston, MA). No individual patient data were available to perform a meta-analysis; however, an overall freedom of AF curve was made to show the results of all studies. A freedom from AF analysis curve was chosen to estimate the combined effect of the different studies based on the reported proportions of success and number of patients. The analysis was performed with the Statistical Package for the Social Sciences, version 15.0 for Windows XP (SPSS, Chicago, IL, USA). The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.
Chapter 2

Results

A total of 24 studies were found using our search query in Embase of whom 22 were also found in PubMed. (5,12-31) Two studies on ≤10 patients were excluded. (32,33) An overview of the remaining 22 studies and the study of Pison et al. is presented in Table 2. All studies were observational in nature and 18/23 studies were performed in a single center. (5,13-18,20-23,26,27,29-31) In total there were five studies by the group of Edgerton et al. who report on overlapping patients. (21-25) Therefore, their papers of 2007 and 2008 have been excluded from analysis in calculations of complications. (21,22) The paper of Wang et al. (31) describes an open-label randomized trial where patients received irbesartan after minimally-invasive surgery. For calculations of the cumulative results only the patients not receiving irbesartan were selected. There were two studies by the group of Speziale and Nasso, who performed a monolateral thoracotomy. As this procedure has different surgical approach, it has been excluded from the cumulative analysis, but the results of these studies can be found in Tables 2 and 3.

Surgery

In all but two studies bilateral thoracotomy or thoracoscopic approach to surgery was performed, only the group of Speziale and Nasso used a monolateral thoracotomy. (12,16) Two studies performed a hybrid procedure; Krul et al. (30) performed extensive electrophysiological measurements epicardially while Pison et al. performed simultaneous transvenous catheter measurements. There were differences in the execution of the minimally-invasive surgical procedure (Table 2). RF energy was used in all studies as this was a selection criterion in including the studies in this paper. GP ablation was performed in 14 of 22 studies in addition to PVI (Table 2). Irrespective of the choice of GP ablation the ligament of Marshall was divided in all but two studies. (12,16) ALAL were made in four studies as shown in Table 2. (17,23,30) The LAA was excluded through suturing or stapling in 20 of 22 studies. (5,13-15,17-31) From studies of which procedure data were available, the mean procedure duration is 208 minutes (n= 12 studies) (5,13,14,17-20,26,28,30,31) and hospital admission is 5 days (n= 17 studies). (5,13,14,17-20,23-28,30,31)
Outcome

Definition of success varied between studies, but unfortunately not all studies report according to the HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of AF (Tables 2 and 3). All papers present a total number of patients of 842 who underwent surgery. The reported population comprised of 752 patients. This number is lower because some patients were lost for follow-up or were still in the 3 months blanking period following the procedure at the time of publication.

In these studies, a mean of 26% (range 5%–45%, n= 15 studies) of patients had a history of a previous catheter ablation (excluding Castella et al., where all patients had a previous catheter ablation). Total follow up varied from 2 to 45 months, with a reported mean ranging from 5.7–18 months. Unfortunately, 6 month and/or 12 months follow-up were not reported in all studies. It was not always possible to assess the success percentage at these times of follow up. Results in the different types of AF and the use of AAD were not specified in every study and as such not all studies could be included in the respective pooled analysis.

Given these restrictions, the overall single procedure success rate of minimally-invasive surgery without AAD is 64% (95% CI, range 55%–72%, n= 7 studies) at a follow-up of 6 months and 69% (95% CI, range 58%–78%, n= 5 studies) at 12 months follow-up.

With AAD the single procedure success rate was 75% (95% CI, range 70%–80%, n= 5 studies) the 6-months of follow up (Fig. 1). At 12-months success rate was comparable at 79% (95% CI, range 71%–85%, n= 7 studies) with AAD (Fig. 1).

In studies with GP ablation the overall success rate is 63% with AAD (95% CI, range 58%–69%, n= 15 studies) while in studies where the investigators refrained from GP ablation, the success rate was 83% with AAD (95% CI, range 63%–94%, n= 6 studies) In studies with ALAL the overall success rate is 77% with AAD (95% CI, range 53%–92%, n= 4 studies) while in studies where the investigators performed only PVI, the success rate was 65% with AAD (95% CI, range 60%–70%, n= 16 studies). Specified to the different type of AF, success in paroxysmal AF was 71% (95% CI, range 65%–77%, n= 5 studies), persistent AF 51% (95% CI, range 36%–65%, n= 5 studies) (Fig. 2) and for LSP AF 33% (95% CI, range 21%–49%, n= 2 studies) at 6 months (Fig. 2). Success at 12 months with paroxysmal AF was 75% (95% CI, range 66%–82%, n= 8 studies) and 67% (95% CI, range 52%–79%, n= 7 studies) in persistent AF (Fig. 2) and 43% (95% CI, range 21%–68%, n= 4 studies) in LSP AF.
Table 2. Minimally-invasive surgery for atrial fibrillation: studies overview.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>No of centres</th>
<th>GP ablation</th>
<th>ALAL ablation</th>
<th>AF endpoints</th>
<th>Follow up</th>
<th>Rhythm monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolf [5]</td>
<td>2005</td>
<td>Single</td>
<td>No</td>
<td>No</td>
<td>Not specified</td>
<td>Office visits, medical records, telephone calls to the patients, records from cardiology visits</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, outpatient telemonitoring</td>
<td></td>
</tr>
<tr>
<td>Sagbas [18]</td>
<td>2006</td>
<td>Single</td>
<td>No</td>
<td>No</td>
<td>Not specified</td>
<td>End of the surgical procedure, 3 months and 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, Holter</td>
<td></td>
</tr>
<tr>
<td>Edgerton [21]</td>
<td>2007</td>
<td>Single</td>
<td>Yes</td>
<td>No</td>
<td>No episodes of AF longer than 15 seconds at 6 months</td>
<td>Outpatient visit at 1, 3 and 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, Holter, event recorder, pacemaker</td>
<td></td>
</tr>
<tr>
<td>Wudel [14]</td>
<td>2007</td>
<td>Single</td>
<td>No</td>
<td>No</td>
<td>Not specified</td>
<td>Outpatient visit at 3, 6, 12 months, and then until end of study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, Holter</td>
<td></td>
</tr>
<tr>
<td>McClelland [34]</td>
<td>2007</td>
<td>Single</td>
<td>Yes</td>
<td>No</td>
<td>Free of AAD (class IC and III) and AF no more than 30 seconds of AF after 3 months</td>
<td>Outpatient visit at 1, 2, 3, 6 weeks, and 3, 6 months, then every 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, Holter, event recorder</td>
<td></td>
</tr>
<tr>
<td>Matsutani [19]</td>
<td>2008</td>
<td>Two</td>
<td>Yes</td>
<td>No</td>
<td>Not specified</td>
<td>Not specified</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, questionnaires</td>
<td></td>
</tr>
<tr>
<td>Edgerton [22]</td>
<td>2008</td>
<td>Single</td>
<td>Yes</td>
<td>No</td>
<td>No episodes of AF longer than 15 seconds at 6 months</td>
<td>Outpatient visit at 1, 3 and 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, Holter, event recorder, pacemaker</td>
<td></td>
</tr>
<tr>
<td>Sirak [17]</td>
<td>2008</td>
<td>Single</td>
<td>Yes</td>
<td>Yes</td>
<td>No episode of AF or AFT lasting 30 s after blanking period of 3 months</td>
<td>Outpatient visit 3, 6 and 13 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, event recorder</td>
<td></td>
</tr>
<tr>
<td>Beyer [28]</td>
<td>2009</td>
<td>Three</td>
<td>Yes</td>
<td>No</td>
<td>Absence of AF or AFT on ECG and Holter</td>
<td>Not specified</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, Holter</td>
<td></td>
</tr>
<tr>
<td>Edgerton [24]</td>
<td>2009</td>
<td>Multi</td>
<td>Yes</td>
<td>No</td>
<td>No episodes of AF and no AAD</td>
<td>Outpatient visit at 1, 3 and 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, Holter, event recorder, pacemaker</td>
<td></td>
</tr>
<tr>
<td>Bagge [29]</td>
<td>2009</td>
<td>Single</td>
<td>Yes</td>
<td>No</td>
<td>No documented symptomatic AF or AT after 12 months of follow up on ECG, 24 h Holter and spot ECG</td>
<td>Outpatient visit at 3, 6 and 12 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, Holter</td>
<td></td>
</tr>
<tr>
<td>Han [20]</td>
<td>2009</td>
<td>Single</td>
<td>Yes</td>
<td>No</td>
<td>No AF/AFT/AT more than 30 s on ECG or Holter monitoring off AAD</td>
<td>Outpatient visit at 6, 12 months and 12 months thereafter</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG, Holter, event recorder, pacemaker</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Study Design</td>
<td>Randomization</td>
<td>AF/AFT/AT Criteria</td>
<td>Follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>------</td>
<td>--------------</td>
<td>---------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>----------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edgerton ELS [23]</td>
<td>2009</td>
<td>Single</td>
<td>Yes</td>
<td>No episodes of AF/AFT/AT more than 15 s during monitoring at 6 months</td>
<td>Outpatient visit at 1, 3, and 6 months ECG, event recorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edgerton [25]</td>
<td>2010</td>
<td>Two</td>
<td>Yes, No</td>
<td>No episodes of AF/AFT/AT more than 30 s on ECG or Holter monitoring</td>
<td>Outpatient visit at 1, 3, 6, 12 months ECG, Holter, event recorder, pacemaker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speziale [16]</td>
<td>2010</td>
<td>Single</td>
<td>No, No</td>
<td>Absence of AF or other SVT 6 months after surgery on Holter</td>
<td>Outpatient visit at 3, 6 and 12 months ECG, Holter, echocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cai [26]</td>
<td>2010</td>
<td>Single</td>
<td>No, No</td>
<td>No AF or AFT more than 30 s on ECG or Holter monitoring</td>
<td>Outpatient visit at 1, 3, 6, 12 months ECG, Holter, echo, pacemaker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castella [27]</td>
<td>2010</td>
<td>Single</td>
<td>No, No</td>
<td>No symptomatic episode of arrhythmia or SVT lasting more than 30 s in any ECG or Holter</td>
<td>Outpatient visit at 1, 4, 6 and 12 months ECG, Holter, echo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yilmaz [13]</td>
<td>2010</td>
<td>Single</td>
<td>Yes, No</td>
<td>No episode of AF more than 30 s after blanking period of 3 months</td>
<td>Outpatient visit at 1 and 3 weeks, and 3, 6, 12 months ECG, Holter, referring physician</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krul [30]</td>
<td>2011</td>
<td>Single</td>
<td>Yes, Yes</td>
<td>No AF/AFT/AT more than 30 s on ECG or Holter monitoring</td>
<td>Outpatient visit at 3, 6, 12, 15, 18, 24 months ECG, Holter, MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pison</td>
<td>2011</td>
<td>Single</td>
<td>Yes, Yes</td>
<td>No AF/AFT/AT more than 30 s on ECG or Holter monitoring of AAD</td>
<td>Outpatient visit at 3, 6, 12 months ECG, Holter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang [31]</td>
<td>2011</td>
<td>Single</td>
<td>Yes, No</td>
<td>No AF/AFT/AT more than 30 s on ECG or Holter monitoring</td>
<td>Outpatient visit at 1, 3, 6, 12 months ECG, Holter, echocardiogram for clinical interview</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasso [12]</td>
<td>2011</td>
<td>Single</td>
<td>No, No</td>
<td>One year clinical results of rate of recurrence of AF, freedom from, antiarrhythmic medications</td>
<td>Outpatient visit at 3, 6, 12 months ECG, Holter, echocardiogram</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a  Left atrial appendage line and mitral line.
b  Roof line, trigone line and left atrial appendage line.
c  Roof line, inferior line and trigone line.
d  Roof line, inferior line and optional left isthmus line and right atrial lines.
Table 3. Minimally-invasive surgery for atrial fibrillation: patient number and results overview of studies

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Operated patients (months)</th>
<th>FU</th>
<th>Overall Total</th>
<th>Overall %</th>
<th>Paroxysmal AF %</th>
<th>Persistent AF %</th>
<th>LSP AF %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolf [5]</td>
<td>2005</td>
<td>29 5.7</td>
<td>23</td>
<td>AAD 91</td>
<td>No AAD 65</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sagbas [18]</td>
<td>2006</td>
<td>26 6</td>
<td>26</td>
<td>AAD 81</td>
<td>–</td>
<td>100 100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Edgerton [21]</td>
<td>2007</td>
<td>83 6</td>
<td>57</td>
<td>AAD 74</td>
<td>No AAD 63</td>
<td>39</td>
<td>82 74</td>
<td>18</td>
</tr>
<tr>
<td>Wudel [14]</td>
<td>2007</td>
<td>23 18</td>
<td>22</td>
<td>AAD 91</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>McClelland [34]</td>
<td>2008</td>
<td>20 16.6</td>
<td>20</td>
<td>AAD 90</td>
<td>No AAD 85</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Matsutani [19]</td>
<td>2008</td>
<td>32 6</td>
<td>66</td>
<td>AAD 74</td>
<td>No AAD 58</td>
<td>43</td>
<td>84 70</td>
<td>23</td>
</tr>
<tr>
<td>Edgerton [22]</td>
<td>2008</td>
<td>74 6</td>
<td>66</td>
<td>AAD 74</td>
<td>No AAD 58</td>
<td>43</td>
<td>84 70</td>
<td>23</td>
</tr>
<tr>
<td>Sirak [17]</td>
<td>2008</td>
<td>32 6</td>
<td>24</td>
<td>AAD 88</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Beyer [28]</td>
<td>2009</td>
<td>100 13.6</td>
<td>100</td>
<td>AAD 87</td>
<td>No AAD 63</td>
<td>39</td>
<td>93 29</td>
<td>96</td>
</tr>
<tr>
<td>Edgerton [24]</td>
<td>2009</td>
<td>114 6</td>
<td>114</td>
<td>AAD 71</td>
<td>No AAD 57</td>
<td>50</td>
<td>87 72</td>
<td>32</td>
</tr>
<tr>
<td>Bagge [29]</td>
<td>2009</td>
<td>43 12</td>
<td>33</td>
<td>AAD 76</td>
<td>No AAD 52</td>
<td>24</td>
<td>79 2</td>
<td>100</td>
</tr>
<tr>
<td>Han [20]</td>
<td>2009</td>
<td>45 12</td>
<td>43</td>
<td>AAD 65</td>
<td>–</td>
<td>70 70</td>
<td>–</td>
<td>58</td>
</tr>
<tr>
<td>Edgerton ELS [23]</td>
<td>2009</td>
<td>30 6</td>
<td>30</td>
<td>AAD 80</td>
<td>No AAD 47</td>
<td>–</td>
<td>–</td>
<td>90</td>
</tr>
<tr>
<td>Edgerton [25]</td>
<td>2010</td>
<td>52 12</td>
<td>52</td>
<td>AAD 81</td>
<td>No AAD 63</td>
<td>50</td>
<td>81 63</td>
<td>–</td>
</tr>
<tr>
<td>Speziale [16]</td>
<td>2010</td>
<td>54 6</td>
<td>46</td>
<td>AAD 87</td>
<td>–</td>
<td>95 27</td>
<td>81 6</td>
<td>–</td>
</tr>
<tr>
<td>Cai [26]</td>
<td>2010</td>
<td>81 12</td>
<td>49</td>
<td>AAD 80</td>
<td>–</td>
<td>80 6</td>
<td>75 7</td>
<td>67</td>
</tr>
<tr>
<td>Castella [27]</td>
<td>2010</td>
<td>38 12</td>
<td>26</td>
<td>AAD 62</td>
<td>–</td>
<td>82 10</td>
<td>60 7</td>
<td>20</td>
</tr>
<tr>
<td>Stamou [15]</td>
<td>2010</td>
<td>20 12</td>
<td>12</td>
<td>AAD 75</td>
<td>–</td>
<td>100 5</td>
<td>40 12</td>
<td>–</td>
</tr>
<tr>
<td>Yilmaz [13]</td>
<td>2010</td>
<td>30 11.6</td>
<td>30</td>
<td>AAD 77</td>
<td>No AAD 50</td>
<td>19</td>
<td>84 8</td>
<td>75</td>
</tr>
<tr>
<td>Knul [30]</td>
<td>2011</td>
<td>31 12</td>
<td>22</td>
<td>AAD 91</td>
<td>No AAD 86</td>
<td>12</td>
<td>100 9</td>
<td>78</td>
</tr>
<tr>
<td>Pison</td>
<td>2011</td>
<td>26 12</td>
<td>22</td>
<td>AAD 92</td>
<td>No AAD 83</td>
<td>14</td>
<td>93 79</td>
<td>11</td>
</tr>
<tr>
<td>Wang [31]</td>
<td>2011</td>
<td>83 24</td>
<td>81</td>
<td>AAD 80</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>81</td>
</tr>
</tbody>
</table>

AAD: antiarrhythmic drugs, AF: atrial fibrillation, ELS: extended lesion set, FU: follow-up, LSP AF: long standing persistent atrial fibrillation.

a Total number of patients who underwent the procedure is higher than overall reported patients because some patients did not complete the procedure or were still in the 3 months blanking period during publication.
Navigating the mini-maze: Systematic review

Figure 1. This figure shows four forest plots representing the proportion of the patients in sinus rhythm at 6 months and 12 months. The top left plot shows the results at 6 months without AAD (n=7 studies) and the top right at 6 months with AAD (n=6 studies). The bottom left plot shows the results at 12 months without AAD (n=6 studies) and the bottom right with AAD (n=7 studies). Note that the 6 months results are mostly results from studies of Edgerton et al. AAD: antiarrhythmic drugs.
Figure 2. This figure shows four forest plots representing the proportion of the patients in sinus rhythm at 6 months and 12 months specified to the different types of AF. The forest plot at the top show the results at 6 months of paroxysmal AF (n= 6 studies) and persistent AF (n=6 studies). The bottom plots show the results at 12 months of paroxysmal AF (n= 9 studies) and persistent AF (n=8 studies) Of the studies marked with an asterisk (*) only results with the use of antiarrhythmic drugs are available.

AF: atrial fibrillation.
Complications

Three casualties have been reported during or within 30 days after the procedure. One occurred during the procedure as a consequence of tearing of the LAA. For one death, the day after the procedure, the cause of death was undetermined and lastly, one late death resulted from cerebral infarction 30 days after the procedure. While mortality is low, surgical and post-procedural complications are relatively more frequently encountered. In 1.7% (14/842) of the procedures a sternotomy was required to control bleeding. Predominantly surgical complications of 3.2%, post-surgical complications of 3.2% and cardiac complications of 2.6% were described in the selected papers. A full list of morbidity related to the minimally-invasive procedure is listed in Table 4.

Table 4. Minimally-invasive surgery for atrial fibrillation: morbidity.

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>N=842</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical complications</td>
<td></td>
</tr>
<tr>
<td>Conversions</td>
<td>14</td>
</tr>
<tr>
<td>Conversions requiring heart-lung machine</td>
<td>4</td>
</tr>
<tr>
<td>Bleeding</td>
<td>12</td>
</tr>
<tr>
<td>LA Bleeding</td>
<td>5</td>
</tr>
<tr>
<td>PV bleeding</td>
<td>4</td>
</tr>
<tr>
<td>LAA bleeding</td>
<td>3</td>
</tr>
<tr>
<td>Other complications</td>
<td>1</td>
</tr>
<tr>
<td>Post-surgical complications</td>
<td></td>
</tr>
<tr>
<td>Hematothorax</td>
<td>12</td>
</tr>
<tr>
<td>Nerve injury</td>
<td>10</td>
</tr>
<tr>
<td>Wound problems</td>
<td>4</td>
</tr>
<tr>
<td>Ribfracture</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td></td>
</tr>
<tr>
<td>Pacemaker implantation</td>
<td>12</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>5</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac effusion</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td></td>
</tr>
<tr>
<td>Ventilation support</td>
<td>9</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>2</td>
</tr>
<tr>
<td>Other complications</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>4</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>4</td>
</tr>
<tr>
<td>Minor complications</td>
<td></td>
</tr>
<tr>
<td>Phlebitis</td>
<td>1</td>
</tr>
<tr>
<td>Coagluation problems</td>
<td>1</td>
</tr>
<tr>
<td>Delirium</td>
<td>1</td>
</tr>
</tbody>
</table>

LA: left atrium, LAA: left atrial appendage, PV: pulmonary vein, TIA: transient ischemic attack
Discussion

Minimally-invasive surgery

This systematic review comprises the first cumulative results of minimally-invasive surgery. These studies report an overall single procedure success rate of 69% without AAD and 79% with AAD at one year. Interestingly the results at 6 months are somewhat lower (64% without AAD and 75% with AAD) (Fig. 3). There can be two explanations for this finding; firstly studies reporting results at 6 months follow-up represent the very first published reports of minimally-invasive surgery as can be appreciated from Table 3. Secondly not all people are weaned of their AAD at 6 months after the procedure. Most studies in this review use similar methods and have a mixed AF population (paroxysmal, persistent and LSP). Only one paper describes the results in a group of paroxysmal AF (25) and three papers in only persistent and LSP AF (17,23,31). Minimally-invasive surgery is most effective in paroxysmal AF, but even in persistent AF and LSP AF more than half of the patients benefit from minimally-invasive surgery (Fig. 2). A recurrence of AF over time appears to be present, similar to the time course of recurrences after catheter ablation (36). Invasive ablation of AF is helpful to the majority of selected patients, but the disease progresses and causes recurrences in part of the patients. Comparison between catheter based PVI and minimally-invasive surgery is not possible; first, these are the first cumulative results of minimally-invasive surgery and secondly, no randomized control trial has been published comparing these two treatment modalities. Yet, while minimally-invasive PVI appear at least equally successful, catheter based PVI and minimally-invasive surgery have the same limitation. Both treatment strategies only aim to eliminate a trigger of AF, namely ectopic triggers from the pulmonary veins. Recently substrate modification with the use of additional left atrial lines has been proposed to increase success rates in non-paroxysmal AF. A substantial part of the population reported in the papers had one or more previous catheter ablation (mean 26%). This might influence the results with minimally-invasive surgery; these patients might have incomplete lesions leading to AT, which are difficult to treat because these lesions are not easily identifiable. However, the pre-existent substrate modification and PVI ablation might also increase the success rate of minimally-invasive surgery. Interestingly, Castella et al. (27) have, compared to other investigators, a moderate procedural success rate (62% with AAD), but they report results of patients with an earlier failed catheter-PVI only. These patients might have had different substrates in which PVI does not eliminate the pathophysiologic mechanism completely. Speziale et al. and Nasso et al. (12,16) used a monolateral approach and only performed PVI, without electrophysiological measurements. With this technique they achieve an average success rate with a low risk of procedure related-morbidity. Currently there is no confirmatory experience with this technique. Two studies perform periprocedural electrophysiological confirmation of conduction block of PVI and ALAL. Krul et al. (30) use epicardial confirmation of conduction block while Pison et al. use an endovascular
approach. These studies demonstrate that electrophysiological measurements are feasible during minimally-invasive surgery and that this hybrid approach might increase the success rate of minimally-invasive surgery.\(^{(37)}\)

**Figure 3.** Overall freedom from atrial fibrillation curve for minimally-invasive surgery. This figure shows the overall freedom of AF curve for minimally-invasive surgery using the reported proportions in the published papers at 6 months and 12 months. The blue line represents the overall results with AAD. The blue dotted line is the confidence interval of the overall results. Blue circles (●) represent the different studies and their outcome. Red lines and diamonds (♦) represent results without AAD. AAD: antiarrhythmic drugs, AF: atrial fibrillation.

**Role of GP ablation**

There is ample evidence from animal studies that neurohumoral influence on the PVs plays an important role in the initiation of AF.\(^{(6)}\) Although the precise role of GPs has not yet been established, the minimally-invasive approach offers access to the epicardial fat pads where the GPs reside and allows their ablation. Additional GP ablation can be performed to modify the local neurohumoral triggers of the atria and it has been hypothesized that this might decrease recurrence of AF. During epicardial surgery localization both visually and with high frequency stimulation and subsequent ablation of the GPs is possible. The absence of a vagal response to high frequency stimulation after ablation is generally considered proof of destruction of the GP. GP ablation has been added as a routine part of the minimally-invasive surgery protocol for AF by some investigators. However, its value in the epicardial treatment of AF has not been established. There is evidence that endocardial ablation of GPs might increase success rate of catheter PVI. A vagal response during a catheter PVI procedure is associated with a lower
Chapter 2

recurrence of AF.\(^{(38)}\) In the studies reviewed here, there is a difference between GP ablation (63\%) and no GP ablation (83\%) in the addition to PVI. This might indicate that GP ablation is not an essential part in the minimally-invasive surgery of AF to prevent recurrence of AF. Clearly, follow-up was short and at the present these data do not allow to draw any meaningful clinical conclusions, and this difference merely underscores the need for further randomized studies.

**Role of left atrial lesions**

Four studies have been published that report the creation of an additional lesion set on the left atrium.\(^{(17,23,30)}\) The types of lesions are not uniform in these studies but compartmentalization of the posterior left atrium, to prevent re-entry around the PVs, is the hallmark of these lesions. These lesions purposefully increase the success rate in patients with persistent and LSP AF. From results with catheter ablation therapy it is suggested that only PVI in these patient may not be sufficient to prevent recurrence of AF.\(^{(39)}\) The application of RF energy and subsequent visualization of the lines is possible in minimally-invasive surgery. In our view, additional electrophysiological testing is required to assess complete block over these lines.\(^{(40)}\) It has been demonstrated in two studies that a large proportion of patients undergoing minimally-invasive surgery might suffer from atrial tachycardia’s.\(^{(41,42)}\) Therefore all effort should be taken to produce a lesion set that actually demonstrates conduction block. Although longer follow-up is needed, a comprehensive set of left atrial lesions might increase freedom of AF in patients with persistent or LSP AF. A reproducible set of lesions with perioperative proof of block can therefore be a valuable addition to the minimally-invasive procedure. Thus the types of left atrial lesions that are most effective, are easy reproducible, and can be thoroughly tested electrophysiologically, should be investigated and their value in the different types of AF should be assessed.

**Mortality and morbidity**

Due to the epicardial approach to PVI minimally-invasive surgery incurs other risk in comparison with catheter PVI. There is for example a risk of conversion to on-pump cardiac surgery due to thoracoscopic surgery on the beating heart. However, there is no radiation exposure during the procedure and therefore there are no radiation related complications. Mortality is limited, especially compared to other cardiac operations, and appears to be similar with catheter PVI (incidence minimally-invasive 0.4\% vs. catheter ablation 0.7\%).\(^{(39)}\) Surgical and post-procedural complications are frequently encountered (Table 4). As can be appreciated from this table the risks of minimally-invasive surgery are mainly periprocedural problems followed by cardiac and pulmonary complications. These complication rates can be explained through the procedural difficulty and the learning curve of the surgery. Even though most complications are transient, the risk of pacemaker implantation of 1.4\% is
substantial. Furthermore, there is still a risk of stroke or TIA (0.5%) during or shortly after minimally-invasive surgery. This risk of occurrence is not abolished through epicardial ablation, but it is smaller than in catheter based PVI.\(^{(39)}\) The anti-coagulation policy before and after surgery (when the LAA is excluded) is difficult; the balance between prevention of embolic events versus prevention of bleeding complications is precarious. There is little evidence of how to manage anti-coagulation after the treatment of AF and guidelines currently suggest maintaining anti-coagulation based on the CHA\(_2\)DS\(_2\)-VASc score.\(^{(39)}\)

**Future developments**

The position of minimally-invasive surgery in the treatment of AF treatment has yet to be established. The results presented in this paper show the first results of minimally-invasive surgery. As such the potential of minimally-invasive surgery is still to be realized. Outcomes may benefit from standardization of the technique, results of longer follow-up and an improved patients selection. Furthermore, recent incorporation of electrophysiological measurements by some groups might increase the success rates the procedure. At the moment there are two ongoing studies comparing minimally-invasive surgery with catheter based PVI (SCALAF-trail and the FAST-trail). In these studies, the two treatment modalities are compared with each other, but a complementary role of these interventions might be envisioned. Patient preference can be the decisive factor in choosing catheter ablation or minimally-invasive surgery when comparing both the risks and the benefits of the two different approaches.

**Limitations**

This systematic review did not have access to all individual patient data and therefore our results and conclusions are based on published data. Furthermore, not all results are reported according to the HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation\(^{(35)}\) which makes a comparison of the different studies difficult. Due to the increasing experience and knowledge with minimally-invasive surgery, the technique has evolved significantly after the first publication. Results of the first studies might not be fully comparable to those published later. Furthermore, this paper is an overview of minimally-invasive surgery based on published reports and therefore might be subject to publication bias and might not reflect current practice in individual centers.
Chapter 2

Conclusions

Minimally-invasive surgery is a new invasive procedure for the non-pharmaceutical treatment of AF. The first studies describe a single procedure success rate of 69% without AAD and 79% with AAD at one-year follow-up. These results show a promising role for minimally-invasive surgery, although these results are likely to increase as the procedure progresses. Similar to catheter ablation it has a higher success rate in paroxysmal AF. Electrophysiological measurements and confirmation of the ablation lines might be an important factor to increase the success of this procedure. Additional research in the creation and type of left atrium lines in patients with persistent and LSP AF should determine a reproducible and effective left atrial lesion set to prevent recurrences in these types AF. Furthermore, the additional value of GP ablation is to be elucidated to assess its role in minimally-invasive surgery.
Navigating the mini-maze: Systematic review

References


Chapter 2


35 Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and
Navigating the mini-maze: Systematic review


CHAPTER 3

Thoracoscopic Video-Assisted Pulmonary Vein Antrum Isolation, Ganglionated Plexus Ablation, and Periprocedural Confirmation of Ablation Lesions First Results of a Hybrid Surgical-Electrophysiological Approach for Atrial Fibrillation

Sébastien P.J. Krul
Antoine H.G. Driessen
Wim J. van Boven
André C. Linnenbank
Guillaume S.C. Geuzebroek
Warren M. Jackman
Arthur A.M. Wilde
Jacques M.T. de Bakker
Joris R. de Groot

Circ Arrhythm Electrophysiol. 2011 Jun;4(3):262-70
Abstract

Background:
Thoracoscopic pulmonary vein isolation (PVI) and ganglionated plexus ablation is a novel approach in the treatment of atrial fibrillation (AF). We hypothesize that meticulous electrophysiological confirmation of PVI results in fewer recurrences of AF during follow-up.

Methods and Results:
Surgery was performed through 3 ports bilaterally. Ganglionated plexi were localized and subsequently ablated. PVI was performed and entry and exit block was confirmed. Additional left atrial ablation lines were created and conduction block verified in patients with nonparoxysmal AF. The left atrial appendage was removed. Freedom of AF was assessed by ECGs and Holter monitoring every 3 months or during symptoms of arrhythmia. Antiarrhythmic drugs were discontinued after 3 months and oral anticoagulants were discontinued according to the guidelines. Thirty-one patients were treated (16 paroxysmal AF, 13 persistent AF, 2 long-standing persistent AF). Thirteen patients with nonparoxysmal AF received additional left atrial ablation lines. After 1 year, 19 of 22 patients (86%) had no recurrences of AF, atrial flutter, or atrial tachycardia and were not using antiarrhythmic drugs (11/12 paroxysmal, 7/9 persistent, and 1/1 long-standing persistent). Three patients had a sternotomy because of uncontrolled bleeding during thoracoscopic surgery. Four adverse events were 1 haemothorax, 1 pneumothorax, and 2 pneumonia. No thromboembolic complications or mortality occurred.

Conclusions:
Thoracoscopic surgery with PVI and ganglionated plexus ablation for AF is a safe and successful procedure with a single procedure success rate of 86% at 1 year. Electrophysiological guided thorough PVI and additional left atrial ablation line creation presumably contributes in achieving a high success rate in the surgical treatment of AF.
Chapter 3

Introduction

Atrial fibrillation (AF) is the most common chronic arrhythmia in the world and has a major health burden to Western society. The lifetime risk of AF for subjects 55 years old is 23.8% in men and 22.2% in women.\(^1\) AF is associated with an increased risk of stroke, heart failure, and dementia.\(^2,3\) Pulmonary vein isolation (PVI) by catheter ablation is a widely accepted intervention of medically refractory AF in patients with no or minimal heart disease.\(^4\) The success percentages of catheter PVI vary greatly by center and the specific technique used, with a single procedure success rate of 57% to 77%.\(^5\) Risks of this procedure include thromboembolic complications, tamponade, and esophagus ulcers. In addition to catheter ablation, surgical techniques, particularly by Cox-Maze III procedure,\(^6,7\) have been effective in the treatment of AF. These are invasive and technically difficult procedures requiring a median sternotomy.\(^6,7\) A minimal invasive procedure aims at combining the success rate of surgical treatment with a minimal invasive approach.\(^8\) Since 2005, multiple studies have been published using minimal invasive surgery with slight variations in operating technique, energy source used, and a success rate varying between 62% to 91% (Krul et al, submitted).

We use a hybrid approach with extensive periprocedural electrophysiological testing during thoracoscopic pulmonary vein antrum isolation, left atrial ablation lines, and ganglionated plexus (GP) ablation. We hypothesize that meticulous electrophysiological confirmation of ablation lines results in fewer recurrences during follow-up.

Methods

Patient Population

Patients with an indication for nonpharmacologic treatment of AF were eligible, as well as patients with a preference for minimal invasive surgery and/or an earlier failed catheter PVI attempt.\(^9\) This indication consisted of: (1) \(>1\) antiarrhythmic drugs (AAD) in standard dosage that failed or were not tolerated and (2) documentation of AF available within the 12 months before the procedure. Age of the patients was between 43 and 77 years. Patients who received an earlier catheter PVI ablation and PVI-naive patients were eligible for this procedure. Definitions of paroxysmal, persistent AF and long-standing persistent AF, success and failure of ablation, major adverse events, and follow-up monitoring were based on the HRS/EHRA consensus statement for catheter and surgical ablation of AF.\(^9\) All patients underwent 12-lead ECG, chest radiography, 24-hour Holter, transthoracic echocardiogram, and laboratory tests before surgery. MRI, exercise test, and pulmonary function test were performed on indication in the first 20 patients but were routinely performed in the last 11.
Preoperative Care

Patients were admitted the day before surgery. Oral anticoagulation was discontinued 3 to 4 days before surgery. AAD were continued during hospital admission. Directly before surgery, a trans esophageal echocardiogram was made to exclude thrombus in the left atrial appendage (LAA).

Surgical Technique

Surgery was performed under general anesthesia. A double-lumen endotracheal tube for selective lung ventilation was placed. Surgery was started on the patient’s right side with 10-mm ports; 2 ports in the fourth and sixth intercostal space midaxillary line, and 1 port in the third or fourth intercostal space anterior axillary line. GPs were localized as described previously[10] with high-frequency stimulation (18 V, 1-ms pulse width, 1000 Hz) on the anterior right GP and inferior right GP. High-frequency pacing was delivered through an AtriCure Cooltip (AtriCure Inc, Cincinnati, OH) ablation pen positioned on the fat pad containing the GP and connected to an external pacemaker device, Oscor Pace 203H DDD External Dual-Chamber Pacemaker (Oscor Inc, Palm Harbor, FL). Localization of GPs was confirmed when high-frequency pacing induced AV block or increased the R-R interval>50%. GPs were subsequently ablated with bipolar radiofrequent energy through the AtriCure Cooltip pen. A lighted dissector (AtriCure Lumitip Dissector) was used to pass a rubber banding under the pulmonary venous (PV) antrum after blunt dissection of the Waterstone groove. An AtriCure Isolator Transpolar Clamp was then connected to the rubber banding and positioned gently around the PV antrum. PV antrum isolation was achieved by application of bipolar radiofrequency energy to the clamps around the PV antrum. After confirmation of PVI (see below), the procedure was repeated on the left side of the thorax. The ligament of Marshall was dissected and ablated in all patients.

In patients with persistent AF and long-standing persistent AF (LSPAF), additional left atrial lines (ALAL) were created. The ALAL consisted of a superior line (SL) and in selected patients an additional inferior line (IL). The SL connects the ablation lines encircling the right and left PVs, preventing reentry around both PV isolation (PVI) scars. In addition, an ablation line between the SL and the left fibrous trigone was made (the trigone line, TL). This ablation line prevents macro reentry around the connected PV antrum ablation lines similar to a mitral isthmus line as commonly used in catheter ablation for AF[11] After the ablation procedure and confirmation of conduction block, the LAA was removed with an endoscopic stapling device (EndoGia stapler, Tyco Healthcare Group, North Haven, CT). On completion of the procedure, single chest drains were inserted; one in each side of the chest.
Electrophysiological Testing

Before PVI, local electrograms were recorded from the PVs with a custom-made multi-electrode (6 gold-plated electrodes positioned in a circle around a central electrode; interelectrode distance, 1 mm). As a reference for atrial activity, we positioned a standard decapolar electrophysiology catheter (C. R. Bard Inc, Murray Hill, NJ) behind the atrium. We recorded electrograms, as described elsewhere, at 7 predefined locations (De Groot et al, submitted): superior side of the superior vein, anterior side of the superior vein, inferior side of the superior vein, the confluence where both veins join, superior side of the inferior vein, anterior side of the inferior vein, and inferior side of the inferior veins. After ablation with the bipolar clamp, PVI was confirmed by placing the recording electrode on the same locations, on the PV side of the ablation scar. Electrograms were interpreted using a mobile electrophysiological work station (Bard Labsystem PRO 2.4A, C. R. Bard Inc). The PV antrum was considered isolated if either no potentials (bipolar recording) were recorded distal from the scar or if potentials were recorded of a slow automatic rhythm, dissociated from the atrial depolarizations (Figure 1). Far-field signals were identified by similar timing and morphology of the electrogram when positioning the recording electrode at varying distance from the scar. If potentials persisted, indicating that the PVs had not been isolated, the clamp was repositioned and further radiofrequency current was applied until PVI was confirmed.

If an IL was made, the electric isolation of the box created by the SL and IL was tested by demonstration of entry block (absence of electrograms either during sinus rhythm or during AF) and exit block (pacing from within the box without capturing the atrium). In patients in AF during this testing of exit block, an attempt to electric cardioversion was undertaken. In patients who remained in AF after electric cardioversion, no further attempts were undertaken to prove exit block. In patients in whom atrial morphology restricted the creation of ALAL, the IL was not made because this line is not necessary to prevent reentry around the PVs.

Conduction block across the TL was tested by recording the activation sequence across the ablation line. The atrium was paced proximal from the one side of the line. The custom-made multi-electrode was positioned at several positions distal to the TL, closer to and more distant from the line. An activation sequence where activation under the multi-electrode propagated toward the ablation line (i.e., activation came around both PVI circles toward the TL) confirmed conduction block across the line. In contrast, an impulse propagating away from the TL, hence coming from the side where the atrium was paced from, proved persistent conduction (Figure 2).
First Results of a Hybrid Surgical-Electrophysiological Approach

Figure 1. PV recordings before and after PVI during sinus rhythm. Shown are leads I and II of the surface ECG and epicardial electrograms of the reference catheter and the custom-made electrode (RIPV). The reference catheter is positioned from the right side behind the atrium. The distal electrodes record from the left side of the atrium. Before ablation, there is activation of the antrum of the RIPV. After ablation, the recordings on the RIPV show no potentials conducted to the RIPV.

ECG: electrocardiogram, PV: pulmonary vein, PVI: pulmonary vein isolation, RIPV: right inferior pulmonary vein

Perioperative and Postoperative Care

After the procedure, patients were transferred to the recovery room and subsequently to the ward of the cardiothoracic surgery department on the same day. Chest drains were removed the day after surgery, and chest radiographs were routinely performed before and after removal. Anticoagulation with Coumadin derivatives was reinstituted in all patients after the procedure, before chest drain removal. Unfractionated heparin was started as soon as bleeding risk allowed and continued until the patient’s international normalized ratio was > 2.0. Oral anticoagulants were continued for at least 3 months after the procedure and AAD were continued. Episodes of AF lasting > 24 hours were treated with an electric cardioversion (ECV). Patients were discharged depending on the rapidity of clinical recovery.
Figure 2. Electrophysiological confirmation of ALAL. Schematic view of the posterior LA during confirmation of conduction block of the TL (B and C) and the SL (D through F). A, Schematic representation of the posterior LA with the ALAL. B and C, Confirmation of conduction block of the TL. Shown are leads I and II of the surface ECG with corresponding epicardial electrogram from the multielectrode. B, Multi-electrode is positioned far to the left from the TL (I); atrial conduction time from the stimulus (S) to the multielectrode is 200 ms. C, Multi-electrode is positioned on the scar of the TL (II). There is a double potential on C, the right of the scar, that is activated after 45 ms and the other side of the scar after 214 ms. The activation sequence confirms conduction block across the TL. D through F, Confirmation of conduction block of the SL. Shown are leads I and II of the surface ECG with corresponding epicardial electrogram from the multi-electrode. D, Multi-electrode is positioned far from the SL; atrial conduction time from the stimulus (S) to the multi-electrode is 60 ms (I). E, Multi-electrode is positioned closer to the SL; conduction time is increased to 100 ms (II). F, Final recording directly under the SL shows a conduction time of 154 ms (III). These sequential measurements determine the direction of atrial activation, which, in this figure, confirms isolation of the SL.

ALAL: additional left atrial lines, IL: inferior line, LA: left atrium, LPV: left pulmonary veins, RPV: right pulmonary veins, LPVI: left pulmonary vein isolation line, RPVI: right pulmonary veins isolation line, S: stimulus, SL: superior line, TL: trigone line.
Follow-Up
Patients were seen at the surgical outpatient clinic 10 days after the procedure for wound inspection and removal of sutures. The first 3 months after the procedure were used as a blanking period for the determination of absence of AF. If AF recurred, within the 3 months, patients received ECV and the same antiarrhythmic treatment as before the surgery. Rate control was instituted to prevent mean ventricular rates >90/min if applicable. Patients were followed up every 3 months with a 24-hour Holter and an ECG until 2 years after the procedure. An MRI was made after 6 months for the detection of PV stenosis. Antiarrhythmic medication was discontinued starting from the first outpatient visit, 3 months after the procedure. After 6 months, oral anticoagulants were discontinued in patients with a CHADS₂ score <1 if, after discontinuation of antiarrhythmic medication, there was absence of documentation of AF on either Holter or ECG or complaints suggestive of AF. In patients with higher CHADS₂ scores, the anticoagulant regimen was adjusted according to the guidelines.⁴

End Points
The primary end point was freedom from episodes of AF, atrial flutter, or atrial tachycardia without the use of AAD after 12 months. The secondary end point was freedom from episodes of AF, atrial flutter, or atrial tachycardia without the use of antiarrhythmic therapy after minimally invasive AF ablation and after the blanking period of 3 months. Freedom from AF was defined as the absence of episodes of AF, atrial flutter, or atrial tachycardia lasting >30 seconds on any ECG or 24-hour Holter monitoring.⁹

Statistical Analysis
Data are presented as mean ± SD (range) or median (interquartile range, IQR) for continuous variables and numbers with percentages for categorical variables. Postoperative AF-free curves were calculated using the Kaplan–Meier method. Statistical analyses were carried out using GraphPad Prism, version 5.0.

Results
Patient Characteristics
Thirty-one patients underwent the procedure between November 2008 and June 2010. The mean age of patients was 57±7 years (range, 43 to 77 years), with 25 of 31 (81%) patients being male. Sixteen patients had paroxysmal AF, 13 patients had persistent AF, and 2 patients had LSPAF. Patient characteristics are shown in Table 1.
## Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Minimal Invasive Surgery (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>57 (43–77)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>25 (81%)</td>
</tr>
<tr>
<td><strong>Body mass index, mean±SD, kg/m²</strong></td>
<td>29 ± 4</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mean±SD, mm Hg</strong></td>
<td>133 ± 16</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mean±SD, mm Hg</strong></td>
<td>79 ± 7</td>
</tr>
<tr>
<td><strong>Type of AF</strong></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal, n (%)</td>
<td>16 (52%)</td>
</tr>
<tr>
<td>Persistent, n (%)</td>
<td>13 (42%)</td>
</tr>
<tr>
<td>Long-standing persistent, n (%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td><strong>Total duration of AF, median, range, y</strong></td>
<td>8 (1–25)</td>
</tr>
<tr>
<td><strong>Previous AAD use, n (%)</strong></td>
<td>31 (100%)</td>
</tr>
<tr>
<td><strong>No. of previous AAD</strong></td>
<td>4 (1–6)</td>
</tr>
<tr>
<td><strong>Previous catheter PVI, n (%)</strong></td>
<td>14 (45%)</td>
</tr>
<tr>
<td>Paroxysmal, n (%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Persistent, n (%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Long-standing persistent, n (%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Previous atrial flutter ablation, n (%)</strong></td>
<td>4 (13%)</td>
</tr>
<tr>
<td><strong>CHADS² score, mean±SD</strong></td>
<td>0.5 ± 0.6</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>10 (32%)</td>
</tr>
<tr>
<td><strong>Age &gt;75 y, n (%)</strong></td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>TIA, n (%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Thromboembolic event, n (%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Other cardiovascular disease, n (%)</strong></td>
<td>31 (10%)</td>
</tr>
<tr>
<td>Myocarditis, n (%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Brugada syndrome, n (%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>Medication at inclusion</strong></td>
<td></td>
</tr>
<tr>
<td>ASA, n (%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Oral anticoagulation, n (%)</td>
<td>30 (97%)</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>ACE-I/ARB, n (%)</td>
<td>14 (45%)</td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>13 (42%)</td>
</tr>
<tr>
<td>Amiodarone, n (%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Diltiazem, verapamil, n (%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>30 (10%)</td>
</tr>
<tr>
<td>Dypyramide, n (%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Flecaïnide, n (%)</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>Sotalol, n (%)</td>
<td>8 (26%)</td>
</tr>
<tr>
<td><strong>Echocardiographic finding</strong></td>
<td></td>
</tr>
<tr>
<td>Left atrial size, parasternal, long axis, mean±SD (mm)</td>
<td>47 ± 7</td>
</tr>
<tr>
<td>LAA thrombus, n (%)</td>
<td>0 (52%)</td>
</tr>
</tbody>
</table>

*Echo available in 30 patients

TIA indicates transient ischemic attack; ASA, acetylsalicylic acid; ACE-I, angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.
Procedure and Admission Details

Median procedure time was 191 minutes (IQR, 53; range, 136 to 355) in patients in whom no ALAL were made, compared with 217 minutes (IQR, 110; range, 166 to 540) in procedures with ALAL (median time of all procedures, 205 minutes; IQR, 78). No vagal response could be evoked using high-frequency stimulation after GP ablation in all patients. One patient refused GP ablation and thus GP ablation was not performed in this patient. PVs were successfully isolated in all patients. In 12 patients, the number of radiofrequency applications was counted. Isolation of the right and left PV required additional radio-frequency applications in 4 of 12 and 7 of 12, respectively (up to 4 times). The total number of radiofrequency applications ranged from 3 to 14. Thirteen patients with persistent AF and LSPAF received ALAL. In 2 patients with persistent AF, no additional ablation lines were made because of anatomic restrictions in one, and the inadvertent presumption of paroxysmal AF in another patient. In 29 of 31 (94%) patients, the LAA could successfully be stapled and removed; in 2 patients, the LAA could not be removed because of bleeding during the procedure. Median hospital stay was 6 days (IQR, 3; range, 4 to 12). Average chest drain duration was 2 days (IQR, 0; range, 1 to 6).

Procedure and admission details are shown in Table 2.

Table 2. Procedure and admission details

<table>
<thead>
<tr>
<th>Minimal Invasive Surgery (n = 31)</th>
<th>Procedure time, median, range, min (205 (136-540))</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP ablation, n (%)</td>
<td>30 (97%)</td>
</tr>
<tr>
<td>ALAL, n (%)</td>
<td>13 (45%)</td>
</tr>
<tr>
<td>Superior line, n (%)</td>
<td>13 (39%)</td>
</tr>
<tr>
<td>Trigone line, n (%)</td>
<td>13 (39%)</td>
</tr>
<tr>
<td>Inferior line, n (%)</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>LAA removed, n (%)</td>
<td>29 (94%)</td>
</tr>
<tr>
<td>Conversion to sternotomy, n (%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Duration of pleural drainage, median, range, d (2 (2-6))</td>
<td></td>
</tr>
<tr>
<td>AF on discharge, n (%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>ECV during hospital stay, n (%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Duration of hospital stay, median, range, d (6 (4-12))</td>
<td></td>
</tr>
<tr>
<td>Discharge with AAD, n (%)</td>
<td>29 (94%)</td>
</tr>
</tbody>
</table>

Follow-Up

Median follow-up was 375 days (IQR, 285; range, 104 to 730). Twenty-two patients (71%) had a follow-up of 1 year or more. During the first 3 months after the procedure, blanked for the analysis of recurrence of AF, 9 (30%) patients received an ECV and 3 (10%) patients received 2 or more ECV. ECV was performed in 4 (13%) patients after the first follow-up visit. One patient (No. 5) was categorized as late responder after receiving an ECV 115 days after the procedure. He remained in sinus rhythm since. Figure 3 illustrates the freedom from AF.
in a Kaplan–Meier plot. Figure 4 shows the duration of follow-up and recurrences of AF in individual patients.

Figure 3. Kaplan–Meier curve representing the percentage estimates of patients with freedom from AF, atrial flutter, and atrial tachycardia up to 2 years after surgery. The number of patients free from recurrence, total patients, and total patients specified by type of AF are shown at the bottom of the figure. AF: atrial fibrillation.

Figure 4. Individual patient time line: Individual patient follow-up including ECVs and blanking period. In this figure, individual follow-up and all recurrences of AF (light gray) are plotted. Bars indicate the total numbers of days since the procedure. Patients with recurrences of AF, atrial flutter, or atrial tachycardia are indicated with an “F.” ECVs are marked with a star (★) on the individual patient bars. Patients with persistent AF have a box (□) around their number, and patients with long-standing persistent AF have a circle (○) around their number. AF: atrial fibrillation, ECV: electrical cardioversion.
First Results of a Hybrid Surgical-Electrophysiological Approach

End Points
A total of 19 of 22 patients (86%) reached the primary end point (11/12 paroxysmal AF, 7/9 persistent AF, and 1/1 LSP AF). These patients were free from AF, atrial flutter, or atrial tachycardia without the use of AAD at 1 year of the procedure. Table 3 elaborates on the 3 patients who did not meet the primary end point.

The secondary end point was reached by 26 of 31 (84%) patients (14/16 paroxysmal AF, 10/13 persistent AF, and 2/2 LSP AF). Of these patients, 16 of 31 (52%) patients discontinued oral anticoagulants. Patients without oral anticoagulants were followed for a median of 636 days (IQR, 180; range, 305 to 730), compared with 325 days (IQR, 90; range, 180 to 469) of follow-up for patients with oral anticoagulants (excluding failed patients). Note that most patients still taking anticoagulants were the patients with the shorter follow-up. In the 5 patients who did not reach the secondary end point, 4 had recurrences and 1 patient required AAD at individual follow-up (Table 3).

Table 3. Patients not reaching end Points

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Type of AF</th>
<th>Recurrence (Days After Type of AF Procedure)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who did not reach primary end point (n 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Paroxysmal</td>
<td>. . .</td>
<td>No recurrences but on AAD at 1-y follow-up (discontinued 492 d after procedure)</td>
</tr>
<tr>
<td>4</td>
<td>Persistent</td>
<td>0</td>
<td>Never attained sinus rhythm Inadvertently no ALAL in persistent AF Redo catheter ablation unsuccessful</td>
</tr>
<tr>
<td>21</td>
<td>Persistent</td>
<td>170</td>
<td>Multiple episodes of AF and atrial tachycardia Brugada syndrome</td>
</tr>
<tr>
<td>Patients who did not reach secondary end point (n 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Paroxysmal</td>
<td>528</td>
<td>One episode of AF of 56 min on Holter</td>
</tr>
<tr>
<td>29</td>
<td>Persistent</td>
<td>115</td>
<td>Multiple episodes of AF and atrial tachycardia</td>
</tr>
</tbody>
</table>
Adverse Events

During the procedures, 3 patients had a sternotomy because of bleeding that could not be controlled with thoracoscopic surgery (2 left atrial bleedings and 1 bleeding from the aorta). We suspect that the sternotomies might have been related to the learning curve of the procedure because this occurred in patients 3, 7, and 19. One patient had a haemothorax resulting from bleeding from the entrance of one of the thoracoscopic ports. There were 3 minor events; during admission, 1 patient had a pneumothorax after removal of the chest drains. Two patients had a pneumonia successfully treated with antibiotic therapy. The MRIs made after 6-month follow-up showed no signs of PV stenosis in any patient. No thromboembolic complications or deaths occurred.

Discussion

In this report, we describe our first experiences with a hybrid approach of thoracoscopic PVI and GP ablation and LAA exclusion for AF. The percentage of patients free from AF and not using AAD after 1 year was 86%. Even with the small number of patients that we report here, these results make this technique a promising approach to the treatment of AF. In our view, the collaboration between surgeon and cardiologist is beneficial to the outcome of the procedure. Potentially, the high single procedure success rate described in this report may be a cost-effective treatment for AF. However, further studies are needed to elucidate this issue.

Electrophysiological Measurements of PVI and ALAL

There are various reports on minimally invasive or thoracoscopic ablation of the PVs. Our approach differs from those reports because we made the electrophysiological confirmation of the ablation the mainstay of the treatment. Frequently, the surgeon had to repeat the ablations because initial ablation did not result in conduction block. We cannot exclude that the increased number of radiofrequency applications rather than the electrophysiological evaluation is responsible for the success of the procedure. However, this matter can only be solved by demonstrating isolation or conduction block. Because of the anatomic aspect of the PVs and the shape of the bipolar radiofrequency clamp, certain areas are more likely to show conduction of atrial activity. These areas comprise the confluens where the PVs join and the superior side of the superior and inferior side of the inferior PVs. In addition to this, the success of radiofrequency application might further be increased by dissection of the epicardial fat surrounding the PV antrum.

It is thought that only PVI is not enough to maintain sinus rhythm in patients with persistent or long-standing persistent AF. There are few data that show which surgical lesions are easy reproducible, safe, and actually benefit the patient and prevent reentry tachycardias or modify
First Results of a Hybrid Surgical-Electrophysiological Approach

the AF substrate.\textsuperscript{(11,14,15)} We use a series of left atrial lines adapted from Edgerton et al.\textsuperscript{(14)} We chose an epicardial approach for confirmation of the ablation lines. Potentially, complications related to additional left atrial catheter-based ablation such as stroke (related to transseptal puncture) and bleeding as a result of full heparinization can be prevented. We think that conduction block, preferably bidirectional conduction block, must be proven. The nature of the procedure, that is, the fact that half of the procedure is carried out from the right side with the right lung collapsed and the other half from the left side with the left lung collapsed, makes a rigid protocol necessary. That is, the right side of the SL and the TL must be completed and confirmed before the additional lines from the left side can be made. Therefore, we accept proof of unidirectional block. Of course we realize that this potentially leaves an arrhythmogenic substrate, but from our follow-up data thus far, this does not seem to play a major role.

Speculations on efficacy of PVI and ALAL in LSPAF would be premature because there were only 2 patients with LSPAF. These patients did not deviate from the rest of the cohort during follow-up.

\textbf{GP Ablation}

With epicardial ablation during thoracoscopic surgery, the fat pads in which the GPs reside can be selectively targeted. There are both experimental\textsuperscript{(16,17)} and clinical\textsuperscript{(18,19)} data showing that autonomic modulation or partial innervation contributes to the success of treating AF. Indeed, a vagal response occurring during catheter ablation of AF was associated with a higher success rate of the procedure.\textsuperscript{(19)} Additionally, the targeted approach of complex fractionated atrial electrograms, a marker of GP activity, has yielded success as a standalone intervention.\textsuperscript{(20)} However, complex fractionated atrial electrograms are a result of multiple causes and do not always correspond that well with the location of the GPs.\textsuperscript{(21)} By ablation of the GPs in addition to PVI, we thus target multiple arrhythmogenic causes of AF. It is unclear how much the GPs affect the PVs once there is a solid PVI. In animal models in which only GPs were ablated, return of GP activity was observed 4 weeks after the procedure.\textsuperscript{(22)} However, ablation of the GPs presumably destructs not only the nerve endings but also the cell bodies. This might potentially prevent the complete recovery and function of the GPs. One might speculate that the favorable results on medium term (>1 year) that we present here are at least in part due to this lack of reinnervation, but without data supporting this hypothesis, this remains a speculation. One might also speculate that even if the effect of GP ablation is temporary, the absence of GP activity during the first few weeks after the procedure affects electrophysiological remodeling and thereby adds to freedom from AF.

\textbf{Limitations}

It cannot be excluded that event monitoring more extensive than serial 24-hour Holter electrograms or the implantation of loop monitor would capture episodes of AF not
documented with our procedure\(^{(22)}\) In a small, nonrandomized, observational study setting, it is hard to justify an invasive rhythm monitoring device. We are confident however, that most asymptomatic episodes come to our attention with our current follow-up protocol.

We report in this article the first patients who underwent this procedure in our institution. The procedure protocol was refined over time. Extensive measurement, GP ablation, and PVI ablation remained unchanged, but the types of lines made in the ALAL varied over the course of time. Because the treatment of AF comprises an elective procedure for a nonlethal condition, we let surgical considerations on safety of the patient always prevail over electrophysiological completeness. Because 45% of the patients reported here underwent a previous catheter ablation for AF, it cannot be excluded that this favorably influenced our results. However, all patients had documented recurrences of AF before being enrolled in this study. Moreover, the PVs were not isolated in any of these patients (data not shown). Therefore, we cannot conclude that previous ablation affected the outcome of the current study.

**Conclusions**

A minimal invasive surgical approach with thoracoscopic video-assisted surgery with PVI and GP ablation for AF is a safe and successful procedure with a single-procedure success rate of 86% at 1 year without the use of AAD. Electrophysiological guided thorough PVI and ALAL creation presumably contribute in achieving a high success rate in the surgical epicardial approach in treatment of AF. Removal of the LAA is an additional advantage compared with the endocardial approach of AF treatment. The contribution of the ALAL and GP ablation in this procedure and their effect on success rate must be evaluated in further studies.
References


11. Lockwood D, Nakagawa H, Peyton MD, Edgerton JR, Scherlag BJ, Sivaram CA, Po SS, Beckman KJ, Abedin M, Jackman WM. Linear left atrial lesions in minimally invasive surgical ablation of
Chapter 3


CHAPTER 4

Epicardial confirmation of conduction block during thoracoscopic surgery for atrial fibrillation - a hybrid surgical-electrophysiological approach

Joris R. de Groot
Antoine H.G. Driessen
Wim J. van Boven
Sébastien P.J. Krul
André C. Linnenbank
Warren M. Jackman
Jacques M.T. de Bakker

Minim Invasive Ther Allied Technol. 2012 Jul;21(4):293-301
Abstract

Background:
Totally thoracoscopic epicardial pulmonary vein ablation is an emerging treatment of atrial fibrillation (AF). A hybrid surgical-electrophysiological procedure with periprocedural confirmation of conduction block might reduce recurrences of AF or atrial tachycardia and improve surgical success.

Methods and results:
We report our joint surgical-electrophysiological approach for confirmation of conduction block across pulmonary vein ablation lines and those compartmentalizing the left atrium during totally thoracoscopic surgery. A diagnostic electrophysiology (EP) catheter positioned under the left atrium is used as reference and a custom-made multi-electrode for recording. Determination of conduction block across the pulmonary vein (PV) ablation lines requires measurement of activation time differences of milliseconds. Second, a stable reference electrogram to which to relate local activation time is required. Third, the recording electrode terminals and the inter-electrode distance should be small to prevent recording of far field activity and to allow recording of very small electrograms. We confirm entry and exit block and determine conduction block across linear ablation lines with differential pacing.

Conclusion:
A joint surgical-electrophysiological protocol for confirmation of conduction block across PV isolation lines and left atrial ablation lines is feasible and might prevent recurrences and further improve the success of minimally invasive surgery for AF.
Chapter 4

Introduction

Epicardial radiofrequency (RF) ablation for isolation of the pulmonary vein antrum (PVI) using minimally invasive or totally thoracoscopic surgery is a recent development in the attempt to restore sinus rhythm in patients with paroxysmal and persistent atrial fibrillation (AF). The aim is to combine the success of surgical treatment of AF (in particular the Cox-Maze III) with a less invasive approach. Studies on minimally invasive surgery for AF report a success rate (defined as freedom from AF at one year with or without the use of antiarrhythmic drugs) of between 65 and 87% (averaging 93% in paroxysmal and 71% in persistent atrial fibrillation). The lower success rate in persistent AF might be attributed to greater structural remodeling (including fibrosis and scar) compared to patients with paroxysmal atrial fibrillation. An alternative explanation is that (several) ablation lesions are not transmural, and that conduction block is not achieved or maintained. Incomplete ablation lesions carry the risk of introducing a new arrhythmogenic substrate: Gaps in the lesions, allowing conduction, may facilitate the reentry that they are designed to prevent.

Indeed, a 40% incidence of atrial tachyarrhythmia’s after minimally invasive surgery for AF, mostly associated with reconnection of the pulmonary veins (PVs) has been described. Reconnection of the PVs to the atrium was also frequently found in patients with recurrent AF after totally thoracoscopic surgery. Simply applying RF energy does not guarantee conduction block. From our own experience, acute isolation during totally thoracoscopic PVI requires >3 RF applications in the majority of patients. Similarly, the creation of conduction block across left atrial lines requires several series of ablation attempts. Because of the relationship with recurrences of AF or atrial tachycardia and conduction across ablation lines it is important to verify the presence of conduction block across all ablation lines. For this, basic understanding of the biophysics of electrograms and electrodes and the periprocedural cooperation of surgeon and electrophysiologist might be mandatory. Indeed, there is a trend towards more hybrid approaches of AF treatment where surgeon and cardiologist/electrophysiologist combine their efforts to treat the patient optimally. We recently published our first results with a totally epicardial approach resulting in 86% freedom of AF after one year in patients with paroxysmal and persistent AF. Pison and La Meir found similar success rates using a combined epicardial/endocardial procedure (Pison et al. submitted). It appears, therefore, that a hybrid surgical-electrophysiological procedure results in fewer recurrences, and can improve the surgical results. Here, we describe our joint surgical-electrophysiological approach for epicardial confirmation of conduction block across the pulmonary vein (PV) isolation lines and of those that compartmentalize the left atrium in a totally thoracoscopic procedure.
Thoracoscopic surgery for AF

The totally thoracoscopic approach that we use is detailed elsewhere. In short, after double lumen intubation and selective ventilation of one lung, two ports are introduced in the fourth and sixth intercostal space, midaxillary, and one port in the third or fourth intercostal space anterior axillary. Under videoscopy, the pericardium is opened and the PVs exposed. PV ablation is performed with a bipolar radiofrequency clamp (AtriCure Isolator™ Transpolar™ Clamp, AtriCure Inc, Cincinnati, OH, USA) positioned around the PV antrum. Additional linear lesions are made, when appropriate, with a bipolar cool rail and ablation pen (AtriCure Cooltip™). All ablation lesions are controlled for acute conduction block. After completion of the right side of the procedure, the patient is ventilated on the other lung and the left side of the procedure is performed similarly. The ligament of Marshall is divided before left-sided PV isolation. The left atrial appendage is removed upon termination of the procedure.

Determination of conduction block after PV isolation

Failure of atrial activation (either during sinus rhythm or during atrial fibrillation) to reach the pulmonary vein muscle distal to the ablation scar (entry block) can be demonstrated by placing a bipolar electrode with small electrode terminals and small interelectrode spacing closely to and more distant from the ablation scar at the PV side of the scar, while recording differences in timing of the local signal with respect to a reference signal. A signal that is sluggish and has the same timing close to and distant from the scar most likely reflects remote atrial activity and does not represent local activation. A sharp electrogram, which times earlier close to than distant from the ablation line, however, probably reflects propagation of activation and therefore conduction across the ablation line. There are several requirements to this recording procedure. First, it should be possible to measure small differences in local activation time. Since differences in activation time are in the order of magnitude of milliseconds, a recording system that allows the precise determination of activation time with respect to a reference signal is mandatory. This requires a dedicated electrophysiology (EP) recording system as used in clinical EP laboratories or an equivalent system.

Second, there should be a reference signal to refer the timing of the recorded signal to. During sinus rhythm, the peak or beginning of p-wave on the surface ECG can function as reference, although this is imprecise. However, a local atrial signal derived from a reference electrode at a stable position within or on the atrium is more accurate than the surface electrogram. Third, the recording electrode should be small (tenth of millimeters) and the interelectrode distance of the bipolar should be small, too. Small electrodes guarantee recording of local electrical activity, while a small interelectrode distance cancels out a large part of remote electrical activity. It must be possible to move the electrode in small steps to demonstrate that the timing of the remote signal remains the same close to and distant from the ablation line (which proves that the signal is indeed remote and does not represent conduction across the
ablation line). Larger electrodes will record more remote activity and thus make it harder to determine the absence of local activity. The interpretation of electrograms and their timing is complex and time-consuming.

After exposure of the PVs and prior to ablation a standard decapolar diagnostic EP catheter (C. R. Bard Inc, Murray Hill, NJ, USA) is introduced through the oblique sinus and positioned under the left atrial posterior wall. All recordings are made with a custom-made small bipolar electrode composed of seven gold-plated terminals with a diameter of 0.2 mm and an interelectrode distance of 1 mm (Figure 1).

Figure 1. Multi electrode.
Seven-polar gold multi-electrode, custom-made for determination of conduction block.

The signals are fed into a mobile electrophysiological workstation (Bard Labsystem PRO 2.4A, C. R. Bard Inc, Murray Hill, NJ, USA). Figure 2 shows electrograms of the right pulmonary veins in a patient who had no previous ablations. Figure 2A shows the posterior side of the heart. We measure standard at seven positions (Figure 2B): Superior side of the superior vein, anterior side of the superior vein, inferior side of the superior vein, confluence where both PVs join together, superior side of the inferior vein, anterior side of the inferior vein and inferior side of the inferior vein. Figure 2B shows that with the isolation confirmation protocol as described here, no signals from the posterior side of the PVs are recorded. Although it is technically possible to position the seven-polar multi-electrode under the PVs, we think that this is potentially dangerous and can cause bleeding. Since there is no visible control, it is not possible to position the electrode closely to the ablation scar. Electrograms of the reference (Ref.) and the recording (Diag.) electrode with the latter positioned on the right PVs (asterisk) before and after ablation are shown in Figure 2C and 2D. Note that remote (atrial) activity in the Diag. electro- grams is absent (panel C). No local electrograms are recorded after ablation (panel D), indicating conduction block from atrium to the right pulmonary veins. This proves entry block. Figure 3 shows a recording of the right superior pulmonary vein (RSPV) in a patient who underwent two failed catheter ablations. Figure 3A shows the posterior aspect of the left atrium with the superior and trigone line. Small but distinct potentials are still present in the PV antrum (Figure 3B, Diag. tracings). To illustrate the importance of small and closely spaced electrodes, Figure 3C shows a recording of the same position on the RSPV in the same
Epicardial confirmation of conduction block, a hybrid approach

patient, now made with the large electrodes of an ablation pen. The local activation cannot be discriminated.

After demonstration of entry block, we pace the PV antrum with maximal pacemaker output (25 mA) to demonstrate exit block. To be able to capture the atrium, sinus rhythm needs to be present; hence AF (if present) is cardioverted. Failure to capture the atrium with maximal pacemaker output proves exit block.

![Figure 2. Anatomic mapping sites on atrium](image)

(A) Posterior view of the heart. AO = aorta, LA = left atrium, RA = right atrium, LV = left ventricle, RV = right ventricle. (B) Anterior view of the right pulmonary veins. Above: Waterstone’s groove and right atrium. VCS = Superior caval vein, VCI = inferior caval vein. Circles indicate the standard positions from where conduction block across the PV isolation line is confirmed. 1: superior side RSPV, 2: anterior side RSPV, 3: inferior side RSPV, 4: confluens between RSPV and RIPV, 5: superior side RIPV, 6: anterior side RIPV, 7: inferior side RIPV. (C) Electrograms recorded before ablation from the right inferior pulmonary vein in a patient without previous ablations. Displayed are standard ECG lead I and II, consecutive bipolar electrograms from the reference catheter (Ref), and bipolar recordings from the right inferior pulmonary vein (asterisk in panel A) recorded with the custom made electrode (Diag). (D) Absence of electrograms from the right pulmonary veins after ablation.
Figure 3. Activation of the right PV, difference between multi electrode and ablation pen (A) Posterior view of the left atrium. (B) Electrograms from the right superior pulmonary vein (asterisk in panel A) in a patient who had two catheter ablations. Tracings as in Figure 1. Activation of the right pulmonary vein indicates conduction. (C) No clear electrogram from the same location recorded with the large electrodes of the ablation pen.

Determination of conduction block across a linear ablation line, role of local activation time and activation direction

In patients with persistent or longstanding persistent AF, we extend the PV isolation with a superior line that connects the two isolated PV antrum (thereby preventing macroreentry around any PV antrum) and a left fibrous trigone line that connects the superior line to the left fibrous trigone, thereby preventing macroreentry around the composite of both connected PV islands.

The confirmation of bidirectional conduction block across left atrial ablation lines is more intricate and requires differential pacing. We pace from one side of the ablation line and record from the opposite side. When conduction across the line is blocked, activation has to travel around anatomical structures to arrive at the opposite side of the line. Moreover, activation direction is toward the line of block. In case of persistent conduction across the ablation line, the opposite side of the line is activated earlier and the activation direction is away from the line. There are reports of small gaps in ablation lines with very long conduction time. Hence, long conduction time does not preclude conduction whereas activation sequence away from the line proves conduction. Determination of activation direction is crucial.

The totally thoracoscopic procedure takes place with the patient being ventilated on the contralateral lung. The right side of the left atrial ablation lines needs to be complete and confirmed before starting the procedure on the left side. It is very unattractive and prolongs the procedure time when incomplete lines cause revision of the right side.
We make the right side of the superior line and the entire trigone line from the right side. This results in a closed corridor, limited by the trigone line, the right side of the superior line and the ablation encircling the right PVs. We position a small screw electrode (Medtronic 6416 temporary transvenous pacemaker lead, Medtronic Inc. Minneapolis, MN, USA) within this corridor from which we pace at approximately 120% of the sinus rate. In patients who are in AF we first cardioverted electrically, if necessary during (temporary) ventilation of both lungs. To avoid anodal stimulation (interelectrode distance 2 cm, and the anode might touch the right atrium or the left atrium at an unwanted location) we pace unipolarly with the cathode screwed in the atrial myocardium and the anode sutured in the skin. We record activation time directly inferior and distant to the superior line. We repeat these measurements close to the PVs, mid superior line and at the merge of the superior line and the trigone line.

Figure 4 demonstrates conduction block across the superior line. Figure 4A shows the posterior side of the left atrium. The myocardium is paced from superior of the line, and measurement of activation times shows that activation reaches point B, distant from the line 108 ms after the pacing artefact (Figure 4B) and point C more close to the line after 135 ms (Figure 4C). This demonstrates that activation propagates toward the line and confirms conduction block across the line.

Figure 4. roofline: activation pattern indicating block
(A) Posterior view of the left atrium. Indicated are left atrial ablation lines. Pacing from above the superior line, rightward from the trigone line. The red arrow shows the course of activation when conduction across the superior line is blocked. (B) Electrograms as in Figure 1. Local activation time is 108 ms (recorded from point B in panel A). (C) Activation time closer to the superior line is 135 ms (recorded from position C in panel A), proving that activation propagates toward the superior line and strongly suggesting conduction block.
Similarly, we record activation time close to the trigone line and more leftward from the trigone line. We repeat this at the level of the aorta and at the merge of the trigone line and the superior line. Figure 5 shows the confirmation of conduction block across the trigone line, once the right side of the procedure is completed. Figure 5A shows the posterior side of the left atrium, the location from where the pacing is performed, and the direction of propagation of activation. Activation arrives earlier at site C away from the line (Figure 5C, 200 ms), then at site B close to the line (Figure 5B, 214 ms). Note that in Figure 5B also the activation at the pacing side of the line is recorded, here with 45 ms delay with respect to the pacing stimulus, which indicates that the recording electrode is positioned on the line.

After completing this part of the procedure, ports at the right side of the chest are closed, three new ones are made at the left side and the left PVs are isolated as described above. Then the superior line is completed from the left. We confirm conduction block across the now intact superior line by pacing from above the line and recording directly inferior and more distantly inferior from the line. Again, activation propagating toward the line at the opposite side of where we pace from confirms conduction block.

**Figure 5. trigoneline: activation pattern suggesting block**

(A) Posterior view of the left atrium. Indicated are the right side of the superior line and the trigone line. Pacing from above the superior line, rightward from the trigone line. (B) recording electrode placed on or very close to the trigone line. Proximal activation time is 45 ms, at the distal side of the line 214 ms. (C) Activation time more leftward is 200 ms, proving that activation propagates from left to right toward the trigone line strongly suggesting conduction block. Asterisk: far field ventricle.
Epicardial confirmation of conduction block, a hybrid approach

Analysis of bipolar and unipolar electrograms

A unipolar electrogram is the potential difference between the local electrode and a reference electrode (theoretically placed at an infinite distance). A bipolar electrogram is the potential difference between two closely spaced electrodes. Both modes of recording allow determination of activation time, but the disadvantage of bipolar recordings is that they are activation direction dependent, and frequently fractionated. This complicates the determination of local activation time. In a bipolar signal, remote activity is recorded by both electrode terminals and because the signals are fed into a differential amplifier, they will cancel out. Indeed, smaller interelectrode distance in permanent atrial pacing leads correlates with the reduction of far field sensing by pacemakers. The same accounts for the recording of electrical noise (50 Hz interference): Because both electrode terminals pick up the same amount of noise, the majority of this is cancelled out in the bipolar electrogram.

In contrast to bipolar electrograms the interpretation of unipolar electrograms is straightforward, but more sensitive to interference and far-field potentials. Because the local recording electrode and the distant reference electrode record different remote potentials there is no cancellation and the far field remains visible. A prominent remote potential might hinder correct determination of local activation time and interfere with the determination of conduction block. The simultaneous display of both unipolar and bipolar electrograms can be useful for interpretation of persistent conduction, particularly because bipolar signals might be very small (Figure 3B). Activation of scarred myocardium results in complex and fractioned electrograms. The interpretation of those was recently reviewed by De Bakker and Wittkampf.

Electrode composition

An ideal recording electrode should record electro- grams and activation direction. Normal conduction velocity in the heart is approximately 80–100 cm/s, resulting in local activation time differences across a distance of 1 mm of 1 to 1,25 msec. It requires high sample rates (several kHz) and closely spaced bipoles to record electrograms with enough resolution to reliably detect such differences.

We use a seven-polar gold multi electrode where six of the electrodes are positioned around a central electrode (Figure 1, electrode diameter 0,1 mm, inter electrode distance 1 mm). This allows recording of seven unipolar electrograms and the choice from many bipolar electrograms (Figure 2 and 3). Recording with a larger, 48-polar multi-electrode (6 x 8 rows) with similar electrode diameter and interelectrode distance allows the online production of activation maps that demonstrate activation direction. The drawing of activation maps currently takes several minutes which makes it less suitable for all recordings in the operation room. An example of an activation map is displayed in Figure 6. Figure 6A shows selected unipolar electrograms from the 48-polar electrode. Figure 6B shows the reconstructed color map indicating the direction
of propagation of activation (from red to blue). Figure 6C shows the activation map on the recording location on the left atrium. Note the fractionated electrograms in this patient which make determination of local activation time troublesome. A considerable number of electrograms is needed to reliably determine activation direction, but the color map shows activation direction at a glance.

Figure 6. 48 multi-electrode, showing activation map
(A) Selected unipolar electrograms recorded with a custom made multielectrode with 48 (6 8) electrode terminals. (B) Activation map of 48 unipolar electrograms. Color scale indicates activation time, from red to purple. The electrograms in panel A correspond to the electrodes at the corners of the multielectrode array. (C) Posterior view of the left atrium, the activation map from panel B is displayed on the recording location. Activation propagates from right to left, proving conduction across the trigone line.

Conclusion

Minimally invasive surgical or totally thoracoscopic ablation of the PV antrum and the creation of additional left atrial lines has emerged as a new strategy to treat paroxysmal and persistent atrial fibrillation. Several series published show promising results of the procedure and intermediate-term follow-up. The nature of the thoracoscopic procedure makes it unattractive to perform redo-procedures, because the access to the heart might be hindered by
the formation of scar and adhesions in the thoracic cavity and the pericardium. It is therefore very important to confirm conduction block across ablation lines around the PVs and within the left atrium during the procedure. Proof of acute conduction block is not equivalent to persistent block, and reconnection of the PVs has been described. Moreover, temporary conduction block can result from the mere mechanical application of the ablation clamp. The presence of residual local electrograms, as small as they may appear, however, proves persistence of conduction.

Hybrid approaches (i.e., close collaboration of surgeon and electrophysiologists during the procedure) have been described with epicardial or endocardial confirmation of PV isolation and conduction block across ablation lines. Data on long-term success of hybrid approaches are limited and, although promising, this approach cannot yet be declared superior to procedures without periprocedural confirmation of conduction block. The large electrode surfaces of bipolar ablation pens that are used in some studies preclude the detection of small potentials and are therefore less suitable for this purpose. In our opinion, and concordant with Stamou et al., this merits the use of small electrodes and the presence of an electrophysiologist with an EP system in the operating theatre during the procedure. Such electrodes are not (yet) commercially available, therefore we manufactured a custom-made recording electrode that is easy to handle for the surgeon.

Reliable confirmation of PV isolation and conduction block across left atrial ablation lines is feasible, under the following conditions. First, there must be a reference signal to relate the activation time of any recorded electrogram to. Second, measurement of differences in activation time of the local electrogram and the reference electrogram should be possible. It is not possible to visually detect differences of only a few milliseconds from a screen which underscores the need for an EP system. Third, the recording electrode should consist of one or more electrode pairs recording multiple unipolar and bipolar electrograms. Electrode terminals should be small and closely spaced to allow measurement of local activation time and limit recording of far field activity. Determination of activation direction is of paramount importance for detection of conduction across left atrial ablation lines. Differential pacing allows detection of conduction block across the line, when local activation time is long and activation is directed toward the ablation line. Small gaps in the ablation line with slow conduction can facilitate the atrial tachycardias they are designed to prevent. Documentation and subsequent ablation of those defects might add to the further success of this procedure.
Chapter 4

References


Epicardial confirmation of conduction block, a hybrid approach


CHAPTER 5

Electrophysiological Evaluation of Thoracoscopic Pulmonary Vein Isolation

Joris R. de Groot
Wouter R. Berger
Sébastien P.J. Krul
Wim Jan van Boven
Sacha P. Salzberg
Antoine H.G. Driessen

Abstract

Although the majority of patients with atrial fibrillation and an indication for non-pharmacological therapy is treated with catheter ablation, thoracoscopic surgery is an emerging technique that aims at combining the results of the classic Cox Maze operation with a less invasive approach. Recurrences after thoracoscopic surgery have been mainly ascribed to incomplete ablation lines, but literature on electrophysiological confirmation of thoracoscopic pulmonary vein isolation is limited.

Currently, surgical confirmation of uni- or bidirectional conduction block may be hampered by insufficient resolution of the mapping material available. Additionally, uncertainty remains on the precise lesions sets required, and how to tailor them to individual patients. In hybrid procedures, electrophysiologists and surgeons join forces to combine their expertise and skills which may lead to increased procedural success rates by minimizing the chance of incomplete PV isolation or absence of conduction block across an alternative ablation line. Here we describe techniques for thoracoscopic mapping and present a literature review.
Chapter 5

**Introduction**

A growing number of patients with atrial fibrillation (AF) is being treated with left atrial catheter ablation. The results of this procedure are favorable in patients with paroxysmal AF but may be modest in persistent or long-standing persistent AF patients.\(^{(1)}\) Moreover, recent publications show that, even in paroxysmal AF, the real-world efficacy of catheter ablation is more modest than expected from the initial randomized studies against antiarrhythmic drugs.\(^{(2-12)}\) Also, multiple procedures are frequently required, and up to 7 ablations were performed in some settings to reach a 5-year efficacy rate of 20-65\%\(^{13,14}\).

The cornerstone of catheter ablation is isolation of the pulmonary veins from which the arrhythmogenic triggers arise.\(^{(15)}\) Historically, the Cox-Maze operation preceded catheter ablation as an invasive treatment modality for AF, but due to complexity and a considerable complication rate including mortality in 1-2\% and a pacemaker implantation rate of up to 7\% of patients, it was never used in a widespread manner. The Cox-Maze 4 operation is an iteration of the originally described Maze operation and constitutes a series of ablation lines to compartmentalize the left and right atrium. The philosophy of that approach lies in the observation that human AF consists of multiple macroreentrant circuits in the left and right atrium, and the linear ablation lines are designed to block all those circuits.\(^{(16)}\) Reported single procedure efficacy of the Cox-Maze operation is excellent, and a freedom of AF in 83\% of patients after 2 years confirmed with modern follow-up techniques has been reported.\(^{(17)}\)

Currently, catheter ablation and also surgical ablation are carried out in an increasing number of centers with a high degree of variability in technique used, volume, and periprocedural confirmation of conduction block.\(^{(18)}\)

In an attempt to combine the efficacy of the Cox-Maze operation with a less invasive approach, Wolf et al described a minimally invasive procedure to isolate the pulmonary veins (PVs) on a beating heart which evolved into a totally thoracoscopic approach.\(^{(19,20)}\) A number of mostly small studies with minimally invasive surgery for AF have recently been reviewed.\(^{(21,22)}\) There is one randomized study comparing catheter with thoracoscopic ablation that shows a twice as high efficacy of surgery at the cost of more procedural complications.\(^{(23)}\) As with catheter ablation of AF, recurrences after thoracoscopic surgery have been ascribed to reconnection of the pulmonary veins or incomplete left atrial lines.\(^{(24-26)}\) This does not imply that all reconnection is indeed responsible for recurrences, as reconnection was demonstrated in AF free patients after ablation as well. Indeed, there was no difference in the number of reconnected veins between patients with and without recurrences of AF\(^{(27,28)}\) and recently it was shown that the vast majority of patients with a complete PVI in the GAP-AF trial had reconnected PVs. However, a number of recurrences relate to iatrogenic substrates and potentially could have been prevented.\(^{(25,26)}\) Indeed, the creation of transmural ablation lesions on a beating heart may be cumbersome due to heat sink of the circulating blood, despite the various energy sources that have been deployed.\(^{(29,30)}\)
Electrophysiological Evaluation of Thoracoscopic Pulmonary Vein Isolation

Therefore, hybrid approaches have been undertaken where electrophysiologists are an integral part of the operation, carrying out mapping and additional ablation either endocardially within the left atrium or epicardially.(31-38) Such procedures, in which surgeons and electrophysiologists join forces to combine their knowledge and skills may increase procedural success rate by minimizing the chance of incomplete PV isolation or absence of conduction block across an additional ablation line. There are no head-to-head comparisons of electrophysiologically guided surgery versus non-hybrid surgery, but the reported results of hybrid approaches, although based on a limited number of small studies, are promising.(31-38) Importantly, electrophysiological guidance of surgical ablation appears not to affect the complication rate of the surgical procedure. In this contribution we will focus on techniques and feasibility of electrophysiological evaluation pulmonary vein isolation during or after thoracoscopic surgery for AF and outline where the electrophysiologist can complement surgery for AF.

**Definition of Endpoints**

In the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Electrophysiology Society (HRS/ EHRA/ECAS) consensus statement, updated in 2012 procedural success is defined as: freedom of atrial fibrillation and any left or right atrial arrhythmia lasting longer than 30 seconds at one year after the procedure and without the use of antiarrhythmic drugs.(39) The minimum monitoring strategy consists of 24-hour Holters every 6 months, and the first 3 months are considered a blanking period. Consequently, patients without AF recurrence but still using antiarrhythmic medication, who may have improved clinically, are classified as failures by definition.

Procedural endpoints are PV isolation, demonstrated by entry block (the inability of an LA impulse to reach the PV muscle) and/or exit block (the inability of a PV potential to reach the LA). Duytschaever et al. reported, using spontaneous PV ectopy after PV isolation, that absence of exit block in the presence of entry block is rare.(40) However, entry block in specific cases may not be equivalent to exit block (A. Bulava, personal communication). Mapping and pacing maneuvers are recommended by the HRS/EHRA/ECAS consensus document to demonstrate bidirectional block across left atrial ablation lines. Finally, we define hybrid procedures as undertaken jointly by surgeons and electrophysiologist. Staged hybrid approaches, where a catheter procedure follows the surgery days to months later, are included in this definition as long as the procedure was performed in all patients undergoing the index procedure. When the endocardial part of the treatment is only employed in patients with AF recurrence this, in our opinion, should be coined a re-do procedure.
Clinical Studies

The literature on electrophysiological evaluation of thoracoscopic PVI is limited. There are only three studies available in the literature where the investigators both organized the follow up and report their results according to the HRS consensus document.\(^{(32-34)}\) Krul et al. describe the initial experience with an entirely epicardial procedure.\(^{(32)}\) Thirty-one patients (median duration of AF was 8 (1-25) years) were treated with thoracoscopic PVI using the AtriCure bipolar system when AF was paroxysmal. Patients with persistent or long standing persistent AF were treated with PVI plus the addition of a superior line, connecting both isolated PV islands at the level of the superior PVs, an inferior line connecting the PV islands at the level of the inferior PVs, and a trigone line connecting the superior line to the left fibrous trigone at the level of the aortic annulus, functioning as a mitral isthmus line.\(^{(41)}\) Conduction block was assessed epicardially across all ablation lines and one year follow-up was available for 22 patients and freedom of AF was present in 86%. Pison et al. describe their experience using a hybrid epicardial-endocardial approach in 26 patients (AF duration 5.6±6.6 years, 42% persistent AF).\(^{(33)}\) The procedures were carried out in one session, surgery was performed with the bipolar AtriCure system and gaps in ablation lines were ablated with standard catheter techniques. Pison et al. use a stepwise approach guiding the addition of left atrial lines dependent on AF conversion during the procedure rather than on AF type.\(^{(33)}\) Sequentially a roof line and inferior line are performed, with a mitral isthmus or cavotricuspid isthmus line in patients with left or right isthmus dependent flutters respectively. After one year, freedom of AF was 83%. Finally, Zembala et al. describe their experience in 27 patients (5 persistent AF, 22 long standing persistent AF), with AF for 3.5±2.5 years undergoing a staged hybrid approach in 21 patients where the catheter treatment followed epicardial ablation with the unipolar nContact system (Visitrax).\(^{(34)}\) One year follow up was available in 10 patients and amounted 80%. Interestingly, complications reported in these papers related to the surgical procedure and not to the electrophysiological procedures, suggesting that electrophysiological guidance of the procedure can be performed safely. Other authors organize the follow-up according to the HRS consensus document but do not report one year results, making comparison impossible. In general, the results are in line with the data reported above.\(^{(31,35-38)}\) It should be noted, however, that more rigorous monitoring for AF recurrences, for example with implantable loop recorders, will undeniably result in the detection of more recurrences, and therefore with a decreased success rate as defined by the HRS/EHRA/ECAS consensus document.\(^{(39,42)}\)
Electrophysiological Evaluation of Thoracoscopic Pulmonary Vein Isolation

Mechanism of Arrhythmia Recurrence After Surgical Ablation

Role of Pulmonary Veins

Many studies on redo procedures demonstrate that re-connection of the pulmonary veins is a general finding, and that reablation may result in freedom of AF. Otherwise, studies also demonstrated reconnection of the pulmonary veins in patients who were completely free of AF after the index procedure.(27,43) Periprocedural isolation of the PVs after ablation may be merely an acute phenomenon, and conduction between the PVs and the left atrial myocardium may restore with healing of the tissue. Acute injury induced block by applying the ablation clamp without applying RF energy has been demonstrated in thoracoscopic surgery for AF.(44) The mechanism of acute but not chronic PV isolation may relate to residual intercellular coupling of damaged cells to principally viable myocytes resulting in depolarization and inexcitability of the latter. This mechanism is consistent with the action of adenosine, which hyperpolarizes myocytes and may restore conduction.(43)

Despite measures taken in an attempt to separate acute from chronic conduction block, the ultimate result of the procedure is whether or not AF recurs and whether the PVs are connected or not at the redo procedure. Still, confirming conduction block is the best and only available measure to take to confirm that PV isolation, at least during the surgical procedure. Demonstrating conduction block is furthermore essential in thoracoscopic AF ablation because thoracoscopic access to the heart may become extremely complicated, although not impossible if performed early, once pleural and pericardial adhesions have been formed after the index procedure.(45) Hence, contrary to catheter ablation, where reentering the left atrium after failure of the previous ablation is feasible and safe, this is not the case in thoracoscopic surgery.

Role of Additional Left Atrial Lines

In persistent or long standing persistent AF, the left atrium might be already remodelled to such an extent that pulmonary vein isolation alone does not suffice, and additional ablation lines may be needed. In paroxysmal atrial fibrillation usually PVI is a sufficient treatment. This is relevant because the chance of incomplete lines increases with the number of lines. Mun et al. performed a study comprising 156 patients with paroxysmal AF, randomized to circumferential PV isolation, circumferential PV isolation plus a roof line, or circumferential PV isolation plus a roof and inferior line (posterior box lesion). The rate of bidirectional block across all lines was 100, 80.8, and 59.6% respectively and after 15.6±5.0 months, Arrhythmias recurred in 11.5, 21.2 and 19.2% respectively, supporting the notion that more lines are not per se better in paroxysmal AF and suggesting a relation between the rate of bidirectional block and the chance of recurrence.(46)
Lockwood et al. described 14 patients in whom, after application of minimally invasive surgery for AF employing the Dallas lesion set, gaps were found in the roof line or trigone line. In fact, after the initial surgical procedure, only 21% of lines were complete. After ablation of the gaps they identified, there was a 50% freedom of AF/AT after a mean follow up of 8 months. Kron et al. investigated the mechanism of arrhythmia recurrence in 13 patients. They demonstrate that up to 40% of patients experience recurrent AT, and that 50% of the pulmonary veins studied were reconnected. Additional ablation was limited to the PVs in only three patients and included more extensive left atrial ablation in the others. Liu et al reported the occurrence of atrial tachycardias in 8 patients after thoracoscopic surgery. They also show that there are gaps in the PV isolation lines in those patients, but demonstrate that these are not responsible for arrhythmia recurrence. Conversely, they demonstrate that macroreentrant arrhythmias relate to clamp associated or LAA excision associated scarring. The important implication of these findings is that there is an important iatrogenic component in arrhythmia recurrence, that may be prevented using electrophysiological confirmation of ablation lines. Furthermore, note that these authors studied patients with recurrences and that their findings can therefore not be extrapolated to all patients undergoing thoracoscopic surgery for AF.

**Role of the Left Atrial Appendage**

It has been demonstrated before that 27% of patients undergoing a redo catheter ablation for AF recurrence have triggers from the LAA. Excision of the LAA potentially results in reduction of the stroke risk, and certainly eliminates arrhythmogenic triggers arising from the LAA. Recent data from long term follow-up of the PROTECT AF trial (LAA closure with the Watchman device versus warfarin in patients with non valvular AF) confirm non-inferiority of LAA closure to warfarin treatment. Although the clinical benefit in relation to potential risks of this procedure has not yet been established unequivocally, and although there are no solid data showing that there is no more need for anticoagulation once the LAA is removed, the option of LAA resection may be an advantage of thoracoscopic surgery over catheter ablation.

**Other Mechanisms of AF Recurrence**

Several mechanisms other than incomplete lines have been implicated in the mechanism of AF, and may therefore contribute to recurrence after invasive therapy. Nishida et al demonstrated in a chronic heart failure model of AF in the dog that ablation of the ganglionic plexi is more important than PVI. Similarly, Nadamanee et al have to be credited for bringing the role of continuous fractionated atrial electrograms (CFAE) to our attention as a mechanism of AF perpetuance. Recently, ablation of rotors with use of the TOPOERA system has been forwarded as an important contributor to the mechanism of AF. These considerations that may affect AF recurrence, are however, outside the scope of this review.
Practical Limitations of Surgical Confirmation of Conduction Block

Many surgical procedures consist of or contain a posterior box lesion. This is a circular lesion, encompassing both left and right pulmonary veins and the posterior wall of the left atrium. This lesion set can also be produced by connecting the pulmonary vein isolation islands with a superior and inferior line. Completeness of the box is confirmed by demonstrating exit block while pacing from within the box. Considering that, in general, surgical ablation tools are optimized for surgical ablation, and have too large electrode surfaces for electrophysiological testing, this approach comes with both technical and conceptual shortcomings. Figure 1A shows the concept of pacing from the box: a pacing stimulus is delivered somewhere central in the box, and activation propagates in all directions until it is blocked by the ablation lines. Crucial in this concept is that there is local capture of homogeneously conducting atrial myocardium within the box. Figure 1B displays a more real world situation, where ablation line width is not one millimeter, but more in the range of one or more centimeters. This results potentially in a very small central viable tissue island that needs to be captured by the pacing electrode. Consequently, while pacing the scar without capturing the central viable tissue island, conduction block may be inadvertently assumed. Alternatively, the output of the pacemaker is set so high that remote capture of one or few connection channels in the proximity of the box are captured, suggesting that there is residual conduction. Further ablation encompassing those channels may inadvertently lead to the conclusion that the line constitutes conduction block, whereas potentially, the output of the pacemaker is insufficient to remotely capture an even more distant reconnecting channel. This is underscored by the fact that patients can be paced transcutaneous in emergency settings, demonstrating that when the output of the pacemaker is sufficient, the entire heart can be captured, despite the presence of any local conduction block (for example at the level of the AV node). Therefore, when relying on pacing from the box, not pacemaker output but local capture is crucial. Without confirmation of local capture, preferably in combination with direct visualization of the site where is paced from, the risk of pacing non-viable tissue is considerable. Clinically important leaks or channels that remain within the ablation line, can very well be arrhythmogenic during further follow-up. Figure 1C demonstrates this concept in a slightly different situation. Here, a standard decapolar diagnostic catheter is thoracoscopically positioned through the oblique sinus under the posterior wall of the left atrium for time reference. After surgical isolation of the right pulmonary veins with a bipolar ablation clamp, the catheter was retracted such that the distal electrodes were now positioned against the epicardium of the left atrium, while the proximal electrode pairs were positioned at the isolated right pulmonary vein antrum. When pacing from the right superior PV, it is clear that there is dissociation of the atrial rhythm (dagger, electrodes 1-2 and 3-4), whereas there is local capture of the PV antrum (asterisk, electrodes 5-6, 7-8 and 9-10). Similar to dissociated PV potentials this is proof of exit block, which
therefore does not per se require pacing at high output. Pacing at just above the threshold potential, resulting in local capture, is sufficient.

**Figure 1. Pacing within a box**

(A) Drawing of the posterior left atrium indicating the concept of pacing from the box to demonstrate completeness of ablation lines. Note that there is homogeneous conduction in the viable myocardium within the box.

(B) Image of the real situation where pacing is not per se confined to viable tissue and conducting channels may be present.

(C) Proof of local capture of the PV antrum (electrodes 5-6, 7-8 and 9-10, asterisks) and dissociation of the distal atrial myocardium (electrodes 1-2 and 3-4, daggers). See text for details

**Electrophysiological Confirmation of Surgical Ablation Lines**

The mainstay of invasive treatment of AF is isolation of the pulmonary veins, and there is consensus that the goal should be electrical isolation of the pulmonary veins. We have shown earlier that the size of the surgical ablation electrode pen is too large to reliably detect very small local potentials.

During standard left sided catheterization thoracoscopic PV isolation may be confirmed or checked using circular mapping catheters. Indeed, this method is employed by most authors reporting hybrid surgical-electrophysiological procedures. Gaps in the lines, when present, can then be subsequently ablated. Also, the use of diagnostic catheters allows differential pacing to demonstrate bidirectional block across additional left atrial ablation lines.
The protocol of electrophysiological testing differs somewhat between studies, whereby some use a stepwise approach with AF inducibility whereas others just complete the epicardial ablation lines. Among the advantages of an epicardial-endocardial approach are that the procedures may be performed days or weeks apart, allowing every operator to perform his work under circumstances he is comfortable with, and the patient to recover from the surgery before undergoing the catheter part of the operation. There is mention of a clear efficacy benefit in the literature, and with increasing time between the two procedures, one may ask the necessity of performing a catheter study once the patient is asymptomatic.

Alternatively, thorough electrophysiological mapping can be performed exclusively epicardial, as demonstrated by us and others. For this, we developed custom-made mapping electrodes that fulfill the following criteria: 1) Electrodes have a rigid but malleable shaft that allows handling by the surgeon and positioning the electrode to the epicardium. The use of standard diagnostic EP catheters in this respect is not impossible but comes with the limitation that such catheters are too flexible and therefore hard to maintain at a certain location on the heart. Moreover, when they are not supported by a vessel through which they are usually introduced, a surgical forceps are needed to position the catheter against the heart, which further complicates positioning of the electrode. 2) The size of the electrode is adapted to the diameter of thoracoscopic ports. 3) The electrode system contains multiple small electrodes with a small interelectrode distance to be able to record bipolar electrograms of truly local activations.

Figure 2 displays an example of entry block after right-sided thoracoscopic PV isolation in a patient with several failed catheter ablations. It can be clearly seen that before ablation, there are distinct potentials on the PV antrum (recordings performed from the location with the star), whereas after 8 RF applications with the bipolar clamp, the area is completely silent. Note the very nice signal to noise ratio and the absence of remote ventricular electrograms in the bipolar recording using closely spaced small electrodes. We previously described the mapping protocol for entry block, which includes testing 7 different sites on the superior and inferior vein as well as pacing from the mapping electrode to demonstrate exit block (not shown). In that manuscript, we outlined that the PV entry block is confirmed using a multipolar catheter at seven distinct positions. The number of electrograms recorded with this approach is higher than with conventional circular catheter mapping.
For patients with persistent or longstanding AF, in our approach the so-called Dallas lesion set, consisting of a roof line and a trigone line is employed. Figure 3 demonstrates recordings from testing conduction block across the right side of the superior line and the trigone line.
It is important to realize that with a bilateral thoracoscopic procedure the right side needs to be completed before the procedure is started on the other side since returning to the first side at the end of the procedure is very unattractive, may be associated with ventilation issues and should therefore be prevented. For local pacing, a screw-in temporary pacemaker wire (Medtronic 6416) is attached to the area cranial to the superior line and right from the trigone line. Figure 3B demonstrates that pacing from there and recording from a site caudal to the superior line, away from the line (asterisk) is associated with a shorter conduction time (128 msec) than when recording close to the line as the asterisk in Figure 3C (214 msec), indicating that conduction propagates around the PV antrum, toward the line and no conduction occurs across the line. Note the fractionated electrograms close to the line, supporting the concept that a thoracoscopic ablation line is usually a wide area of damaged tissue (compare Figure 1B). Pacing from the two locations recorded from in figure 3 results in differential activation time of the tissue under the screw-in electrode, demonstrating bidirectional block (not shown).

Figure 3. Right sided roofline, epicardial confirmation Confirmation of block across the right side of the roof line. Pacing is performed from above the line, recording away from the line (A, star) results in activation time of 128 msec. Recording close to the line (B, star) results in activation time of 214 msec, indicating that activation propagates toward the line and there is no conduction through the line. Note the fractionated potentials close to the line, see text for further details. Organization of the tracings as in figure 2.
Figure 4 subsequently shows demonstration of block across the trigone line. Pacing is performed from the same position as in Figure 3. When recording from a position left sided of the trigone line, and away from the line, activation time is 186 msec (Figure 4B, asterisk). When the recording electrode is now moved toward the line, activation time becomes 224 msec (Figure 4C, asterisk), indicating that activation propagates around the mitral valve and not through the ablation line.

Figure 4. Trigone line, epicardial confirmation
Confirmation of block across the trigone line. Pacing is performed from above the line, recording away from the line (A, star) results in activation time of 186 msec. Recording close to the line (B, star) results in activation time of 224 msec, indicating that activation propagates toward the line and there is no conduction through the line. Organization of the tracings as in figure 2.

After completion of the left PV isolation, the left side of the superior line is tested using the same protocol. Figure 5A shows the custom made multi electrode probe placed cranial to the superior line, and the decapolar reference catheter positioned parallel to the line, under visual control. Pacing from different bipoles on the reference catheter results in changes in activation time of the tissue under the mapping electrode (Figure 5A and B). An intact line forces activation propagation parallel to the superior line and around the isolated PV antrum. Hence, the distance between the distal electrode pairs to the mapping electrode is shorter than that from the more proximal pairs. In case of a gap in the line, these distances are similar with no difference in activation time cranial to the superior line. Bidirectional block is proven by
Electrophysiological Evaluation of Thoracoscopic Pulmonary Vein Isolation

Pacing from the multi electrode and observing reversal of the activation sequence (compared to activation during sinus rhythm) over the decapolar reference catheter (Figure 5C). Lines with gaps present with a bracketing pattern over the reference electrode (not shown).

Figure 5. Left sided roofline, epicardial confirmation
Confirmation of block across the left side of the roof line. Pacing is performed from the distal electrodes of the decapolar diagnostic catheter positioned parallel to the roof line, recording above the roof line, leftward to the trigone line (A, star) results in activation time of 126 msec. Recording from the same position, but pacing from an electrode pair more proximal on the decapolar catheter (B, star) results in activation time of 145 msec, indicating that activation travels longer around the PV island and that there is no conduction through the line. C. Pacing from the multielectrode above the roof line results in activation of the posterior left atrium from left to right (reversal activation sequence decapolar catheter). Dagger indicates the electrogram from the screw-in pace electrode (Medtronic 6416) positioned above the roof line rightward from the trigone line. Organization of the tracings as in figure 2.
Chapter 5

Discussion

Atrial fibrillation can be a symptomatic, complex arrhythmia with frequent recurrences under antiarrhythmic drug treatment or after catheter ablation. Thoracoscopic surgery for AF is a relatively novel approach and can be complementary to other invasive treatment modalities. It aims at combining the high success rates of the Cox-Maze operation with a less invasive approach. The literature on this topic, however, is limited and most studies are single center, non-randomized reports with different patient selection and different follow up.

A key component of every invasive treatment of AF is the isolation of the pulmonary veins, and therefore consequently achievement of conduction block across any atrial ablation line. Indeed, reconnection of the pulmonary veins is a frequent finding at redo ablation procedures. Although PV isolation is not similar to absence of AF, and reconnection has also been described in patients after catheter ablation but without recurrences, assessment of isolation at the index procedure is the best measure available for procedural success. The lack of information about integrity of ablation lines may be futile, but more likely should be considered a missed chance for improving procedural outcome. This is even more pertinent in thoracoscopic surgery, where there is usually only one procedure possible.

There is limited literature on periprocedural electrophysiological testing during thoracoscopic surgery, indeed, we are aware of only 3 manuscripts in which both the follow up is organized and the data presented according to the HRS consensus. However, what these papers do show is that confirmation of the ablation lesions is both feasible and comes with no or very limited additional risk. Whether hybrid procedures do eventually result in a better procedural outcome has yet to be determined, and head-to-head comparisons with stand-alone surgery are lacking. However, the literature available provides promising data.

In most centers, the electrophysiological part of the procedure is carried out using standard EP catheters and equipment. With this, both surgeon and cardiologist can act in their comfortable environment. However, transseptal access is needed and can potentially induce complications. A fully epicardial procedure requires no fluoroscopy or heparinization, and is technically feasible given the use of the right materials. In our experience, standard diagnostic catheters are not suitable in the thoracic cavity because of lack of support. Therefore, as outlined above, we developed a custom made multi electrode that can be handled easily by the surgeon. The small electrode terminals and small inter electrode distance assure bipolar recordings of high quality as displayed in the figures. The fully epicardial approach has limitations in the sense that endocardial touch up ablation is not possible in the case of detected gaps in the lines. However, there seems to be no difference in procedural outcome using a fully epicardial versus an epicardial/endocardial approach (SPJ Krul and L Pison, unpublished data), nor are there differences in complications related to the electrophysiological procedure.
The need for a hybrid approach is evident when the ablation lesion set cannot be completed surgically due to the techniques used. Here, endocardial ablation is mandatory to achieve pulmonary vein isolation and bidirectional block across other left atrial lines. Whether the electrophysiological part of the procedure has to be performed simultaneously with the surgery is unclear, and there are no data supporting superiority of a direct hybrid versus a sequential or staged approach or vice versa. However, one could argue that the longer the index surgical procedure and the electrophysiological procedure are placed apart, the less urgent the hybrid procedure may be for patients who are asymptomatic after the surgical procedure. There is little sense in subjecting an asymptomatic patient without apparent AF to an extra endocardial study. Indeed, in that case the endocardial procedure is carried out exclusively in patients with residual AF and symptoms, and defined as a redo procedure.

Another unresolved issue remains which lesions to make in which patients. Generally, the more ablation lines are constructed, the higher the chance of residual conduction or reconnection. Indeed, reconnection of the PVs as well as gaps in atrial ablation lines have been described after thoracoscopic surgery for AF. Interestingly, Liu et al demonstrated that atrial tachycardia after thoracoscopic surgery for AF was caused by macroreentry through iatrogenic constructed isthmuses. They showed that there were gaps in the PV Lines, but those were not implicated in the arrhythmia mechanism.

For patients with a normally sized left atrium and paroxysmal AF, pulmonary vein isolation alone may suffice, whereas in patients with more progressed disease additional atrial lines may be pertinent.

**Conclusions**

In summary, electrophysiological evaluation of thoracoscopic pulmonary vein isolation is feasible and may add to better outcomes of this procedure. Specifically, understanding how to measure conduction block with electrophysiological tools and techniques may provide an addition to the surgical procedure. Which ablation line set to create, and whether such a hybrid approach where surgeon and electrophysiologist join forces is cost effective remains incompletely understood and may be subject of further investigation.
Chapter 5

References


Electrophysiological Evaluation of Thoracoscopic Pulmonary Vein Isolation


PART 2
CHAPTER 6

Ganglion Plexus Ablation in Advanced Atrial Fibrillation

The AFACT Study.

Antoine H.G. Driessen *
Wouter R. Berger *
Sébastien P.J. Krul
Nicoline W.E. van den Berg
Jolien Neefs
Femke R. Piersma
Dean R.P.P. Chan Pin Yin
Jonas S.S.G. de Jong
Wim Jan P. van Boven
Joris R. de Groot

*These authors contributed equally

Abstract

Background:
Patients with long duration of atrial fibrillation (AF), enlarged atria, or failed catheter ablation have advanced AF and may require more extensive treatment than pulmonary vein isolation.

Objectives:
The aim of this study was to investigate the efficacy and safety of additional ganglion plexus (GP) ablation in patients undergoing thoroscopic AF surgery.

Methods:
Patients with paroxysmal AF underwent pulmonary vein isolation. Patients with persistent AF also received additional lines (Dallas lesion set). Patients were randomized 1:1 to additional epicardial ablation of the 4 major GPs and Marshall’s ligament (GP group) or no extra ablation (control) and followed every 3 months for 1 year. After a 3-month blanking period, all antiarrhythmic drugs were discontinued.

Results:
Two hundred forty patients with a mean AF duration of 5.7 ± 5.1 years (59% persistent) were included. Mean procedure times were 185 ± 54 min and 168 ± 54 min (p = 0.015) in the GP (n = 117) and control groups (n = 123), respectively. GP ablation abated 100% of evoked vagal responses; these responses remained in 87% of control subjects. Major bleeding occurred in 9 patients (all in the GP group; p < 0.001); 8 patients were managed thoracoscopically, and 1 underwent sternotomy. Sinus node dysfunction occurred in 12 patients in the GP group and 4 control subjects (p = 0.038), and 6 pacemakers were implanted (all in the GP group; p = 0.013). After 1 year, 4 patients had died (all in the GP group, not procedure related; p = 0.055), and 9 were lost to follow-up. Freedom from AF recurrence in the GP and control groups was not statistically different whether patients had paroxysmal or persistent AF. At 1 year, 82% of patients were not taking antiarrhythmic drugs.

Conclusions:
GP ablation during thoroscopic surgery for advanced AF has no detectable effect on AF recurrence but causes more major adverse events, major bleeding, sinus node dysfunction, and pacemaker implantation.
Introduction

The most common arrhythmia, atrial fibrillation (AF) is associated with increased morbidity and mortality. Ablation is indicated for patients remaining symptomatic despite a trial with antiarrhythmic drugs (AADs).\(^1,2\) Therefore, catheter ablation and stand-alone thoracoscopic surgery are increasingly being used. The arrhythmogenic trigger from the pulmonary veins (PVs) is the target for ablation in patients with paroxysmal AF without concomitant atrial or cardiac disease; the mechanism is less well established in patients with advanced AF, defined as persistent AF, enlarged left atria, or previously failed catheter ablation. Various treatment strategies have been advocated, combining more extensive myocardial ablation and ablation of non-PV and nonmyocardial targets, including stepwise catheter ablation approaches,\(^3\) in which PV isolation (PVI) is followed by linear left atrial (LA) ablation, ablation of continuous fractionated atrial electrograms,\(^4\) or ablation of rotors.\(^5\) As it has become clear that the autonomous nervous system plays a central role in initiating AF and in atrial autonomic remodeling,\(^6,7\) partial atrial denervation through ablation of the major autonomic ganglion plexus (GP), either alone or in combination with PVI, has been pursued.\(^8,9\) GP stimulation promotes AF by a combined parasympathetic and sympathetic action resulting in action potential duration (APD) shortening and increased sarcoplasmic reticulum calcium release in PV myocardium, allowing early after-depolarizations to emerge and trigger AF.\(^10\) Aside from AF induction, GP stimulation affects local and global LA conduction time, consistent with a predominantly parasympathetic effect.\(^11\) Thus, the stimulation of the autonomic nerves within the GPs, beyond triggering AF, may also have a proarrhythmic effect on the atrial myocardium that perpetuates the arrhythmia.\(^11\) Studies investigating the role of GP ablation in addition to PVI have demonstrated mixed results,\(^8,12,13\) as have nonrandomized studies during concomitant cardiac surgery.\(^14,15\) The GPs reside in epicardial fat pads and cannot be ablated endocardially without (much) more atrial myocardial ablation. This may induce post-ablation atrial tachycardias (ATs). However, more rigorous myocardial ablation around the PVs may also lower the chance of reconnection. Second, most studies have focused on patients with paroxysmal AF with few cardiovascular comorbidities. Epicardial ablation during thoracoscopic surgery for AF may allow more selective GP ablation without ablating the underlying atrial myocardium; however, only observational data on thoracoscopic GP ablation are available.\(^16-19\)

The aim of the prospective, randomized, controlled AFACT (Atrial Fibrillation Ablation and Autonomic Modulation via Thoracoscopic Surgery) study was to investigate epicardial GP ablation during thoracoscopic surgery for advanced AF. We hypothesized that GP ablation in these patient results in a higher percentage of freedom from AF, without inducing more periprocedural or late complications.
Methods

AFACT is a single-center study, performed at the Academic Medical Center in Amsterdam, that enrolled patients between April 2010 and January 2015. The study conformed to the Declaration of Helsinki and was approved by the Institutional Review Board. All patients provided written informed consent.

Pre-operative Workup

The inclusion and exclusion criteria are listed in the Online Appendix. All patients had electrocardiographic documentation of AF and underwent the following pre-operative tests: nontriggered cardiac magnetic resonance imaging angiography for LA anatomy, 24-h Holter recording for AF burden and rate control assessment, transthoracic echocardiography for LA diameter and volume (determined using the Simpson method), spirometry for vital capacity and forced expiratory volume in 1 second to assess the ability to undergo perioperative single-lung ventilation, and treadmill testing to exclude clinically significant coronary artery disease (followed by coronary angiography when appropriate). Hepatic and renal failure, as well as clinically relevant anemia, were excluded. All patients were adequately anticoagulated with vitamin K antagonists or non–vitamin K oral anticoagulant agents (NOAC) ≥ 4 weeks prior to surgery.

Randomization

Randomization was computer guided and performed in blocks with varying block sizes at the time of pericardial opening. With 110 patients in each arm (α=0.8, two-sided significance level=0.05), AFACT was powered to detect a 17.5% difference in AF absence after 1 year, on the basis of previous studies.(16,20,21) We enrolled 240 patients to allow for about 10% of patients not completing follow-up.

Surgical Procedure

The surgical procedure has been described previously.(16) In short, bilateral video-assisted thoracoscopy was performed. Oral anticoagulant agents were discontinued 2 days before surgery, and transesophageal echocardiography excluded LA thrombi before the atria were manipulated. All patients underwent PVI, specifically, ≥6 radiofrequency applications to the PV antrum, until a conductance drop within 10 s was observed (Isolator Synergy clamp, AtriCure, West Chester, Ohio). In patients with persistent AF, additional LA ablation lines were made, specifically, a Dallas lesion set involving a superior line connecting the right and left antral PVI and left fibrous trigone line, connecting the superior line to the left fibrous trigone at the aortic annular level (22) (Isolator Transpolar pen or Coolrail linear pen. AtriCure). All ablation lines were extensively tested for bidirectional block with epicardial electrodes connected to an
Chapter 6

electrophysiologic system in the operating theater, as reported earlier.\textsuperscript{(16,23,24)} The LA appendage was excluded using an endoscopic stapler. Patients stayed in the recovery room for 3 to 6 h and were admitted to the ward afterward. Thorax drains were removed within 24 h, and patients were usually discharged on post-operative day 3.

**GP Ablation**

Before any PV or linear ablation, the anterior right (located in the epicardial fat pad anterior to the right superior and inferior PVs) and inferior right (located in the fat pad inferior to the right inferior PV, extending to the inferior side of the LA posterior wall) GPs were localized using anatomic landmarks and high-frequency stimulation (HFS). The GP between the superior caval vein and aorta was not ablated or tested. Online Figure 1 shows the location of the main GPs (posterior LA view). A positive HFS response was defined as \( \geq 50\% \) increase in the R-R interval. HFS was delivered using a bipolar ablation pen (Isolator Transpolar pen) with cycle length 60 ms, 16 Hz, pulse width 1.0 ms, and output incrementing from 1 to 25 mA.

In patients randomized to GP ablation, GPs were subsequently ablated. Notably, ablation on the basis of anatomic landmarks was performed when HFS did not evoke a vagal response. On the left side, the superior left and inferior left GPs (located in the fat pads on the LA roof, medial to the left superior PV, and inferior to the left inferior PV, extending toward the LA posterior wall) were identified similarly and ablated in these patients. The ligament of Marshall (between the pulmonary artery and the left superior PV) was subsequently dissected. In both groups, HFS of the 4 major GPs was repeated after all ablation was complete to confirm the absence or presence of a vagal response. Additional GP ablation was applied when necessary.

**Clinical follow-up**

All patients were treated with colchicine 0.5 mg once daily from the first post-operative day for 30 days to prevent pericarditis. Follow-up at 10 days after discharge was for wound control. Clinical follow-up for endpoints was performed every 3 months with a clinical visit, electrocardiography, and 24-h Holter monitoring. Symptomatic patients were encouraged to obtain additional rhythm recording. The first 3 months formed a blanking period, during which recurrences of AF or other atrial arrhythmias were not considered recurrence.\textsuperscript{(2)} All AADs were discontinued after 3 months. When AF was present at the 3-month visit, electric cardioversion was performed. Anti-coagulation was discontinued only in patients with CHA\(2\)DS\(2\)-VASc (congestive heart failure, hypertension, age \( \geq 75 \) years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category[female]) scores of 0 (or 1 when based solely on sex) at 6 months.\textsuperscript{(1)}
Online Figure: Anatomical localization of the Major Ganglion Plexi
This posterior view of the left and right atrium displays the anatomical location of each major ganglion plexus (GP) and the ligament of Marshall (LOM). ARGP = anterior right GP; ILGP = inferior left GP; IRGP = inferior right GP; IVC = inferior caval vein; LIPV = left inferior PV; LSPV = left superior PV; PA = pulmonary artery; PV = pulmonary vein; RIPV = right inferior PV; RSPV = right superior PV; SLGP = superior left GP; SVC = superior caval vein.

Endpoints definition
The efficacy endpoint was freedom from AF or any atrial tachyarrhythmia lasting ≥30 s, documented on electrocardiography, Holter monitoring, or pacemaker or implantable cardioverter-defibrillator electrogram, without AAD use, as per the guidelines. Safety endpoints included any procedure-related complication, stroke, and bleeding. Major complications were defined as those causing hospital admission within 30 days, inability to complete the procedure, or permanent injury or death. An independent clinical endpoint committee, whose members were unaware of study assignment, adjudicated all efficacy and safety endpoints.

Statistical Analysis
Statistical analysis was performed with SPSS version 23.0 (IBM, Armonk, New York) and R version 3.2.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria). Continuous values are expressed as mean ± SD. Categorical variables are expressed as numbers and percentages. The Mann-Whitney U test, paired Student t test, and Fisher exact test were used for comparisons. For freedom from AF recurrence, event-free survival was plotted and estimated by Kaplan-Meier curves. Clinical parameters associated with AF recurrence were studied using univariate and stepwise multivariate analysis in a Cox regression model. All variables with p values <0.10 in univariate analysis, plus 3 well-established risk factors for AF recurrence (left ventricular ejection fraction, AF duration, and previous PVI) were entered into the multivariate regression. A p-value <0.05 indicated statistical significance.
Chapter 6

Results

Of 318 patients screened, 240 provided written informed consent. Patients were randomized 1:1 to standard thoracoscopic ablation (n=123) or additional GP ablation (n=117) (Figure 1). Patients were 60 ± 8 years of age, and 73% were men. Overall, 68% had enlarged left atria (LA volume index [LAVI] >33 ml/m2), and 43% had severely enlarged left atria (LAVI ≥40 ml/m2). AF was present for 4 years (inter-quartile range: 2 to 8 years; range: 1 to 35 years). Nearly one-quarter of patients had undergone previous catheter ablation; only 26 patients (11%) had normal left atria and no persistent AF or previous ablation. Baseline characteristics were balanced (Table 1).

![Study Flowchart](image)

**Figure 1. Study Flowchart**
From the original 318 patients screened, data for analysis of the primary endpoint were available for 117 patients in the control group and 110 in the ganglion plexus (GP) ablation group. AF = atrial fibrillation; LVEF = left ventricular ejection fraction.
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n = 240)</th>
<th>No GP Ablation (n = 123)</th>
<th>GP Ablation (n = 117)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>59.9 ± 8.2</td>
<td>60.2 ± 8.2</td>
<td>59.5 ± 8.2</td>
<td>0.525</td>
</tr>
<tr>
<td>Male</td>
<td>175 (73)</td>
<td>91 (74)</td>
<td>84 (72)</td>
<td>0.813</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3 ± 3.9</td>
<td>27.1 ± 3.5</td>
<td>27.6 ± 4.3</td>
<td>0.283</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>42.2 ± 5.6</td>
<td>42.3 ± 5.5</td>
<td>42.1 ± 5.6</td>
<td>0.740</td>
</tr>
<tr>
<td>LAVI, ml/m²</td>
<td>39.4 ± 11.8</td>
<td>40.3 ± 13.0</td>
<td>38.3 ± 10.4</td>
<td>0.198</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>49.6 ± 14.4</td>
<td>51.2 ± 9.1</td>
<td>47.9 ± 18</td>
<td>0.071</td>
</tr>
<tr>
<td>Creatinine, μmol/l</td>
<td>85 ± 18</td>
<td>83 ± 17</td>
<td>87 ± 19</td>
<td>0.115</td>
</tr>
<tr>
<td>Previous catheter PVI</td>
<td>56 (23)</td>
<td>30 (24)</td>
<td>26 (22)</td>
<td>0.780</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11 (5)</td>
<td>8 (7)</td>
<td>3 (3)</td>
<td>0.263</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>29 (12)</td>
<td>14 (11)</td>
<td>15 (13)</td>
<td>0.866</td>
</tr>
<tr>
<td><strong>AF characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, yrs</td>
<td>4 (2–8)</td>
<td>5 (2–10)</td>
<td>4 (2–6)</td>
<td>0.063</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>98 (41)</td>
<td>55 (45)</td>
<td>43 (37)</td>
<td>0.238</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>142 (59)</td>
<td>68 (55)</td>
<td>74 (63)</td>
<td>0.238</td>
</tr>
<tr>
<td>CHA2DS2-VASc (range)</td>
<td>1.4 ± 1.3 (0–7)</td>
<td>1.4 ± 1.3 (0–7)</td>
<td>1.4 ± 1.2 (0–6)</td>
<td>0.770</td>
</tr>
<tr>
<td>CHA2DS2-VASc 0</td>
<td>67 (28)</td>
<td>34 (28)</td>
<td>33 (28)</td>
<td>1</td>
</tr>
<tr>
<td>CHA2DS2-VASc 1</td>
<td>76 (32)</td>
<td>38 (31)</td>
<td>38 (33)</td>
<td>0.890</td>
</tr>
<tr>
<td>CHA2DS2-VASc ≥2</td>
<td>97 (40)</td>
<td>51 (41)</td>
<td>46 (39)</td>
<td>0.793</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>12 (5)</td>
<td>5 (4)</td>
<td>7 (6)</td>
<td>0.700</td>
</tr>
<tr>
<td>Hypertension</td>
<td>102 (43)</td>
<td>54 (44)</td>
<td>48 (41)</td>
<td>0.749</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (7)</td>
<td>8 (7)</td>
<td>8 (7)</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/embolus</td>
<td>19 (8)</td>
<td>10 (8)</td>
<td>9 (8)</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>25 (10)</td>
<td>14 (11)</td>
<td>11 (9)</td>
<td>0.771</td>
</tr>
<tr>
<td>Female</td>
<td>65 (27)</td>
<td>33 (27)</td>
<td>32 (28)</td>
<td>0.813</td>
</tr>
<tr>
<td>Age ≥65 yrs</td>
<td>67 (28)</td>
<td>36 (29)</td>
<td>31 (27)</td>
<td>0.738</td>
</tr>
<tr>
<td>Age ≥75 yrs</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acenocoumarol</td>
<td>182 (76)</td>
<td>87 (71)</td>
<td>96 (82)</td>
<td>0.007</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>27 (11)</td>
<td>16 (13)</td>
<td>11 (9)</td>
<td>0.419</td>
</tr>
<tr>
<td>NOAC</td>
<td>30 (13)</td>
<td>20 (16)</td>
<td>10 (9)</td>
<td>0.081</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>15 (7)</td>
<td>7 (6)</td>
<td>8 (7)</td>
<td>0.793</td>
</tr>
<tr>
<td>AADs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IA</td>
<td>6 (3)</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>0.516</td>
</tr>
<tr>
<td>Class IC</td>
<td>81 (34)</td>
<td>41 (33)</td>
<td>40 (34)</td>
<td>0.843</td>
</tr>
<tr>
<td>Class II</td>
<td>122 (51)</td>
<td>56 (45)</td>
<td>66 (56)</td>
<td>0.261</td>
</tr>
<tr>
<td>Class III</td>
<td>92 (38)</td>
<td>48 (39)</td>
<td>44 (37)</td>
<td>0.264</td>
</tr>
<tr>
<td>Class IV</td>
<td>32 (13)</td>
<td>20 (16)</td>
<td>12 (10)</td>
<td>0.367</td>
</tr>
<tr>
<td>Digoxin</td>
<td>30 (13)</td>
<td>16 (13)</td>
<td>14 (12)</td>
<td>0.618</td>
</tr>
<tr>
<td>Any AAD</td>
<td>234 (98)</td>
<td>118 (96)</td>
<td>116 (99)</td>
<td>0.214</td>
</tr>
</tbody>
</table>

Values are mean ± SD, n (%), or median (interquartile range), unless otherwise indicated.

AAD 1⁄4 antiarrhythmic drug; AF 1⁄4 atrial fibrillation; BMI 1⁄4 body mass index; CHA2DS2-VASc 1⁄4 congestive heart failure, hypertension, age $75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (female); GP 1⁄4 ganglion plexus; LA 1⁄4 left atrial; LAVI 1⁄4 left atrial volume index; LVEF 1⁄4 left ventricular ejection fraction; NOAC 1⁄4 non-vitamin K oral anticoagulant drug; PCI 1⁄4 percutaneous coronary intervention; PVI 1⁄4 pulmonary vein isolation; TIA 1⁄4 transient ischemic attack.
Surgical procedure and complications

The procedure durations were 185 ± 54 min in the GP group and 168 ± 54 min in the control group (p=0.015). The difference was driven by procedure in patients with paroxysmal AF (PVI alone: 144 ± 40 min vs. 127 ± 38 min; p=0.04). There was no difference in procedure duration when additional LA lines were performed for persistent AF (GP 205 ± 49 min vs. control 202 ± 40 min; p=0.609).

Isolation of all PVs was confirmed by demonstration of entry and exit block as previously described. Block across all LA lines was confirmed with differential pacing. After ablation, HFS-evoked vagal response was absent in 100% of patients in the GP group, whereas a residual vagal response could be provoked in at least 1 GP in 87% of control patients (p<0.001).

Major bleeding occurred in 9 patients (LAVI 40.3 ± 11.6 ml/m2, which was not different from patients without bleeding; p=0.833), all in the GP group (p<0.001). Bleeding was managed thoracoscopically in 8 patients, resulting in termination of the procedure and thoracoscopic reoperation after several weeks in 4 patients, and in 3 patients, at least 1 of the LA lines could not be completed. Furthermore, 1 major bleed consisted of thoracoscopic access-port bleeding, necessitating a second thoracoscopic procedure. In 1 patient, a sternotomy was needed after trocar perforation of the right ventricle and the left anterior descending coronary artery, resulting in tamponade followed by sternotomy with suturing of the perforation and arterially grafting the left anterior descending coronary artery. Minor bleeds, all managed thoracoscopically without affecting the procedure, occurred in 12 patients, 6 in each group (p=1.00).

Hospital Stay

Average hospital admission lasted 5.3 ± 2.1 days (range: 2 to 15 days) and 5.0 ± 1.8 days (range: 3 to 14 days) in the GP and control groups, respectively (p=0.242). Symptomatic sinus node dysfunction, necessitating admission to the cardiac medium care unit, treatment with isoprenaline, and/or (temporary) pacing occurred in 12 GP patients and 4 control subjects (p=0.038). Pacemakers were implanted in 3 patients for sinus node dysfunction with asystole pauses during admission. Shortly after discharge, another 3 pacemakers were implanted because of sinus node dysfunction: syncope in 2 patients and postoperative total atrioventricular (AV) block in 1 patient. All 6 pacemakers were implanted in GP patients (p=0.013). These patients had no pre-existing conduction disorders, apart from 1 with first-degree AV block (P-Q interval 210 ms). Major procedure-related complications occurred in 22 GP patients and 10 control subjects (p=0.022) (Table 2).
### Table 2. Adverse events after thoracoscopic ablation for atrial fibrillation

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No GP Ablation (n = 123)</th>
<th>GP Ablation (n = 117)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedure-related, major</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10 (8)</td>
<td>22 (19)</td>
<td>0.022</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0 (0)</td>
<td>9 (8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sternotomy</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.488</td>
</tr>
<tr>
<td>Tamponade</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Phrenic paralysis</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0.498</td>
</tr>
<tr>
<td>Sinus node dysfunction</td>
<td>4 (3)</td>
<td>12 (10)</td>
<td>0.038</td>
</tr>
<tr>
<td>Pacemaker implantation</td>
<td>0 (0)</td>
<td>6 (5)</td>
<td>0.013</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>0.622</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>0.614</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.488</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.488</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.488</td>
</tr>
<tr>
<td><strong>Procedure-related, minor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12 (10)</td>
<td>10 (9)</td>
<td>0.825</td>
</tr>
<tr>
<td>Bleeding (minor)</td>
<td>6 (5)</td>
<td>6 (5)</td>
<td>1</td>
</tr>
<tr>
<td>Hypothermia during surgery</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>0.622</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>0.237</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.488</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Non-procedure-related, major</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4 (3)</td>
<td>10 (9)</td>
<td>0.101</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>4 (3)</td>
<td>0.055</td>
</tr>
<tr>
<td>PCI during follow-up</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.488</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>2 (2)</td>
<td>4 (3)</td>
<td>0.677</td>
</tr>
<tr>
<td><strong>Non-procedure-related, minor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are n (%).

Abbreviations as in Table 1.

* Major adverse events are defined as causing (prolongation of) hospital admission within 30 days, inability to complete the procedure, or permanent injury or death.

† Minor adverse events are defined as complications that did not result in termination of the procedure or permanent injury.
Follow up

Four patients died during follow-up, none procedure related and all in the GP group (p=0.055) (Table 3). One-year follow-up was incomplete for 9 patients (4%), who were considered lost to follow-up. Complete information on the primary endpoint was ascertained in 227 patients (95%). AF recurrences during the blanking period were noted in 40 of 117 GP patients and 36 of 123 control patients (p=0.407), with cardioversions performed in 25 and 28 patients, respectively.

Table 3. Patient Deaths

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Sex</th>
<th>Age at Death (yrs)</th>
<th>Cause of Death</th>
<th>Number of Days Post-Procedure Death Occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>76</td>
<td>Sepsis and multiorgan failure during admission for decompensated restrictive cardiomyopathy (sarcoidosis)</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>54</td>
<td>Metastasized esophagus carcinoma</td>
<td>195</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>66</td>
<td>Pancreatic cancer from liver metastases</td>
<td>264</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>66</td>
<td>Sudden death</td>
<td>316</td>
</tr>
</tbody>
</table>

At 1-year follow-up, no AF recurrences were observed in 70.9% and 68.4% of patients in the GP and control groups (p= 0.696) (Central Illustration) and 82% of patients were off AADs. Cardioversions were performed in 22 and 21 patients, respectively. There were no differences according to clinical AF type; AF was absent in 80.0% and 74.5% (p=0.512) of patients with paroxysmal AF and 65.7% and 62.9% (p=0.767) of those with persistent AF in the GP and control groups, respectively (Figure 2). In subgroup analysis, there were no differences between GP ablation and control (Figure 3).

AT was the most common recurrent arrhythmia and occurred significantly more often in patients in the GP group (78.1% AT and 21.9% AF) than in the control group (51.4% AT and 48.6% AF) (p=0.026).

There were no differences in mean heart rate on Holter monitoring at baseline or 3-month follow-up. After discontinuation of AADs, mean heart rate on Holter monitoring increased by 5.5 ± 19.2 beats/min versus 2.6 ± 17.7 beats/min at 6 months (p= 0.013) and by 6.4 ± 19.2 beats/min versus 2.3 ± 16.1 beats/min at 9 months (p=0.004) in the GP and control groups, respectively. At 1 year, mean heart rate did not differ from baseline in either groups, although office heart rate during follow-up was higher in the GP group than in control subjects during follow-up (data not shown).
Central illustration: Thoracoscopic ganglion plexus ablation for atrial fibrillation ablation:

Efficacy and Safety

In a comparison of groups that did or did not undergo ganglion plexus (GP) ablation in addition to pulmonary vein isolation for advanced atrial fibrillation (AF), the primary endpoint of AF recurrence at 1 year was not statistically different (A). The addition of GP ablation did produce significantly more major procedure-related adverse events (B), which occurred in 19% of patients in the GP ablation group versus 8% in the control group (p = 0.022).
Figure 2. Primary endpoint

The primary endpoint of atrial fibrillation (AF) recurrence within 1 year was not significantly different between the ganglion plexus (GP) ablation and control groups for the overall population (Central Illustration, panel A), (A) patients with paroxysmal AF \( n = 98 \), or (B) patients with persistent AF \( n = 141 \).
Ganglion Plexus Ablation in Advanced Atrial Fibrillation - The AFACT Study

Figure 3. Subgroup analyses: Ganglion plexus ablation efficacy
There were no subgroups in which ganglion plexus (GP) ablation added to thoracoscopic ablation was associated with less atrial fibrillation (AF) recurrence during follow-up. CHA2DS2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65-74 years, sex category (female); CI = confidence interval; LA = left atrial; PVI = pulmonary vein isolation.

Predictors of AF absence after thoracoscopic ablation
Univariate and multivariate regression analysis was performed on AF recurrence (Figure 4). LAVI was the only determinant of AF recurrence (hazard ratio: 1.38 per 10-ml increase; 95% confidence interval: 1.03 to 1.83; p=0.029) that remained significant in multivariate analysis.
Chapter 6

Figure 4. Determinants of atrial fibrillation recurrence
All variables with p values <0.10 in univariate analysis plus 3 well-established risk factors for atrial fibrillation (AF) recurrence (AF duration, left ventricular ejection fraction, and history of previous pulmonary vein isolation [PVI]) were included in the multivariate model. BMI = body mass index; HR = hazard ratio; other abbreviations as in Figure 3.

Discussion

The first randomized study of GP ablation in thoracoscopic surgery, AFACT is the largest study to date of minimally invasive AF surgery. Our study demonstrated that in patients with advanced AF, of whom 68% had enlarged LAs, GP ablation did not reduce AF recurrence (Central Illustration). GP ablation was associated with more major procedural complications (19% vs. 8%), in particular bleeds leading to termination of the procedure or sternotomy, and significantly more pacemaker implantations because of sinus node dysfunction and AV block. Additionally, recurrences were more often ATs in the GP group than in control subjects. There was no difference in AF recurrence rates during the so-called blanking period between groups. The various hierarchical levels of extrinsic (nuclei and axonal fields in the brain), intrathoracic (spinal cord ganglia), and intrinsic (major GP and the atrial neural network, consisting of axons...
Ganglion Plexus Ablation in Advanced Atrial Fibrillation - The AFACIT Study

and smaller ganglia extending from these) autonomous nervous systems are interdependently
defect connected but can function independently once disconnected. Injection of cholinergic agents
into the GPs, electric stimulation of nerves, and pacing-induced AF produce proarrhythmic
autonomic hyperactivity, leading to shortening of the atrial and PV APD (para-sympathetic
effect) and increases intracellular [Ca2+] (sympathetic effect), resulting in triggered firing and
induction of AF. GP stimulation also directly affects atrial myocardial electrophysiology
in a proarrhythmic manner, consistent with a predominantly parasympathetic action. Disconnecting extrinsic from intrinsic cardiac innervation resulted in shortened regional
refractory periods in dogs and an increased burden of AF or AT starting after 4 to 5 weeks.

Thus, removing the inhibitory effect of the extrinsic on the intrinsic autonomous cardiac
innervation causes proarrhythmic GP hyperactivity, which provides the rationale for GP
ablation. Indeed, Katritsis et al. demonstrated fewer recurrences in patients with paroxysmal
AF randomized to catheter ablation of 4 major GP areas and Marshall’s ligament in addition
to PVI compared with either treatment in isolation. An anatomic approach to GP ablation
confers less AF recurrence than an evoked vagal response–based localization. These were
catheter ablation studies, and it cannot be discerned whether these effects were caused by GP
ablation or by more atrial myocardial ablation, resulting in more rigorous PVI. Observational
thoracoscopic studies showed that GP ablation combined with PVI conferred a high rate
of freedom from AF. However, in advanced AF, when electric, structural, and autonomic
remodeling has occurred, GP ablation would be expected to be ineffective. Many minimally
invasive studies reported observational evidence on procedures where PVI (with or without LA
lines) was standarly combined with ablation of the GPs, but a systematic review found no
benefit of GP ablation in this setting, which may relate to the advanced nature of AF in these
patients and autonomic remodeling. Indeed, Mao et al. demonstrated that 8 weeks after
GP ablation in dogs, APD was shorter than in sham-operated animals, and AF inducibility
increased. In contrast, the acute effect of GP ablation results in APD prolongation and
decreased AF inducibility but coincides with abundant reinnervation of the atrium, which may
promote AF inducibility. Such reinnervation might have contributed to our findings, supported
by the observation that increased heart rate (on Holter monitoring) in the GP group was no
longer present after 1 year. Similarly, there is abundant clinical evidence for structural and
autonomic remodeling and increased non-PV triggers in advanced and long-standing AF.

AFACIT randomized patients with advanced AF, undergoing thoracoscopic surgery for AF.
There was no difference in AF recurrence in the entire population or in subgroups with
paroxysmal or persistent AF. It has been suggested that autonomic hyperactivity, occurring
over the hierarchical gradient from the GP via the axonal field to the atrial neural network, is
responsible for this. Instead, we observed more major bleeding in the GP ablation group.
Whereas these bleeds may not be caused directly by GP ablation, more rigorous surgical
dissection in the patients randomized to GP ablation and the longer procedure time might have
promoted bleeding. Indeed, several bleeds occurred during positioning of the ablation clamp around the right PVs, just after dissection and ablation of the anterior right and inferior right GP. Patients with major bleeding did not have larger LAs. Eight of 9 major bleeds could be managed thoracoscopically but resulted in termination of the procedure and resumption after weeks or in an inability to subsequently complete the ablation lines.

Furthermore, GP ablation more often resulted in conduction disorders requiring prolonged monitoring or isoprenaline therapy as well as pacemaker implantation in 6 patients (vs. 0 control subjects). As the procedural endpoint of GP ablation is not defined, and the absence of HFS-evoked vagal response merely shows the interruption of the trajectory between GP and end organs (i.e., sinus node or AV node), it can be questioned whether denervation was complete in the GP ablation group or, conversely, whether there was no inadvertent GP ablation during PVI or ablation of additional lines in the control group. We found that a residual HFS-evoked vagal response of at least 1 GP was present in 87% of control patients compared with 0% in the GP ablation patients. Moreover, there was an increase in heart rate in the GP group, reaching statistical significance after 6 and 9 months, but not in the control group. Finally, sinus node dysfunction occurred significantly more frequently in the GP group, as did pacemaker implantation, indicating that the autonomic modulation was indeed different among groups.

The observation that recurrences constituted AT (as opposed to AF) more frequently in the GP groups might point to more inadvertent myocardial ablation during GP targeting, despite an epicardial approach.

AF recurrence was absent in 76.8% and 64.4% of patients with paroxysmal and persistent AF, respectively, without the use of AADs after a single thoracoscopic procedure. These were slightly higher recurrence rates than in our earlier study in less affected patients and higher than those reported for full maze surgery with cardiopulmonary bypass and biatrial ablation. 

An earlier systematic review reported 69% freedom from AF (without the use of AADs) after minimally invasive surgery. AF ACT’s single-procedure surgical ablation results compared favorably with catheter ablation in this group of patients.

**Study limitations**

The optimal lesion set in this setting remains a matter of debate and might have affected outcomes in AF ACT. Similarly, progression of the underlying disease might have contributed to AF recurrence. These hypotheses were not tested systematically, because AF ACT tested GP ablation on top of a systematic AF ablation protocol.
Conclusions

GP ablation on top of PVI and additional LA lines in patients with advanced AF did not reduce AF recurrence but resulted in more major procedural complications, in particular major bleeds and pacemaker implantations. Therefore, GP ablation should not be performed in these patients.

Perspectives

Competency in patient care and procedural skills
In patients with advanced AF that is long-standing and associated with LA enlargement or unsuccessful catheter ablation, augmenting PVI with thoracoscopic GP ablation increased the risk for procedural complications, including bleeding and the need for pacemaker implantation, without reducing the incidence of recurrent of AF.

Translational outlook
Further research is needed to determine if particular subgroups of patients with AF can be identified who would benefit from thoracoscopic GP ablation in conjunction with other therapeutic interventions.
Online Appendix, Inclusion and Exclusion criteria

Patients could be included in the study if they agreed to undergo thoracoscopic ablation because of persistent AF, enlarged left atria (left atrial volume index (LAVI) > 33 ml/m², previously failed catheter ablation, or patient preference, and had failed at least 1 class Ic or III AAD, were 18 to 80 years old, and had a life expectancy ≥ 2 years.

Exclusion criteria were: unable or unwilling to take AADs; catheter ablation for AF within the preceding 4 months; myocardial infarction within the preceding 2 months; cerebrovascular accident (any sudden neurological deficit lasting ≥ 24 h, with or without pathological computed tomographic cerebrum) within the preceding 6 months; New York Heart Association (NYHA) III/IV heart failure, NYHA II or III/IV heart failure with recent hospitalization for decompensation (unless related to or aggravated by AF); left ventricular ejection fraction (LVEF) < 35%; documented carotid stenosis > 80%; planned cardiac surgery for other purposes than AF alone; active infection; pregnant or being of childbearing potential without adequate anticonception; requiring AADs for ventricular arrhythmias; documentation of an intracardiac mass or thrombus; being unable to undergo transesophageal echocardiography (TEE); previous thoracic radiation; comorbid conditions possessing undue risks for general anesthesia or thoracoscopic port access; or being unwilling/unable to adhere to the follow-up protocol.
**Ganglion Plexus Ablation in Advanced Atrial Fibrillation - The AFACT Study**

**References**


CHAPTER 7

Electrophysiologically Guided Thoracoscopic Surgery for Advanced Atrial Fibrillation

5-Year Follow-up

Antoine H.G. Driessen *
Wouter R. Berger *
Dean R.P.P. Chan Pin Yin
Femke R. Piersma
Jolien Neefs
Nicoline W.E. van den Berg
Sébastien P.J. Krul
Wim Jan P. van Boven
Joris R. de Groot

*These authors contributed equally

Published as letter. Article in full in manuscript

Abstract

Background
Electrophysiologically guided, thoracoscopic surgery may be employed to treat patients with advanced symptomatic atrial fibrillation (AF), usually with severely enlarged left atria or long AF duration, previous ablation and refractory to anti-arrhythmic drugs (AAD). Data on efficacy of this procedure during long term follow-up is lacking. We therefore assessed AF freedom at 5 years in consecutive patients with advanced paroxysmal or persistent AF following a single thoracoscopic procedure.

Methods
Patients were followed-up prospectively with ECGs and 24-hour Holter monitoring every 3 months, and when symptoms were reported, for 2 years after the procedure. All patients were invited for a follow-up visit after 5 years. Additionally, all medical charts, clinical data, all ECGs and Holters from referring hospitals, obtained during the entire follow-up, were reviewed.

Results
Sixty-six consecutive patients (49 men, mean age 57±8 years, mean left atrial volume index 36±12 ml/m2) underwent thoracoscopic surgery for paroxysmal (n=33) or persistent advanced AF (n=33) between 2008 and 2010. ECG and clinical data were complete in all. Fifty-eight patients (88%) attended the 5-year visit after 66 (60-82) months. Of all patients (n=66), 33 (50%) were free of AF recurrence, without AAD. Seventy-four percent of patients had no or <1 AF recurrence/year, 91% had no or <3 recurrences. More than 3 AF recurrences/year or permanent AF was documented in 9% of all patients; 6% in paroxysmal and 12% in persistent AF. At 5 years, 88% of patients had sinus rhythm, 30% were prescribed AAD.

Conclusions
Thoracoscopic surgery for advanced AF is associated with complete absence of AF, without AAD use, in 50% of patients after a single surgical procedure at 5 years. At that time 88% of patients had sinus rhythm and 70% discontinued AAD. Only 9% of patients had frequent AF recurrences or permanent AF.
Introduction

Atrial fibrillation (AF) affects 30 million subjects worldwide and its incidence and prevalence of AF are expected to double over the forthcoming decades.\(^\text{1,2}\) Many patients suffer from AF symptoms. Therefore, after the unsuccessful trial of at least one class 1 or class 3 antiarrhythmic drug (AAD), symptomatic patients may qualify for catheter or surgical ablation.\(^\text{3}\) The seminal discovery that AF is often triggered from the pulmonary veins resulted in a plethora of ablation approaches aiming at isolating the pulmonary veins from the left atrium.\(^\text{4}\) Whereas catheter ablation is increasingly being employed worldwide, the surgical Cox-Maze procedure, reported to have highly successful outcomes, was never adopted on a large scale due to its surgical complexity, invasiveness and associated morbidity and even mortality, and the available evidence is derived from a few expert centers.\(^\text{5,6}\)

Thoracoscopic surgical approaches have been developed to combine the reported efficacy of the Cox-Maze procedure with a less invasive approach.\(^\text{7,8}\) One randomized study comparing thoracoscopic ablation with catheter ablation in patients with recurrent AF after previous ablation, enlarged left atrium with or without hypertension demonstrated absence of AF after one year in 36.5 and 65.6\% of patients undergoing catheter and surgical ablation respectively, at the cost of more periprocedural complications with surgery.\(^\text{9}\) Endocardial and epicardial hybrid approaches, where the surgeon is guided by electrophysiological confirmation of ablation lesions, seem to yield higher rates of absence of AF (79\% after one year in a retrospective study) than thoracoscopic surgery alone, without increasing the rates of periprocedural complications.\(^\text{8,10,11}\)

Procedural complications associated with catheter ablation of AF, albeit fewer than with surgery, occur in 6.4\%, more frequently than generally assumed.\(^\text{12}\) Using variable definitions and variable follow-up periods, a meta-analysis showed absence of AF after a single catheter procedure in 57\% of patients after a median follow-up of 9 months.\(^\text{13}\) However, this number may be lower in real life.\(^\text{14}\) Despite the increasing global uptake of catheter ablation as a primary invasive therapy of atrial fibrillation, longer-term follow-up data is limited and the results are very modest at best. The most experienced centers report freedom of AF after a single procedure of 29\% in patients with mainly paroxysmal AF and normally sized left atria after 5 years.\(^\text{15}\) After up to 7 procedures, this number increased to 63\%. Similarly, the group in Hamburg shows freedom of AF of 47\% in paroxysmal and 20\% in persistent AF after a single procedure, whereas after multiple procedures 79% and 45\% were free from AF respectively after a 5-year follow-up period, with approximately 25\% of patients continuing anti-arrhythmic medication.\(^\text{16,17}\)

Currently, data on long-term follow-up of patients undergoing thoracoscopic surgery for AF are not available. We investigated the single surgical procedure efficacy of totally thoracoscopic, electrophysiologically guided, surgery for patients with advanced AF, that is, usually persistent, with severely enlarged left atria or long AF duration, after 5 years of follow-up.
Methods

All patients with paroxysmal, persistent or longstanding persistent AF who underwent thoracoscopic surgery for AF at our center between 2008 and the end of 2010 were included. Persistent and longstanding persistent AF were combined for this analysis and reported as persistent AF. All patients had symptomatic AF, refractory or intolerant to at least one class I or III AAD. All patients consented to the surgical procedure. The current study and follow-up after 5 years conformed to the Declaration of Helsinki and was approved by the Institutional Review Board of the Academic Medical Center. All study subjects provided written informed consent.

Surgical Procedure

The surgical procedure has been described previously. In short, after deflation of the right lung, a videoscope and surgical instruments were introduced through 3 trocars. The pericardium was opened. Entry and exit block of the right pulmonary veins were tested using a custom made epicardial mapping electrode, before and after ablation with the AtriCure Isolator® Synergy™ bipolar RF ablation clamp. At least 6 RF applications were delivered. The four main Ganglion Plexus (GP) were localized as described previously and were subsequently ablated. Patients included in the prospective AFACt study were per protocol randomized to GP ablation or no GP ablation. After closing the pericardium, the procedure was repeated on the left side.

All patients were treated with pulmonary vein isolation, in patients with persistent AF, a superior line connecting both antral pulmonary vein isolation islands, an inferior line in certain patients, and a left fibrous trigone line, connecting the superior line to the left fibrous trigone were made. All ablation lines were tested for bidirectional block as reported earlier. The left atrial appendage (LAA) was removed using an endoscopic stapler.

Patients were admitted to the recovery room for 3-6 hours and to the ward afterwards. Thorax drains were removed within 24 hours and patients were discharged usually on the third postoperative day.

Follow-up

All patients were followed up prospectively with clinical visits, 12-lead ECG and 24-hour Holter at 3, 6, 9, 12, 15, 18 and 24 months in our center. Patients were encouraged to have additional rhythm recordings obtained when symptomatic. All AAD were discontinued 3 months after surgery. Anticoagulants were continued in all patients with a CHA2DS2-VASc score≥1 (unless solely based on female gender), irrespective of the (presumed) absence of AF or the exclusion of the LAA. After 2 years, patients were followed in a non-standardized manner by their referring cardiologist. For this 5-year follow-up analysis, all patients were invited for a standardized office visit, physical examination and 12-lead ECG. Additionally, demographic
Chapter 7

and clinical data were collected through medical chart review and consultations with referring physicians. All ECGs and 24-hour Holter data obtained during this period were collected and included in the current analysis. The municipal administration confirmed that all patients were still alive. At 5-year follow-up, patients were explicitly asked for AF symptoms, cardioversion or ablation procedures over the preceding years, and, where pertinent, electrocardiographic evidence for AF recurrence was collected. Figure 1 displays the follow-up strategy.

Figure 1. Study flow chart
Flow chart of the study. ECG and Holter data were prospectively collected during the first 2 years of follow-up. Patients returned for a 5-year follow-up visit, and all ECGs and Holters performed in the time between were collected.

**Outcome definition**
AF absence was defined as the absence of any atrial arrhythmia $>30$ seconds without the use of AADs. The first 3 months following surgery formed a blanking period, during which recurrences of AF or other atrial arrhythmias were not considered a recurrence. In addition to the Kaplan-Meier analysis of AF absence, we investigated the actual rhythm at the 5-year follow-up visit, and analyzed patients with $<1$, $<3$ or $\geq 3$ AF recurrences/year.

As a consequence of the protocol, where all AADs were discontinued after 3 months, there were no patients on AAD treatment without any AF recurrence. Those patients without AF recurrences after restarting AAD following their index post procedural recurrence were considered to be free of AF with the use of AAD. We performed univariable and multivariable analysis of clinical parameters associated with AF recurrence.

**Statistical Analysis**
Statistical analysis was performed with SPSS version 23.0 and R version 3.2.1 for Windows. Continuous values are expressed as mean ($\pm$SD). Categorical variables are expressed as numbers and percentages. The Mann-Whitney U and Wilcoxon tests were used for comparisons. For the primary endpoint, AF freedom, event-free survival was plotted and estimated by Kaplan-Meier curves. Clinical parameters associated with AF recurrence were studied using univariable and stepwise multivariable analysis in a Cox regression models. A p-value of $<0.05$ was considered statistically significant.
Results

Sixty-six consecutive patients with advanced paroxysmal or persistent AF underwent thoracoscopic surgery for AF between January 2008 and December 2010. Mean age of the patients was 57.4±8.9 years (range 38-76), and 49 (74%) were male. Thirty-three (50%) patients had paroxysmal, 31 persistent and 2 long standing persistent AF. Twenty-nine patients (44%) had a history of at least one previous percutaneous catheter ablation. Median duration of AF was 5 (range 1-25) years. Mean left atrial volume was 35.9±11.9 ml/m², 30 patients had an enlarged (>33 ml/m²) of whom 16 had a severely enlarged (≥40 ml/m²) left atrium. Baseline demographics are detailed in table 1.

Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>n=66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.4±7.9 (38-77)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>49 (74)</td>
</tr>
<tr>
<td>Body mass index, (kg/m²)</td>
<td>27.8±5.4</td>
</tr>
<tr>
<td>Left Atrial Volume Index (mL/m²)</td>
<td>35.9±11.9</td>
</tr>
<tr>
<td>Previous catheter PVI, n (%)</td>
<td>29 (44)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AF Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF duration, years, median (range)</td>
</tr>
<tr>
<td>Paroxysmal, n (%)</td>
</tr>
<tr>
<td>Persistent, n (%)</td>
</tr>
<tr>
<td>CHA₂DS₂VASc-score (mean).</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Age ≥ 75, n (%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
</tr>
<tr>
<td>Stroke/TIA/Embolus, n (%)</td>
</tr>
<tr>
<td>Vascular disease, n (%)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
</tr>
<tr>
<td>Age ≥ 65, n (%)</td>
</tr>
<tr>
<td>CHA₂DS₂VASc-score = 0, n (%)</td>
</tr>
<tr>
<td>CHA₂DS₂VASc-score = 1, n (%)</td>
</tr>
<tr>
<td>CHA₂DS₂VASc-score ≥ 2, n (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-arrhythmic medication</td>
</tr>
<tr>
<td>Class IA, n (%)</td>
</tr>
<tr>
<td>Class IC, n (%)</td>
</tr>
<tr>
<td>Class II, n (%)</td>
</tr>
<tr>
<td>Class III, n (%)</td>
</tr>
<tr>
<td>Class IV, n (%)</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
</tr>
<tr>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Coumarins, n (%)</td>
</tr>
<tr>
<td>Antiplatelets, n (%)</td>
</tr>
</tbody>
</table>
Chapter 7

Surgical Procedure
Isolation of all PVs was achieved in 100% of patients. Additional lines were ablated in patients with persistent AF. The LAA was excised in 65 patients (98.5%). In one patient, the size and anatomy was deemed unsafe for exclusion. Periprocedural adverse events occurred in 18 patients (27%, Table 2). Of note, all three sternotomies were performed in the first 20 patients, indicating a learning curve of the surgeon and the team as these included our first procedures, and have been reported earlier.(8)

Table 2. Procedural adverse events n, (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternotomy</td>
<td>3</td>
<td>(15)</td>
</tr>
<tr>
<td>Sinus node dysfunction</td>
<td>3</td>
<td>(7)</td>
</tr>
<tr>
<td>Pacemaker implant</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1</td>
<td>(5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
<td>(4)</td>
</tr>
<tr>
<td>Procedural bleeding, thoracoscopically managed</td>
<td>2</td>
<td>(4)</td>
</tr>
<tr>
<td>Late Bleeding, requiring intervention</td>
<td>4</td>
<td>(9)</td>
</tr>
</tbody>
</table>

Follow-up
Electrocardiographic and clinical data were collected from 66 patients (100%). Fifty-eight patients attended the clinical follow-up visit with ECG. Of the remaining, 7 refused the follow-up visit and 1 could not be traced, although his ECG and clinical data were collected from the referring hospital. Median follow-up was 66 months (60-82). 51/58 patients (88%) were in sinus rhythm at the clinical follow-up. Thirty percent of patients were using AAD. At 5 years, all patients were alive, and none had experienced a stroke or systemic embolism.

Absence of AF
Figure 2 shows the Kaplan-Meier curve for absence of AF without the use of AAD (21). No AF recurrence was documented, and all AAD remained discontinued in 67% of patients with paroxysmal and in 33% of patients with persistent AF respectively after 5 years. Absence of AF in the entire cohort was 73%, 61%, 52%, 52%, 50% after 1, 2, 3, 4 and 5 years. Excluding patients in whom a previous catheter ablation proved unsuccessful resulted in absence of AF in 60% of patients after 5 years (76% in paroxysmal and 38% in persistent AF). AAD were restarted in 20 patients with recurrences (30%, 6 with paroxysmal and 14 with persistent AF), of whom 3 did not experience any other AF recurrence thereafter. Hence, AF absence with or without AAD was 55% in the combined cohort and 67% and 42% in patients with paroxysmal or persistent AF respectively.
Thoracoscopic Surgery for Advanced Atrial Fibrillation - 5-Year Follow-up

Figure 2. Kaplan-Meier of absence of AF recurrence, without AAD
Kaplan-Meier analysis of absence of AF recurrence, without the use of antiarrhythmic drugs, after a single thoracoscopic procedure. Continuous line=patients with paroxysmal AF; dashed line=patients with persistent AF.

Recurrence of AF

The recurrent atrial tachyarrhythmia in 33 patients was AF in 67%, atrial tachycardia in 24% and atrial flutter in 9%. AF recurrence was detected with symptom-driven ECG recording in 64%, clinical visit in 9% and Holter in 27% of patients. One patient was classified a recurrence based on a single atrial tachycardia lasting 31 seconds on Holter, without any other clinical or electrocardiographic evidence of recurrence during the rest of the follow-up. Similarly, another patient experienced AF recurrence during an episode hyperthyroidism and had no further recurrences during the course of follow-up. Of the patients classified with AF recurrences, four underwent a redo catheter ablation procedure for AF and two others for typical right atrial flutter, all of whom experienced AF recurrences thereafter.

Figure 3 displays AF burden during 5 years of follow-up. Seventy-four percent of all patients had no or <1 AF recurrence/year, 91% had no or <3 AF recurrences/year. Nine percent of patients had >3 recurrences/year or permanent AF. Of patients with paroxysmal AF, 91% had no or <1, and 94% no or <3 AF recurrences/year. Of patients with persistent AF 58% had no or <1, and 88% had no or <3 AF recurrences/year.

Figure 4 shows the univariable and multivariable analysis of clinical determinants of AF recurrence. AF type (i.e. paroxysmal or persistent) at the time of surgery was associated with AF recurrence (HR 2.28, 95% confidence interval 1.09 – 4.74, p<0.028). Interestingly, also a history of one or more previous catheter ablations was associated with AF recurrence (HR 1.44, 95% confidence interval 1.02 – 2.05, p<0.041). Left atrial volume was enlarged in a large proportion of patients and not associated with long-term AF absence.
Chapter 7

Figure 3. Numbers of episodes / year
Number of episodes/year, first bar: all patients; second bar: patients with paroxysmal AF; third bar: patients with persistent AF. White tinted: no AF recurrence without the use of AAD; light blue tinted: <1 AF recurrence/year; intermediate blue tinted: <3 AF recurrences/year; dark blue tinted: ≥3 AF recurrences/year or permanent AF. Numbers indicate the cumulative percentage.

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariable</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF Type</td>
<td>2.54</td>
<td>[1.23–5.25]</td>
<td>0.012</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.02</td>
<td>[0.98–1.06]</td>
<td>0.366</td>
</tr>
<tr>
<td>Female Gender</td>
<td>1.44</td>
<td>[0.68–3.02]</td>
<td>0.338</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.02</td>
<td>[0.96–1.09]</td>
<td>0.512</td>
</tr>
<tr>
<td>AF Duration</td>
<td>1.02</td>
<td>[0.96–1.09]</td>
<td>0.485</td>
</tr>
<tr>
<td>LAVI (ml/m²)</td>
<td>0.98</td>
<td>[0.95–1.02]</td>
<td>0.413</td>
</tr>
<tr>
<td>Previous PVI</td>
<td>1.52</td>
<td>[1.09–2.12]</td>
<td>0.014</td>
</tr>
</tbody>
</table>

|                |       |              |         |
| **Multivariable**|      |              |         |
| AF Type        | 2.23  | [1.11–4.82]  | 0.025   |
| Previous PVI   | 1.43  | [1.01–2.03]  | 0.042   |

Figure 4. uni and multivariable regression of determinants of AF recurrence
Univariable and multivariable regression of determinants of AF recurrence. BMI=body mass index; LAVI=left atrial volume index; PVI=pulmonary vein isolation.
Thoracoscopic Surgery for Advanced Atrial Fibrillation - 5-Year Follow-up

Discussion

We, for the first time, report 5-year outcomes of thoracoscopic, electrophysiologically guided ablation of advanced AF. Using a rigorous follow-up protocol and endpoint definition, with all patients prospectively followed for two years, 88% of patients returned for an outpatient visit at 5 years. All available electrocardiographic and clinical data were collected for 100% of the entire cohort, we show that 50% of patients (67% with paroxysmal and 33% with persistent AF) discontinued AAD and had no AF recurrence after a single thoracoscopic procedure at 5 years. After 5 years, and irrespective of recurrent episodes, 88% of patients were in sinus rhythm.

Seventy-four percent of patients experienced no or <1 recurrent episodes/year, 91% had no or <3 recurrences/year and only 9% had ≥3 recurrences/year or permanent AF. We further show that AF type (i.e. paroxysmal or persistent) at the time of surgery is associated with AF recurrence, and that patients with prior catheter ablations have a higher chance of AF recurrence during 5 years of follow-up. Previous catheter ablation was a predictor for AF recurrence and exclusion of those patients resulted in AF absence in 60% of patients naive to invasive therapy at 5 years.

Procedural complications

The number of periprocedural complications in this cohort is high, with 3 sternotomies for uncontrolled bleeding. Boersma et al. reported similar complication rates for thoracoscopic surgery for AF. However, most of the complications described here have been reported previously in an analysis of the one-year results of this procedure.(8) Indeed, all sternotomies occurred in the first 20 procedures, strongly suggesting a learning curve for both surgeon and team when the procedure was first introduced at our center. In the AFACT study the total number of major procedural complications was approximately 50% lower with one sternotomy in 240 patients.(19)

However, thoracoscopic surgery is associated with a longer hospital stay and more periprocedural complications than catheter ablation, albeit that with multiple catheter procedures the number of complications may accumulate.

Relation with other surgical and catheter techniques

Using the most stringent definition of outcome, 50% of the entire cohort had no single AF recurrence and discontinued all AAD, and 88% had sinus rhythm at 5 years. The initial publications of the Cox-Maze procedure reported success rates >95%, but the means of follow-up were looser than contemporary methods.(22) Using contemporary follow-up methods, Weimar et al. reported 82% and 83% freedom of AF after two years for the Cox-maze 3 and 4 respectively (5). Using repetitive Holter recordings in 144 patients (in 88% the Cox-Maze procedure was performed, the remainder were treated with a more limited approach), Ad et al.
demonstrate AF absence in 63.5% of patients. At 5 years, 71% of patients had sinus rhythm and did not use AAD. Of note, this patient cohort was a selection of the 300 patients that were eligible for this analysis, as the majority of these patients had insufficient rhythm recordings. Henn et al. describe 576 patients (41% paroxysmal AF) who underwent a Cox-Maze procedure between 2002 and 2014; 5-year follow-up was available for 139 patients, of whom 52% had prolonged monitoring. Fifty-nine percent of patients with a stand-alone procedure, were free of AF without AAD at 5 years. Although these rates seem slightly higher than in our study, we report complete data from consecutive patients, who all were prospectively followed for two years, and in whom all ECGs and Holters performed thereafter were retrieved and included in the analysis. Approximately 2/3 of recurrences were derived from symptom driven ECGs, and Holter recording detected 27% of recurrences only. In addition, we verified in every patient that no cardioversion or catheter ablation had been performed elsewhere. At 5 years, 88% of the patients in this study were in sinus rhythm, compared to 71% in the cohort of Ad et al.. Our analysis of AF burden shows that 74% and 91% of patients had no or <1 or no or<3 AF recurrences/year respectively, indicating a very high percentage of clinical success. With a less invasive approach, only 9% of our patients had frequent AF recurrence or permanent AF. In the available randomized studies, employing variable lesion patterns, lower success rates have been reported for concomitant maze surgery, with a considerably higher percentage of complications. Similarly, the groups in Bordeaux and Hamburg report AF absence in only 29 and 47% of patients with mostly or exclusively paroxysmal AF after 5 years, which increased to 63 and 79% after multiple (up to seven in selected patients) procedures. In persistent AF, single procedure result was 20%, increasing up to 45% after multiple procedures. Also here the follow-up protocol was less rigorous than employed in the current study. Hence, and despite that this study is not a randomized comparison of techniques, the efficacy of thoracoscopic surgery for advanced AF appears similar to Cox-Maze surgery and superior to that achieved with catheter ablation. In multivariable analysis, previous catheter ablation and persistent AF were associated with AF recurrence at five years. This differs from the one-year results of the AFACT study, where LAVI was the only predictor for AF recurrence.

Role of Lesion set and Energy Source

All patients in this cohort underwent a standardized approach with bilateral thoracoscopic pulmonary vein isolation using a bipolar radiofrequency clamp. In patients with persistent AF, additional lines conforming to the Dallas lesion set were added to the procedure and in most patients GPs were ablated. Pulmonary vein isolation alone may be insufficient for treating more advanced AF, but which additional lesion set is preferred remains matter of debate. Different lesion patterns are being employed, also in randomized clinical trials. There is,
to the best of our knowledge, no randomized trial comparing the Cox-Maze with alternative lesion sets. Recent data from the STAR-AF 2 trial demonstrated that adding additional ablation was ineffective compared to PVI alone.\(^\text{(28)}\) Contrary to a fixed lesion set, there is vast evidence on stepwise procedures where the lesion patterns are driven by periprocedural AF conversion or organization.\(^\text{(29)}\) Taken together, as of to date there is no consensus in clinical practice, nor in the literature, on which approach is superior in the treatment of advanced paroxysmal or persistent AF. All patients in the current cohort were treated using the same ablation platform, and the lesion set was prospectively and consistently tailored to the clinical AF type. A different lesion set or energy source, however, could have resulted in different rate or time course of AF recurrences.

**Limitations**

This study is a single center study, including our very first experience with this procedure. Most of the complications reported here have been published previously.\(^\text{(8)}\) Therefore, the reported adverse events during surgery may be an overestimation of the true complication risk. This hypothesis is supported by the notion that virtually all complications occurred in the first 20 procedures, and that data from the AFACT trial show far lesser surgical complications.\(^\text{(19)}\) Data were collected prospectively in a standardized manner for 2 years, and subsequently retrospectively for the time period between 2 and 5 years (Figure 1). During the first two years 24-hour Holters were performed every 3 months, and we invited every patient back to our hospital for a clinical visit and ECG, and specifically inquired on AF recurrence or cardioversions. With this, our study still provides the most comprehensive data set on 5 years follow up of surgical AF ablation currently available. We can, however, not exclude that we missed asymptomatic episodes of AF, but our follow-up protocol conforms to, and is in fact more rigorous than, the consensus.\(^\text{(21)}\) Furthermore, by performing ECGs at the 5-year clinical visit we ruled out asymptomatic permanent AF. In addition, all Holter recordings and ECGs performed after two years were collected and included in this analysis.
Conclusion

Thoracoscopic, electrophysiologically guided surgery for advanced AF is associated with AF absence and discontinuation of AAD in 50% of patients during a follow-up period of ≥5 years. At 5 years, 88% of patients had sinus rhythm. Seventy-four percent of patients had no or <1 AF recurrence/year, 91% had no or <3 recurrences. More than 3 AF recurrences/year or permanent AF was documented in 9% of all patients. Persistent AF and a history of previous catheter ablations were independently associated with AF recurrence.
Thoracoscopic Surgery for Advanced Atrial Fibrillation - 5-Year Follow-up

References


CHAPTER 8

Quality of Life improves after Thoracoscopic Surgical Ablation of Advanced Atrial Fibrillation

Results of the AFACT study.

Antoine H.G. Driessen *
Wouter R. Berger *
Mark F.A. Bierhuizen
Femke R. Piersma
Nicoline W.E. van den Berg
Jolien Neefs
Sébastien P.J. Krul
Wim Jan P. van Boven
Joris R. de Groot

*These authors contributed equally

J Thorac Cardiovasc Surg. 2017 Sep 27, Accepted
Abstract

Introduction
We evaluated health-related Quality of Life (QoL) at 12 months after thoracoscopic surgical ablation in patients enrolled in the AFACT study. AFACT assessed the efficacy and safety of ganglion plexus (GP) ablation in patients with symptomatic advanced atrial fibrillation (AF) undergoing thoracoscopic surgical ablation.

Methods
Patients (n=240) underwent thoracoscopic pulmonary vein isolation with additional ablation lines in patients with persistent AF. Subjects were randomized to additional GP ablation or control. Short form 36 (SF-36) QoL questionnaires were collected at baseline, at 6 and 12 months of follow-up.

Results
201 patients were eligible for QoL analysis (age 59±8 years, 72% men, 68% enlarged left atrium, 57% persistent AF). Patients improved in physical and mental health at 6 (both p<0.01) and 12 months (both p<0.01) relative to baseline, with no difference between the GP (n=101) or control (n=100) groups. SF-36 subscores in patients with one or no AF recurrences were similar to those in the general Dutch population after 12 months. Patients with multiple AF recurrences (30%) improved in mental (p<0.01), but not physical health, and 6/8 SF-36 subscales remained below the general Dutch population. Patients with irreversible, but not with reversible procedural complications had persistently diminished QoL scores at 12 months.

Conclusion
Thoracoscopic surgery for advanced AF results in improvement in quality of life, regardless of additional GP ablation. QoL in patients with no or one AF recurrence increased to the level of the general Dutch population, whereas in patients with multiple AF recurrences QoL remained lower. Irreversible, but not reversible procedural complications were associated with persistently lower QoL.
Perspective statement

We show, using the SF-36 questionnaire, that quality of life improves after thoracoscopic surgery for atrial fibrillation. Patients with irreversible surgical complications or multiple atrial fibrillation recurrences demonstrated no improvement of Quality of Life. A single atrial fibrillation recurrence was associated with the same QoL improvement as were no atrial fibrillation recurrences at all.

Central Message

Quality of life improvement after thoracoscopic surgery for atrial fibrillation relates to AF recurrences and procedural complications.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, estimated to affect 33.5 million people worldwide. Its prevalence is increasing, as a result of the ageing population and the improved survival of chronic cardiovascular disease.\(^1,2\) Health related quality of life (QoL) in AF patients is generally lower than the population norms.\(^3\) Rhythm control with catheter or surgical ablation is recommended for patients remaining symptomatic despite a trial with antiarrhythmic drugs (AAD), and invasive AF treatment may improve QoL.\(^4\) Following catheter ablation, QoL has been reported to improve, regardless of procedural success. It has been demonstrated that a substantial reduction in AF burden results in a significant improvement of QoL, whereas QoL changes less in patients with more AF recurrences.\(^5-7\) Similar to catheter ablation, thoracoscopic surgery for AF is performed to achieve freedom of AF and may further even reduce risk factors for stroke and heart failure.\(^8\) However, improvement of the patient’s symptoms remains central in the indication for invasive AF management.\(^4\) Thoracoscopic surgery for AF has been associated with high efficacy rates. It has been suggested that its higher efficacy goes at the cost of more procedural complications compared to catheter ablation, and therefore potentially negatively affects QoL.\(^9\) However, prospective data on QoL in patients undergoing thoracoscopic surgery for AF is lacking. The Atrial Fibrillation Ablation and AutonomiC Modulation via Thoracoscopic Surgery (AFACT) study demonstrated no efficacy of additional ganglion plexus (GP) ablation in patients with advanced AF undergoing thoracoscopic AF surgery, but an increased incidence of complications compared to the control group.\(^10\) The aim of this prespecified substudy of AFACT was to determine the change in QoL following thoracoscopic AF ablation in relation to additional GP ablation, freedom of AF recurrence and procedural complications.
Methods

Study Design
The AFACT study compared efficacy and safety of additional GP ablation to no additional GP ablation in patients with advanced paroxysmal or persistent AF undergoing thoracoscopic surgery for AF. The study was registered at clinicaltrials.gov (NCT01091389) and approved by the IRB of the Academic Medical Center. All patients provided written informed consent. The methods and main clinical findings have been published. In brief, the study included patients with advanced AF, that is, mostly persistent AF, with enlarged left atria or previously failed catheter ablation, refractory or intolerant to at least one anti-arrhythmic drug, undergoing thoracoscopic surgical ablation. All patients (n=240) were subjected to thoracoscopic pulmonary vein isolation (≥6 RF applications to the pulmonary vein antrum with the AtriCure Isolator® Synergy™ bipolar RF ablation clamp). In patients with persistent AF additional left atrial lines were ablated conforming to the Dallas lesion set. Patients were randomized to either additional ablation of the four major ganglionic plexi and Marshall’s ligament (n=117) or no additional GP ablation (control group, n=123).

Clinical follow-up
Patients were followed-up every three months with ECG and 24-hour Holter performed at every follow-up visit for one year. Patients were encouraged to obtain additional rhythm recording when symptomatic. AF recurrences were defined as any episode of AF, atrial tachycardia or atrial flutter documented on ECG or 24-hour Holter lasting >30 seconds. A blanking period of three months after the procedure was instituted during which AF recurrences were not considered a clinical endpoint. All AAD were discontinued three months after the procedure, unless the patient remained to have AF. Procedural complications were defined as major when causing (prolongation of) hospital admission within 30 days. Of those, events were defined as irreversible when injury was permanent (i.e. pacemaker implantation, stroke or phrenic paralysis) or when the thoracoscopic procedure could not be completed.

Health-Related Quality of Life Form
Assessment of change in QoL was a pre-specified analysis of the AFACT study and SF-36 QoL questionnaires were filled out before randomization, and at 6 and 12 months follow-up. The SF-36 QoL questionnaire is a validated generic questionnaire to measure physical and mental health in individuals. It consists of 36 questions, grouped into eight scales, namely physical functioning (PF), role physical (RP), bodily pain (BP), social functioning (SF), mental health (MH), role emotional (RE), vitality (VT) and general health perception (GH). The eight scales are summarized in two dimensions, physical and mental component summary (PCS and MCS), normalized to an overall population mean ± SD of 50 ± 10. The eight scales and two summary...
dimensions are transformed to a scale from 0 to 100, where 100 is the best possible health, as described by Ware et al.\textsuperscript{(13)} The scores from a dataset displaying the QoL in the general Dutch population was used as a reference.\textsuperscript{(14)}

**Statistical Analysis**

Statistical analyses were performed using SPSS version 23.0 and R for Windows version 3.1.1. Continuous data is reported as mean±SD and categorical data as number of subjects and proportions. As there were no differences in any of the SF-36 subscales, the treatment arms of AFACT were combined for the current analysis. The baseline characteristics were compared using the Chi-square test for categorical data and Student’s unpaired t-test for normally distributed data or the Mann-Whitney U-test for non-normally distributed data. Normal distribution was tested with the Kolmogorov-Smirnov test. Student’s unpaired t-test was used to compare the mean scores in SF-36 subscales between groups. To compare data from the SF-36 questionnaire with the reference population, a one-sample t-test was used. For comparing QoL on the eight subscales and two summary dimensions after thoracoscopic ablation relative to baseline the paired sample t-test was used. For univariable and multivariable analysis, simple linear regression and stepwise multivariable regression were used to study predictors for the change in MCS and PCS scores after 12 months. Graphic analyses of the residuals indicated that the assumptions of linear regression were met. All variables with p<0.01 in univariable analysis were entered in the multivariable regression. A p-value of <0.05 was considered significant.

**Results**

**Study Population**

Of the 240 patients included in the AFACT study, 13 patients were not included in the present analysis: 4 patients died, 2 procedures were aborted and 7 patients were lost to follow-up. An additional 26 patients did not complete the SF-36 questionnaires either at baseline or at 6 or 12 months follow-up (9 in the GP group and 17 in the controls). For the present study, 201 patients with complete SF-36 questionnaires at baseline, 6 and 12 months (101 in the GP group and 100 in the control group) were analyzed. Mean age was 59±8 years, 72% were men, mean left atrial volume index was 39.0±11.6ml/m2, and 114 (57%) patients had persistent AF. Baseline characteristics are displayed in table 1.
Quality of Life - Results of the AFACT study

Table 1. Baseline characteristics

| Patients, n | 201 |
| Age (years), mean±SD (range) | 59.6±7.8 (39-73) |
| Male, n (%) | 145 (72) |

- **Type AF**, n (%):  
  - Paroxysmal, n (%) | 87 (43)  
  - Persistent, n (%) | 114 (57)  
- **AF Duration (years), median [IQR]** | 4 [2-8] |
- **Congestive heart failure, n (%)** | 7 (4)  
- **Hypertension, n (%)** | 87 (43)  
- **Age ≥ 75, n (%)** | 0 (0)  
- **Diabetes, n (%)** | 13 (7)  
- **Stroke/TIA/Embolus, n (%)** | 16 (8)  
- **Vascular disease, n (%)** | 18 (9)  
- **Female gender, n (%)** | 56 (28)  
- **Age ≥ 65, n (%)** | 56 (28)  
- **CHA₂DS₂-VASc-score,**  
  - 0, n (%) | 56 (28)  
  - 1, n (%) | 66 (33)  
  - ≥ 2, n (%) | 79 (39)  
- **Previous catheter PVI, n (%)** | 51 (25)  
- **Previous PCI, n (%)** | 22 (11)  
- **Myocardial Infarction, n (%)** | 9 (5)  
- **BMI (kg/m²), mean±SD** | 27.1±3.8  

- **Echocardiographic parameters,**  
  - Left Atrial Volume (ml), mean±SD | 81.1±23.2  
  - Left Atrial Volume Index (ml/m²), mean±SD | 39.0±10.6  
  - Left Atrial Diameter (mm), mean±SD | 42.2±5.4  
  - Left Ventricular Ejection Fraction (%), mean±SD | 50.6±9.7  

- **Anti-arrhythmic drugs,**  
  - Class IA, n (%) | 4 (2)  
  - Class IC, n (%) | 69 (35)  
  - Class II, n (%) | 122 (49)  
  - Class III, n (%) | 79 (39)  
  - Class IV, n (%) | 27 (13)  
  - Digoxin, n (%) | 23 (11)  

- **Anticoagulants,**  
  - Acenocoumarol, n (%) | 153 (76)  
  - Fenprocoumon, n (%) | 21 (10)  
  - NOAC, n(%) | 26 (14)  
  - Antiplatelets, n (%) | 13 (7)  

Health Related Quality of Life

There were no differences in QoL with respect to any of the eight SF subscales, nor on PCS or MCS between the GP ablation group and no GP ablation group at baseline, 6 months or 12 months (figure 1, table 2). Patients with advanced AF scored significantly lower than the general Dutch population before the ablation procedure in seven of the eight scales in SF-36, with the exception of bodily pain. PCS and MCS were 44.6±9.4 and 45.0±10.9 respectively. Table 3 shows that scores in all 7 subscales were significantly higher after 12 months in the full cohort. This increase was reached after 6 months and persisted up to 12 month. Subsequently, PCS and MCS were significantly higher after 6 and 12 months (p<0.001 and p<0.001 respectively).

Figure 1. PCS and MCS at baseline, 6 and 12 months after thoracoscopic ablation
PCS (A) and MCS (B) scores at baseline and 6 and 12 months after thoracoscopic ablation are shown for the GP ablation (blue) and control (white) arms of the study. PCS, Physical Component Summary; MCS, Mental Component Summary.
Quality of Life - Results of the AFACT study

Table 2. Baseline SF-36 Quality of Life stratified to randomization in AFACT

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>All</th>
<th>NO GP</th>
<th>GP ablation</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 Summary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS, mean±SD</td>
<td>44.4±9.5</td>
<td>44.3±9.9</td>
<td>44.6±9.1</td>
<td>0.81</td>
</tr>
<tr>
<td>MCS, mean±SD</td>
<td>44.6±11.0</td>
<td>43.5±10.6</td>
<td>45.7±11.3</td>
<td>0.15</td>
</tr>
<tr>
<td>SF-36 Domaines:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning, mean±SD</td>
<td>66.5±25.6</td>
<td>67.3±25.8</td>
<td>65.7±25.5</td>
<td>0.66</td>
</tr>
<tr>
<td>Role Physical, mean±SD</td>
<td>37.2±42.7</td>
<td>36.4±42.15</td>
<td>38.0±43.4</td>
<td>0.79</td>
</tr>
<tr>
<td>Bodily Pain, mean±SD</td>
<td>81.7±21.9</td>
<td>79.5±22.5</td>
<td>83.7±21.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Social Functioning, mean±SD</td>
<td>67.4±24.7</td>
<td>64.8±23.5</td>
<td>70.0±25.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Mental Health, mean±SD</td>
<td>72.0±17.6</td>
<td>70.9±16.8</td>
<td>73.5±18.3</td>
<td>0.30</td>
</tr>
<tr>
<td>Role Emotional, mean±SD</td>
<td>71.9±41.6</td>
<td>68.7±43.0</td>
<td>75.0±40.0</td>
<td>0.29</td>
</tr>
<tr>
<td>Vitality, mean±SD</td>
<td>49.1±21.2</td>
<td>48.2±21.9</td>
<td>50.0±20.6</td>
<td>0.54</td>
</tr>
<tr>
<td>General Health Perception, mean±SD</td>
<td>60.9±19.2</td>
<td>59.7±19.7</td>
<td>62.2±18.7</td>
<td>0.37</td>
</tr>
</tbody>
</table>

SF-36: Short Form-36, QoL: Quality of Life, PCS: Physical Component Summary, MCS; Mental Component Summary

Adverse Events

The complications during the course of the study have previously been published, and major procedural complications occurred more often in patients undergoing GP ablation (10). In the present analysis, 31 patients (15%) had major procedural complications and 16 patients (8%) had minor complications. Ten major complications (5%) were irreversible. Table 4 shows that there was no difference in any of the SF-36 subscales or on PCS and MCS at baseline in patients with compared to patients without any major procedural complications. Figure 2A shows that patients with irreversible procedural complications (most often consisting of pacemaker implantation) did not demonstrate improvement on MCS and subscales, compared to the patients without complications. Patients with reversible periprocedural events or bleeding, eventually improved to the same extent as patients without (Figure 2B). Consequently, there were no significant differences on the combined scores or any of the subscores between patients with and without reversible complications at 12 months.
Table 3. Mean changes between baseline and 12 months of follow up

<table>
<thead>
<tr>
<th></th>
<th>12 months change vs baseline</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entire cohort, n 201</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>4.0 (2.7 to 5.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>13.7 (10.4 to 17.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Role physical</td>
<td>31.5 (24.2 to 38.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>-1.4 (-4.6 to 1.9)</td>
<td>0.41</td>
</tr>
<tr>
<td>General health perceptions</td>
<td>5.2 (2.6 to 7.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCS</td>
<td>5.3 (3.8 to 6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Social functioning</td>
<td>13.3 (10.1 to 16.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mental health</td>
<td>7.1 (5.0 to 9.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Role emotional</td>
<td>11.3 (5.1 to 17.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vitality</td>
<td>15.6 (12.9 to 18.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>No AF recurrence group, n 141</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>5.8 (4.3 to 7.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>16.9 (13.1 to 20.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Role physical</td>
<td>38.0 (29.4 to 46.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>-0.1 (-3.7 to 3.6)</td>
<td>0.976</td>
</tr>
<tr>
<td>General health perceptions</td>
<td>8.8 (5.7 to 11.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCS</td>
<td>5.3 (3.5 to 7.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Social functioning</td>
<td>15.9 (12.0 to 19.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mental health</td>
<td>8.1 (5.6 to 10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Role emotional</td>
<td>9.7 (2.2 to 17.3)</td>
<td>0.012</td>
</tr>
<tr>
<td>Vitality</td>
<td>17.8 (14.5 to 21.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>AF Recurrence group, n 60</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>-0.4 (-2.7 to 1.9)</td>
<td>0.719</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>6.1 (0.0 to 12.2)</td>
<td>0.051</td>
</tr>
<tr>
<td>Role physical</td>
<td>15.9 (2.5 to 29.4)</td>
<td>0.021</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>-4.5 (-11.2 to 2.2)</td>
<td>0.189</td>
</tr>
<tr>
<td>General health perceptions</td>
<td>-3.2 (-7.9 to 1.5)</td>
<td>0.182</td>
</tr>
<tr>
<td>MCS</td>
<td>5.3 (2.4 to 8.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Social functioning</td>
<td>7.3 (1.4 to 13.2)</td>
<td>0.016</td>
</tr>
<tr>
<td>Mental health</td>
<td>4.9 (-0.9 to 8.8)</td>
<td>0.017</td>
</tr>
<tr>
<td>Role emotional</td>
<td>14.9 (4.3 to 25.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Vitality</td>
<td>10.7 (5.7 to 15.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean (95% CI). AF; Atrial Fibrillation, PCS; Physical Component Summary, MCS; Mental Component Summary
Table 4. Physical Component Summary and Mental Component Summary at baseline and during follow-up

<table>
<thead>
<tr>
<th></th>
<th>No GP</th>
<th>GP</th>
<th>P</th>
<th>No AF Recurrence</th>
<th>AF Recurrence</th>
<th>P</th>
<th>No Major AE</th>
<th>Major AE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=</td>
<td>101</td>
<td>100</td>
<td></td>
<td>141</td>
<td>60</td>
<td></td>
<td>170</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>44.3±9.9</td>
<td>44.6±9.1</td>
<td>0.814</td>
<td>44.8±9.7</td>
<td>43.6±8.8</td>
<td>0.415</td>
<td>44.8±9.4</td>
<td>42.6±9.7</td>
<td>0.234</td>
</tr>
<tr>
<td>MCS</td>
<td>43.5±10.6</td>
<td>45.7±11.3</td>
<td>0.151</td>
<td>45.4±10.2</td>
<td>42.7±12.6</td>
<td>0.112</td>
<td>44.4±11.0</td>
<td>45.8±10.9</td>
<td>0.534</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>47.5±9.7</td>
<td>49.6±9.0</td>
<td>0.128</td>
<td>50.3±8.9</td>
<td>44.6±9.5</td>
<td>&lt;0.001</td>
<td>49.1±9.0</td>
<td>45.3±11.1</td>
<td>0.039</td>
</tr>
<tr>
<td>MCS</td>
<td>48.6±9.7</td>
<td>50.7±8.8</td>
<td>0.106</td>
<td>50.5±8.8</td>
<td>47.7±10.1</td>
<td>0.05</td>
<td>49.7±9.0</td>
<td>49.3±10.8</td>
<td>0.831</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>48.2±9.1</td>
<td>49.3±9.8</td>
<td>0.436</td>
<td>51.0±8.3</td>
<td>43.6±10.0</td>
<td>&lt;0.001</td>
<td>49.3±8.9</td>
<td>45.8±11.7</td>
<td>0.062</td>
</tr>
<tr>
<td>MCS</td>
<td>49.4±9.1</td>
<td>51.1±9.1</td>
<td>0.181</td>
<td>51.2±8.4</td>
<td>48.0±10.3</td>
<td>0.023</td>
<td>50.8±8.7</td>
<td>47.6±10.7</td>
<td>0.083</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. GP; Ganglion Plexus ablation, AF; Atrial Fibrillation, AE; Adverse Event, PCS: Physical Component Summary, MCS; Mental Component Summary
Chapter 8

Figure 2. Radar chart with the SF-36 scores
Radar chart with the SF-36 scores. The octagonal axes for each SF-36 subscale read excentric from central (30) to peripheral (100). The different conditions within 1 subscale can be read from the individual axes, whereas the surface of the entire graph indicates the aggregate QoL. QoL at baseline (red), 6 months follow-up (blue), and 12 months follow-up (green) are shown for (A) patients with an irreversible procedural complications and (B) patients with a reversible complication during the procedure or 12 months follow-up. Dutch population means are denoted by the dashed orange lines. RE, Role emotional; VT, vitality; PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; SF, social functioning; MH, mental health.

Absence of AF
Of the total study population, 141 patients (70%) discontinued AAD and did not experience AF recurrence during one year of follow-up. Irrespective of AF absence, 83% of patients (n=167) were not using AAD at 12 months follow-up.

At baseline, no significant differences were observed in any of the SF-36 subscales and PCS and MCS between patients who would experience AF recurrence versus those without AF recurrence. As expected, and consistent with the finding in the entire cohort, BP was similar
in AF patients at baseline as in the general Dutch population. Table 3 summarizes the change in SF 36 subscales during follow-up in patients with and without AF recurrences. Thirty-three patients (16%) had an AF recurrence before they completed the 6 months follow-up SF-36 questionnaire. These patients did not show improvement on any of the eight subscales, whereas patients without recurrence at 6 months showed significant improvement on 7/8 subscales, except on BP and in PCS and MCS (PCS: p<0.001, MCS: p<0.001) at 6 months. After 12 months, patients with AF recurrences had lower scores on 6/8 subscales than those without AF recurrences with exception of BP and RE. Similarly, PCS and MCS were significantly lower in patients with AF recurrences, compared to patients without AF recurrence (p=0.001 and p=0.023 respectively).

In the AF recurrence group PCS did not significantly change compared to baseline (p=0.567), but MCS did increase after 12 months (p=0.001). QoL-scores remained decreased in PF, RP, SF, VT and GH in these patients (figure 3). Twenty-seven (13%) patients had no recurrence at 6 months but at least one recurrence at 12 months follow-up. In those patients, PCS was significantly lower than in patients without AF at both 6 (p=0.021) and 12 months (p=0.001). MCS was equal compared to the non-recurrence group at 6 months (p=0.332), but was significantly decreased at 12 months follow-up (p=0.032).
Chapter 8

Figure 3. Follow up radar chart, divided by recurrence rate
A radar chart with the SF-36 scores at baseline (red), 6 months follow-up (blue), and 12 months follow-up (green) is shown for (A) patients without AF recurrence, (B) patient with 1 AF recurrence, (C) and patient with more than 1 AF recurrence. Dutch population means are denoted by the dashed orange lines. RE, Role emotional; VT, vitality; PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; SF, social functioning; MH, mental health.

Role of the number of documented AF recurrences
To evaluate the effect of the AF burden, we compared the change in SF-36 scores in patients with one AF recurrence (n=19), versus those with multiple AF recurrences (n=41). There were no significant differences in any of the subscales or in PCS and MCS at baseline. Furthermore, baseline QoL subscale scores were not different from the patients without AF recurrences. The central figure summarizes that patients with only one AF recurrence improved on the SF-36 subscales, similar to the group with no AF recurrence, whereas in patients with multiple AF recurrences SF-36 subscales did not change after the procedure and remained significantly lower than that of the general Dutch population.
**Predictors of change in Quality of Life**

Table 5 displays the univariable and multivariable predictors of change in MCS and PCS scores after 12 months relative to baseline. In multivariable analysis, AF recurrence within 12 months (p=0.001) and PCS at baseline (p<0.001) remained independent predictors of decreased PCS. For MCS, only the experience of having a major procedural complications (p=0.049) and MCS-score at baseline (p<0.001) were predictors of decrease at 12 months in univariable analysis. In multivariable analysis, these factors remained independent predictors of decreased MCS.

**Table 5. Univariable and multivariable predictors of change in PCS and MCS scores at 12 months after thoracoscopic surgical ablation**

<table>
<thead>
<tr>
<th>Change in PCS after 12 months</th>
<th>Change in MCS after 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable</td>
</tr>
<tr>
<td>B</td>
<td>P</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.097</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.103</td>
</tr>
<tr>
<td>Type AF (persistent)</td>
<td>-0.384</td>
</tr>
<tr>
<td>AF duration (years)</td>
<td>-0.098</td>
</tr>
<tr>
<td>History of PVI (yes)</td>
<td>-2.436</td>
</tr>
<tr>
<td>CHADS-VASc</td>
<td>-0.424</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.196</td>
</tr>
<tr>
<td>AF Recurrences at 6 M (yes)</td>
<td>-5.049</td>
</tr>
<tr>
<td>AF Recurrences at 12 M (yes)</td>
<td>-6.037 &lt; 0.001</td>
</tr>
<tr>
<td>AAD at 6 months (yes)</td>
<td>-5.841</td>
</tr>
<tr>
<td>AAD at 12 months (yes)</td>
<td>-0.004</td>
</tr>
<tr>
<td>Major Adverse Events (yes)</td>
<td>-1.574</td>
</tr>
<tr>
<td>GP ablation (yes)</td>
<td>1.175</td>
</tr>
<tr>
<td>QoL at baseline</td>
<td>-0.485 &lt; 0.001</td>
</tr>
</tbody>
</table>

PCS, Physical Component Summary; MCS, Mental Component Summary; AF, atrial fibrillation; PVI, pulmonary vein isolation; CHADS-VASc, congestive heart failure [C], hypertension [H], age > 75 years (2 points) [A2], diabetes [D], previous stroke (2 points) [S2], vascular disease [V], age 65-74 years [A], female sex [Sc]; BMI, body mass index; AAD, Antiarrhythmic drug; GP, ganglion plexus; QoL, quality of life.
Chapter 8

Figure 4. Improvement of QoL in relation to AF recurrences. A radar chart with the SF-36 scores of patients with more than 1 AF recurrence (red), 1 AF recurrence (blue), and no AF recurrences (green) is shown at 12 months follow-up after thoracoscopic AF surgery. Dutch population means are denoted by the dashed orange lines. RE, Role emotional; VT, vitality; PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; SF, social functioning; MH, mental health; AF, atrial fibrillation.

Discussion

In this predefined subanalysis of the AFaCT study we demonstrate that QoL significantly increases after thorascopic surgery in all patients with advanced AF, both with and without GP ablation. We show that QoL improves in the entire cohort following thorascopic surgery. The most important determinant of absence of QoL improvement was AF recurrence. Patients with AF recurrences had a lower QoL than those without. Also, patients with a recurrence after >6 months showed a decreased at 12 month QoL compared to 6 months. One single AF recurrence appears to only temporarily decrease QoL, as in those patients there was no difference in the SF-36 subscales or in the domains compared to patients without AF after 12 months. Multiple AF recurrences, however, were associated with a significantly decreased QoL. Baseline QoL, AF recurrence and procedural complications independently predicted a lower QoL. This observation suggests that AF recurrence and the burden of recurrences, rather than the characteristics or invasiveness of the surgical procedure drive the change in QoL. Also that a baseline low QoL, is associated with limited improvement after surgery. These data support the use of AF symptoms, as advocated in the guidelines, as an indication for invasive therapy.\(^{(8,15)}\) Patients with complications of the procedure had no increase of the SF-36 subscales. However,
Quality of Life - Results of the AFACT study

in patients in whom the procedural complications appeared reversible, the lack of QoL increase was temporary, as these patients had a similar QoL as patients without complications at 12 months. Hence, the higher number of reversible complications after surgical ablation compared to catheter ablation, as reported by Boersma et al., appears not to affect QoL during follow-up in patients with advanced AF included in the AFACT study. Conversely, in patients with irreversible complications, pacemaker implantation in particular, QoL remained at the same decreased level as compared to before the procedure. The AFACT study reported more irreversible adverse effects in patients with GP ablation. Potentially, omitting GP ablation may decrease the number of irreversible complications and consequently increase QoL after thoracoscopic surgery for AF.

Quality of Life - Results of the AFACT study

Quality of Life after AF ablation

Improvement of AF related symptoms is the primary objective of invasive treatment strategies for AF. However, improvement of QoL (beyond AF related symptoms) is the most important objective of the patient undergoing the treatment. Subsequently, the results of QoL questionnaires may influence the cost-effectiveness of AF ablation and therefore affect the choice of therapy in patients with AF refractory to AAD. Previous studies on QoL after catheter ablation demonstrated significant improvement after ablation, particularly in patients without AF recurrence. Studies that compared catheter ablation to antiarrhythmic drug therapy reported that QoL scores were significantly higher in patients who underwent catheter ablation than in patients with AAD treatment. Small, non-randomized studies have reported an improvement of QoL after thoracoscopic surgery for AF, similar to the change in QoL that was observed after catheter ablation. These observations are in line with the current study in patients with advanced AF undergoing a thoracoscopic procedure, which is more invasive than a catheter procedure. The absolute change in the different SF-36 scales in our study was larger than in the QoL substudy of the SAFE-T study, investigating restoration of sinus rhythm with antiarrhythmic drugs, but a minimal clinically important difference in SF-36 scales has not been defined for AF. Our results imply that the recurrence of arrhythmia and not the perceived invasiveness of the procedure drives the change in QoL. In this prespecified subanalysis of the AFACT study, we demonstrate that in the overall population of patients undergoing thoracoscopic surgical ablation for AF, there is a significant increase in SF-36 assessed QoL at 6 months after ablation, which remains after 12 months after the procedure. A relatively constant and remaining increase in QoL after various cardiac surgery procedures has been described. We further show that the rhythm outcome of the procedure influences the gain in QoL. Patients without recurrence improved significantly more than patients with AF recurrences. The latter showed an increase in mental health status after the procedure, but not in physical health. AF recurrence was defined as at least one episode of symptomatic or asymptomatic AF recorded on ECG or on 24-hour Holter, lasting more than 30 seconds. As this
is an all-or-none definition, it does not take into account how symptoms relate to the burden of AF. We here show that patients in whom a single AF recurrence is documented during one year of follow-up, improve in QoL similar to patients without AF recurrences. However, multiple AF recurrences is associated with absence of QoL improvement. We found no QoL difference with regard to gender.(26)

Previous studies investigated the impact of the AF burden or symptom burden on QoL after catheter ablation. Similar to the results after thoracoscopic surgery presented here, patients with a high burden of AF show no improvement or even a decrease of QoL after catheter ablation. Furthermore, patients with demonstrated AF recurrences, but with a low AF burden, showed significant QoL improvement after ablation.(27) Also, it has been shown that patients with symptomatic AF before ablation may experience asymptomatic episodes after the procedure.(28) Evidently, asymptomatic AF recurrences are unlikely to affect QoL.

Study Limitations

AFACT was designed to evaluate the efficacy of GP ablation on AF outcome in patients undergoing thoracoscopic surgery for AF. Although the study was not designed, nor powered for specific changes in QoL, changes in the overall QoL as measured by the SF-36 questionnaire were a prespecified endpoint. The main driver of QoL outcome in this analysis was AF recurrences, although one of the multivariable predictors of lack of QoL increase was a preexisting low PCS or MCS. It cannot be excluded that patients were more likely to report improved QoL, because all underwent a procedure. However, the difference in reported outcome between patients with and without AF recurrences or irreversible complications argues against that. It should be noted that, although we followed up patients more rigorously than the guidelines require,(8) periodic Holter monitoring may underestimate the true incidence of AF recurrences. However, as asymptomatic AF recurrences are not expected to affect general QoL, this likely did not affect our conclusions. The current analysis was restricted to one year of follow-up. Is cannot be excluded that during a longer follow-up period different results are achieved, in particular with respect to patients with (irreversible) procedural complications.

Conclusion

Patients with symptomatic advanced AF undergoing thoracoscopic surgery for AF had a substantial improvement in quality of life, regardless of additional GP ablation. AF recurrences were the most important determinant for lack of QoL improvement. QoL in patients without or with a single AF recurrence increased to values similar to the Dutch reference population. Patients with multiple AF recurrences had no increase in QoL and remained at the low baseline level. Irreversible, but not reversible, complications of the procedure were associated with lack of QoL improvement.
References


PART 3
CHAPTER 9

Second Chance for a Totally Thoracoscopic Video-Assisted Pulmonary Vein Isolation for Atrial Fibrillation

Antoine H.G. Driessen
Sébastien P.J. Krul
Bas A.J.M. de Mol
Joris R. de Groot

Abstract

Thoracoscopic surgery for atrial fibrillation (AF) is an attractive and emerging treatment modality. However, when a bleeding occurs access for hemostasis is limited. Therefore, a sternotomy might be necessary to stop the bleeding and continue the operation. We report 2 patients with a periprocedural bleeding in whom sternotomy could be prevented by tamponading the bleeding, interrupting the operation and resuming 3 weeks later. Our cases show that sternotomies can be prevented and that there is a second chance for thoracoscopic surgery for AF.
Introduction

Minimally invasive, off-pump surgery for atrial fibrillation (AF) is a promising new approach toward the non-pharmacologic treatment of AF.(1,2) From the first report onward,(3) the procedure has evolved from radiofrequency pulmonary vein isolation (PVI) through a bilateral minithoracotomy to a totally thoracoscopic PVI with the addition of left atrial lines for compartmentalization of the left atrium and advanced periprocedural confirmation of conduction block across the ablation lines, using electrophysiological endpoints.(4) The increasing complexity of the operation and the limited access through the endoscopic ports may urge a sternotomy in life-threatening periprocedural bleeding.(1,2,5) Sternotomy and continuation of the procedure is often preferred because it is very unattractive to perform a redo procedure, and pericardial and pleural adhesions after the initial operation may preclude access to the heart and increase the risk of a new bleed. However, for the patient, the minimally invasive nature of the thoracoscopic approach might be crucial. Indeed, the classic Cox-maze III operation was abandoned as a stand-alone procedure because of its invasive nature.(6)

We here report 2 patients undergoing totally thoracoscopic PVI in whom a bleeding occurred. The operation was interrupted and resumed 3 weeks later. This is a save approach and prevents sternotomies in patients undergoing stand-alone, totally thoracoscopic surgery for AF.

Case Reports

Patient 1

The patient is a 43-year-old woman with persistent AF. She had 2 previous catheter ablations and used sotalol and acenocoumarol. After double lumen intubation and collapse of the right lung, endoscopic ports were introduced in the right chest wall and the pericardium was opened as described previously.(1) Before isolation of the right PVs, the fat tissue over the roof of the atrium was dissected to prepare for the superior line. An arterial bleeding from a small coronary branch occurred behind the superior caval vein, which precluded continuation of the dissection. The bleeding was tamponaded with Surgicel (Ethicon, Inc, Somerville, NJ), applied through the thoracoscopic ports. Upon removal of the Surgicel, the bleeding continued. It was tamponaded again and after a 1-hour observation period the pericardium was closed with a single suture. Total blood loss was 450 ml. Figure 1 shows the location of the bleeding. Figure 2 shows photos from different stages of the bleeding and how it stopped. Video 1 demonstrates the cause of the bleeding in case 1: dissection of a coronary branch, subsequent tamponade with Surgicel, and end result at closure of the pericardium are shown (an accompanying video for this article can be viewed on the Internet at:
Patient 2

The patient is a 65-year-old man with diabetes, hypertension, typical atrial flutter, and persistent AF. His medication included acenocoumarol, amiodarone, and metoprolol, and medication for diabetes and hypertension. After double lumen intubation, introduction of the trocars on the right side, and opening of the pericardium, the light dissector perforated the posterior left atrium and caused a venous bleeding. Perforation was evident from visualization of the light dissector within the superior right pulmonary vein. Figure 1 indicates the location of that bleeding. The light dissector was retracted and the bleeding stopped as a consequence of contracture of the muscular atrial wall. No material was left within the pericardium. The bleeding recurred during a second attempt to pass the light dissector. The pericardium was approximated and a pericardial drain was left for 24 hours. Total blood loss was less than 200 mL and the patient was discharged on the fourth postoperative day. There was no evidence for pericardial effusion on the transthoracic echocardiogram.

Three weeks later the procedure was resumed. First, the left side of the procedure was completed. The PVs were isolated and entry and exit block confirmed. The left atrial appendage was removed and the left side of the superior line was constructed. After completion of the left side, the light dissector was positioned from cranial to caudal around the right PVs and PV isolation was established with the bipolar clamp. Thereafter, the right side of the superior
line and the trigone line were constructed. Bidirectional block was confirmed across all ablation lines. Drains were left in both pleurae and the patient was discharged at the third postoperative day. His typical atrial flutter was treated successfully with a catheter ablation of the cavotricuspid isthmus. After 6-months follow-up there have been no more episodes of atrial arrhythmias (without the use of amiodarone and metoprolol).

Figure 1. Posterior side of the heart, indicating bleeding. Posterior side of the heart. The thoracoscopic procedure is started from the right side. The location of bleeding in both patients is indicated with asterisks.

Comment

Totally thoracoscopic surgery for AF aims at combining the favorable results of the Cox-maze III operation with a less invasive approach. This is evident from the mere presence of 3 scars of only 1 cm bilaterally, and from the favorable follow-up results. The smaller the entry to the thorax, the more limited is the ability for hemostasis. Increasing complexity of the operation with the addition of left atrial lines and periprocedural confirmation of the conduction block might further increase the risk of bleeding. This might urge an emergency sternotomy. Although we are not aware of casualties after a sternotomy for bleeding during a thoracoscopic approach, a sternotomy is not truly “minimally invasive.” We, and others, therefore aim at preventing this conversion. In this contribution we show that even when a bleeding occurs during thoracoscopic surgery of the heart, it can be tamponaded safely and the procedure can be resumed later. Our 2 cases demonstrate that there is a second chance for the totally thoracoscopic approach once a complication precludes continuation of the first attempt, and that sternotomies can be prevented even when an arterial or venous bleeding occurs.
Figure 2. Surgical overview of bleeding. A) Coronary vessel just before bleeding. (B) and (C) Bleeding from vessel. (D) Tamponade of the bleeding with Surgicel. (E) Closed pericardium after 1 hour observation. (F) Surgicel 3 weeks later at resumption of the operation.
Chapter 9

References


CHAPTER 10

Previous Cardiac Surgery does not Preclude Thoracoscopic Ablation of Advanced Atrial Fibrillation

A Case serie.

Antoine H.G. Driessen *
Jan M. Leerink *
Wouter R. Berger
Nicoline W.E. van den Berg
Jolien Neefs
Sébastien P.J. Krul
Wim Jan P. van Boven
Joris R. de Groot

*These authors contributed equally

Submitted
Abstract

Objectives
Thoracoscopic surgery for atrial fibrillation (AF) appears to be associated with a higher efficacy than catheter ablation. An important shortcoming is that it is conceived a single procedure. We studied the feasibility and safety of thoracoscopic AF ablation procedure years after thoracoscopic or other cardiac surgery.

Methods
We describe six procedures performed between 2014 and 2017 by a single operator (AHGD). Pulmonary veins were ablated. If applicable and safe, additional superior and trigone lines were ablated. Bidirectional conduction block was tested. The left atrial appendage was excised if deemed safe using an Endogia. The primary procedural endpoint was defined as completing the procedure. Freedom of AF was defined as absence of AF episodes >30 seconds without the use of antiarrhythmic drugs.

Results
Six patients underwent thoracoscopic surgery for AF long (1-49 years) after previous cardiac surgery. Three had an aborted thoracoscopic procedure more than one year earlier, one had AF recurrences 7 years after thoracoscopic AF surgery. The other patients had previous mitral valve surgery (12-49 years). Median follow up was 29 (20-42) months, for patients with more than 1 year follow up. Two patients were recently operated.

Conclusions
We show that redo thoracoscopic surgery for AF can be performed safely. Procedures were completed in all patients. Among patients with more than 1 year of follow-up, 3 out of 4 were in sinus rhythm at the latest follow-up. However, only one was without any recurrence.
Atrial fibrillation (AF) is the most common cardiac arrhythmia, which prevalence and incidence continue to increase as a result of the aging population and the improved survival of chronic cardiovascular disease.\(^{(1,2)}\)

In patients remaining symptomatic despite adequate control of the ventricular rate, and a trail of antiarrhythmic drugs, invasive treatment is recommended.\(^{(3,4)}\) For this purpose and frequently after failed catheter ablation, stand-alone thoracoscopic surgery is increasingly being employed. Although direct comparisons are limited, thoracoscopic surgery for AF appears to be associated with a higher efficacy in the prevention of AF recurrence than catheter ablation, at the cost of more procedural complications. Boersma et al. showed that in patients with prior failed catheter ablation, enlarged left atria and hypertension or severely enlarged left atria, thoracoscopic surgery was associated with an approximately two times higher rate of AF absence compared to catheter ablation (66 vs 36% after one year). The single procedure efficacy of a single catheter ablation, with variable and non-standardized follow-up was reported 57%.\(^{(5)}\) Conversely, applying the strict endpoint definitions of the HRS/EHRA/ECAS consensus, stand alone thoracoscopic surgery was associated with AF absence without antiarrhythmic medication in 69% (79% with antiarrhythmic drugs).\(^{(6)}\) A hybrid approach, where surgeons and electrophysiologists join forces, seems slightly more efficacious with 83-86% AF absence without antiarrhythmic drugs.\(^{(7-9)}\) Also in patients with advanced AF, that is, usually associated with (severely) enlarged left atria, persistent AF and/or failed catheter ablations, thoracoscopic surgery is feasible with 50% complete AF absence without antiarrhythmic drugs after 5 years of follow-up, when 88% of patients were in sinus rhythm.\(^{(10,11)}\)

Aside from the higher procedural complication rate compared to catheter ablation, an important shortcoming of thoracic surgery for advanced atrial fibrillation is that it is conceived a single procedure, since pericardial and pleural adhesions after previous (thoracoscopic) cardiac surgery may hamper safe access to the pericardium and the left atrium. We have previously reported 2 patients who underwent a successful second thoracoscopic procedure several weeks after abortion of the first procedure due to bleeding.\(^{(12)}\) The feasibility and safety of a thoracoscopic AF ablation procedure many years after thoracoscopic or other cardiac surgery has not been described.

Here, we describe six patients with advanced AF and (severely) enlarged left atria, who underwent thoracoscopic surgery for AF long (1-49 years) after previous cardiac surgery. Three of these patients had a thoracoscopic procedure because of an earlier aborted thoracoscopic ablation more than one year earlier, or late AF recurrences 7 years after thoracoscopic surgery for AF. The other three patients had previous mitral valve surgery (12-49 years earlier). We show that in experienced hands redo thoracoscopic surgery for AF can safely be performed, without procedural complications.
Materials and Methods

All six procedures took place between 2014 and 2017 and were performed by a single operator (AHGD). All operations were performed under general anesthesia. Selective lung ventilation was accomplished by placing a double-lumen endotracheal tube. The procedure consisted of a bilateral approach, where the patient was ventilated on the contralateral lung. Surgery was typically started on the patient’s right side with 10-mm ports; two ports in the fourth and sixth intercostal space midaxillary line, and one 5 mm port in the third or fourth intercostal space anterior axillary line. Pleural adhesions, when present, were carefully dissected, and the pericardium was opened. The sinus transversus and sinus obliquis were opened with blunt dissection, and the ligament of Marshall was cut. The surgical approach toward thoracoscopic AF ablation has been published previously. In short, pulmonary veins were ablated using the AtriCure bipolar clamp (AtriCure Inc, Mason, Ohio). In patients with a clinical diagnosis of persistent or long standing persistent AF, an additional superior line, connecting the bilateral PV islands and a trigone line from the superior line to the left fibrous trigone at the level of the aortic root were ablated if possible, conforming to the Dallas lesion set. Bidirectional conduction block was tested across all ablation lines and additional ablations were performed if necessary. The left atrial appendage was excised if deemed safe by the operator using an Endogueia stapling device. The autonomic ganglionated plexi (GPs) were ablated according to institutional guidelines or according to randomization in the AF ACT study. The primary procedural endpoint for the current study was defined as the ability to unevenly complete the thoracoscopic procedure. Freedom of AF was defined as the absence of atrial fibrillation, atrial flutter, atrial tachycardia and junctional tachycardia lasting longer than 30 seconds after a blanking period of three months as defined by the 2012 HRS/EHRA/ECAS expert consensus. Clinical follow-up was performed every 3 months with a clinical visit, electrocardiography, and 24-h Holter monitoring. Symptomatic patients were encouraged to obtain additional rhythm recording. Median follow up duration was 29 (20–42) months, for the patients with a longer follow up than 1 year. Two patients were recently operated and have not completed one-year follow-up.
Chapter 10

Results

Cases

Patient 1.
The patient is a 47-years-old female with a mitral valve repair 12 years before for severe mitral valve regurgitation with retraction of the posterior valve leaflet. She suffered from symptomatic paroxysmal AF for 11 months. AF recurred despite treatment with sotalol, flecainide and multiple electrocardioversions (ECV). The CHA2DS2VASc score was 1 based on female gender. The left atrium was severely enlarged with an echocardiographic measured left atrial volume index of 42mL/m2. No previous catheter ablation was performed. Patient was scheduled for a thoracoscopic ablation consisting of pulmonary vein isolation, GP ablation and confirmation of bidirectional block. Thoracic access was uneventful, starting from the right side. There were no pleural adhesions and the pericardium could be opened without any problems on both sides. Intrapercardial, adhesions from the previous atriotomy were noted but did not preclude successful completion of the procedure. As there were only mild adhesions on the posterior wall of the atrium encircling of both pulmonary vein pools was relatively easy. Unfortunately, after 3 months AF recurred, antiarrhythmic drugs were restarted and the patient received multiple electrical cardioversions (ECV). At this moment the patient is sinus rhythm.

Patient 2.
The patient is a 69-years-old male with symptomatic persisting AF since 5 years. His medical record stated a primary PCI for an inferoposterior and lateral infarction 15 years earlier, hypertension, rheumatic valve disease, mild mitral stenosis and a mildly reduced right ventricular function. Forty-nine years earlier, he underwent a left-lateral thoracotomy for a mitral valve commissurotomy. AF was persisting despite multiple ECV’s and multiple anti-arrhythmic drugs including sotalol and amiodarone. The echocardiographic measured left atrial volume index was enlarged with 34mL/m2. His CHA2DS2VASc score was 3 based on hypertension, age and vascular disease. No previous catheter ablation was performed. The intended ablation strategy consisted of pulmonary vein isolation and additional left atrial lines. Placement of the thoracoscopic ports was uneventful, starting from the right side. There were evident pleural and pericardial adhesions bilaterally. During the procedure, additional left atrial ablation lines were made because of the persisting nature of AF. Pericardial adhesions precluded ablating a trigone line. The procedure was complicated by a self-terminating bleeding and a new first degree AV-block on the ECG. GP ablation was not performed. After two years follow up the patient is free from any recurrences of atrial arrhythmias and not using antiarrhythmic drugs.
Patient 3.
The patient is a 56-years-old male with hypertension and symptomatic paroxysmal AF since 2 years. His main symptoms included a reduced exercise tolerance during AF. The arrhythmia was refractory for multiple antiarrhythmic drugs including sotalol and flecainide as well as for multiple ECV’s. The left atrium was severely dilated with an echocardiographic measured left atrial volume index of 54ml/m2. No previous catheter ablation was performed, as the patient preferred a surgical approach. The CHA₂DS₂-VASc score was 1 based on hypertension. The first thoracoscopic procedure was aborted because of clinically relevant bleeding while encircling the right pulmonary vein. One year later, another attempt was undertaken, and a successful thoracoscopic procedure, consisting of pulmonary vein isolation and left atrial appendage excision, was performed. The procedure was started from the left side, as the previous bleeding occurred while encircling the right pulmonary veins. Thoracic access was uneventful. There were no pleural adhesion on the left side and only mild adhesions on the right side (Figure 1). Intrapericardial, the amount of adhesions was considerable, but could be dissected. The procedure was completed uneventfully. Unfortunately, after a blanking period of 3 months atrial fibrillation and atrial flutters recurred. Antiarrhythmic drugs were restarted and multiple ECV’s followed. Eventually, a rate control strategy was chosen.

Figure 1. Right sided view after entering the thorax
Upper panel: right sided view with pleural adhesions in patient #3. Lower panel: cartoon clarifying anatomical landmarks of the upper panel
Chapter 10

Patient 4.
This patient is a 71-years-old male with typical atrial flutter and later in the course symptomatic persisting AF for 10 years. His medical record stated tenting of the mitral valve with moderate mitral regurgitation. AF persisted despite medical treatment with flecainide and amiodarone therapy and multiple ECV's. Seven years earlier, a thoracoscopic ablation consisting of pulmonary vein isolation was performed in another hospital. No catheter ablation was performed. The left atrium was enlarged with an echocardiographic measured left atrial volume index of 40mL/m2. Because of persistent AF recurrence, patient was scheduled for a redo thoracoscopic approach with the creation of the Dallas lesion set and excision of the left atrial appendage. Access to the heart was hampered by pleural and pericardial adhesions, but was achieved without problems. Conduction block across the pulmonary vein lesions created 7 years earlier, was confirmed in a hybrid setting (9, 10). Entry- and exit block were proven. Therefore, pulmonary vein isolation was not repeated, and additional ablation lines were made and the left atrial appendage was excised. The procedure was uneventful. Eight months after the last thoracoscopic procedure, one single recurrence of atrial fibrillation treated with a successful elektrocardioversion was documented. Therefore, technically no freedom from AF after 1 year was obtained. However, no more recurrences followed during a follow-up period of 16 months. The patient is currently asymptomatic and in sinus rhythm.

Patient 5.
This patient is a 64-years-old male with symptomatic persisting AF for 3 years. His medical record stated a diminished left ventricle function at onset of AF, recovering under treatment. AF persisted despite medical treatment with flecainide and sotalol therapy and multiple ECV's. The left atrium was dilated with an echocardiographic measured left atrial volume index of 37 ml/m2. No previous catheter ablation was performed. The CHA2DS2VASc score was 1, based on hypertension. The first thoracoscopic procedure was aborted because of a bleeding while encircling the right pulmonary vein. One year later, another attempt was undertaken, and a successful thoracoscopic procedure, consisting of pulmonary vein isolation, roofline and trigone line and left atrial appendage excision, was performed. Surgery this time was started on the right side, and thoracic access was uneventful. Only mild pleural adhesions existed around the pericardium (Figure 2). However, a considerate amount of pericardial adhesions were present. The procedure was completed uneventfully as planned. No GP ablation was performed. Currently, the patient is still in the 3-month blanking period and, 2 month after the procedure, in SR without cardioversion or the use of antiarrhythmic drugs.
Previous Cardiac Surgery does not Preclude Thoracoscopic Ablation - A Case series

Figure 2. Left sided view of the pericardium after entering the thorax
Upper panel: thoracoscopic image of the left sided approach in patient #5. Note the previously opened pericardium. Lower panel: anatomical clarification as in figure 1

Patient 6.
This patient is a 71-years-old male with hypertension and symptomatic persistent AF since 3 years. He was operated for a mitral valve endocarditis in 1987 and a redo surgery in 1994 with a replacement of his mitral valve, both via a midsternal approach.

Medical history revealed multiple longer periods in sinus rhythm initially. Subsequently, atrial fibrillation progressed and became refractory for multiple antiarrhythmic drugs including metoprolol, sotalol and flecainide as well as for multiple ECV’s. He developed tachycardia induced heart failure with a severely diminished left ventricle function while in atrial fibrillation (EF was 58% before) with a severe reduced exercise capacity during AF.

The left atrium was severely dilated with an echocardiographic measured left atrial volume index of 102ml/m2. No previous catheter ablation was performed. The CHA2DS2-VASc score was 5 based on age, hypertension, TIA, heart failure.

The thoracoscopic access was uneventful with only minimal pleural adhesions. Intra-pericardial, a considerable amount of adhesions was found, that could be dissected. The procedure consisted of pulmonary vein isolation and a roof line. Anatomically, the right inferior pulmonary vein was displaced far to the left, probably due to the sever enlarged left atrium. Safe encircling
of the right inferior vein could not be accomplished. Therefore, only the right superior vein was ablated. The veins on the left side were encircled and ablated without problems. The trigone line was not performed for safety reasons. No GP ablation was performed, according to institution guidelines at the time of surgery. Extensive adhesions prevented resection of the left atrial appendage. After 2 months, the patient is in atrial fibrillation after failure of one cardioversion and still on antiarrhythmic drugs. Cardioversions will be repeated after titrating his antiarrhythmic drugs.

Figure 3. Inter pericardial adhesions, here from the left side
Upper panel: left sided opening if the pericardium in patient #5. Clear pericardial adhesions are present.
Lower panel: Anatomical clarification as in figure 1,2

Discussion

These cases show feasibility to perform a safe and successful minimally invasive thoracoscopic ablation procedure after previous surgery during which the pericardium was opened. In all of the patients presented here there was a procedural success without major complications. However, complete freedom from AF was only obtained in one patient, albeit that clinical success was achieved in 3/4 patients with longer follow up. Potentially, this lower success rate
in comparison with previous studies relates to a longer duration of AF in our patients. Similarly, the inability to complete the trigone line because of pericardial adhesions could have precluded a higher recurrence of atrial fibrillation. Because of the previous cardiac surgery, a different type of atrial scarring may have occurred. It is unknown whether this is indeed the case and how this may have affected the procedure and procedural outcome.

The nature and time since previous surgery was very heterogeneous in our cases, with two patients having a relatively recent and one a semi-recent thoracoscopic operation for AF, in contrast with the other patients having mitral valve surgery 12, 23 (two procedures) and 49 years before. One can imagine that these are two different patient groups with different types of scarring of the atria. Interestingly, the patient with the longest time between the current procedure and the previous surgery was one of the patients who obtained freedom of AF in our cases.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.00 ± 8.85 years</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>16.67 %</td>
</tr>
<tr>
<td>AF duration</td>
<td>4.16 ± 2.91 years</td>
</tr>
<tr>
<td>Type of Surgery</td>
<td></td>
</tr>
<tr>
<td>Mitral valve</td>
<td>3</td>
</tr>
<tr>
<td>Previous VATS PVI</td>
<td>3</td>
</tr>
<tr>
<td>LAV index</td>
<td>52.67 ± 22.79 ml/m2</td>
</tr>
<tr>
<td>LVEF</td>
<td>67.28 ± 8.45 %</td>
</tr>
<tr>
<td>CHADVASC</td>
<td>1.33 ± 0.75</td>
</tr>
<tr>
<td>Time from previous surgery</td>
<td>15.50 ± 16.75 years</td>
</tr>
<tr>
<td>FU duration</td>
<td>20.00 ± 13.75 Months</td>
</tr>
</tbody>
</table>

In three of six patients GP ablation was performed. However, as the AFACT trial showed that GP ablation is futile in terms of freedom of AF after one year but leads to more major complications,(11) standardized GP ablation in patients with advanced AF may be considered obsolete. This study is a non-randomized observation of cases undergoing thoracoscopic surgery, performed in a high volume center (> 500 thoracoscopic AF procedures). Although the rate of complete AF absence appears low, a thoracoscopic procedure can be an alternative in selected patients who underwent previous thoracic surgery. Evidently, a safe procedure is key, emphasizing that the surgeon should be skilled and experienced, and the number of ablation lines, although tailored to the patients needs, should be kept limited. A hybrid setup, where an electrophysiologist can confirm conduction block across lesions perioperatively, gives the opportunity to perform fewer ablation lines.(15) Electrophysiological guidance of thoracoscopic surgery can be accomplished with both endocardial and epicardial approaches, with similar results, as described before.(10)
Chapter 10

**Conclusion**

Thoracoscopic surgery for symptomatic, advanced AF is feasible and safe in patients who had previous cardiothoracic or thoracoscopic surgery. A patient tailored ablation lesion set, as well as intra operative confirmation of conduction block may add the experienced surgeon to achieve a favorable result.

Future series, including more patients, are needed to investigate efficacy on freedom of AF.
Previous Cardiac Surgery does not Preclude Thoracoscopic Ablation - A Case serie

References

CHAPTER 11

General discussion and future perspectives
In this thesis, the surgical treatment of atrial fibrillation with a focus on the role of the ganglionated plexi, was studied. This treatment was performed totally epicardially in a video-assisted, hybrid setup. Unlike alternative treatment modalities, it provides us with epicardial surface mapping in which activation block and conduction velocities can be mapped, and atrial tissue sampling in which scarring can be seen. Together with the obtained effectiveness of treatment, it can be correlated to preoperative parameters such as MRI-derived atrial scarring and patient characteristics. This may help in predicting the effectiveness of this and other treatment options.

Currently, atrial fibrillation affects approximately 300,000 people in the Netherlands alone and more than 6 million people throughout the European Union.\(^\text{(1,2)}\) It is expected that in Europe, the number of people with this condition will reach between 14–17 million by 2030.\(^\text{(1,3)}\) The average monthly cost per patient in the chronic phase of AF treatment is $640. If it is not yet a major economic health care problem, it has been projected that the cumulative costs will rise to over 100 billion euro per year in Europe at that time.\(^\text{(4)}\)

AF patients have a five-fold increased risk of developing a stroke.\(^\text{(2)}\) Oral anticoagulation with vitamin K antagonists or non-vitamin-K oral anticoagulants decrease that risk by approximately two-thirds,\(^\text{(5)}\) still, in the presence of risk factors as measured by the CHA\(_2\)DS\(_2\)VASc score, anticoagulation should be continued lifelong, even after successful restoration of sinus rhythm.\(^\text{(2)}\) Similarly, patients with atrial fibrillation have a two-fold increased mortality.

Collectively, this means that atrial fibrillation is increasingly influencing health care, economics and society. This situation has caused investigators to design hybrid treatments where surgeons and electrophysiologists join forces to develop new, more effective and innovative treatments. Also, it is necessary to be able to predict which treatments are beneficial to which category of patients, and more importantly, which are not.\(^\text{(6-9)}\) It helps us in establishing the balance between offering effective therapy to those who need it and will benefit from it, and those in whom invasive therapy will not ultimately effect heart rhythm.

**Evolving a mapping system**

Thromboembolic and bleeding complications are a major problem, associated not only with chronic treatment, but also with invasive treatment. Minimizing potential bleeding and thromboembolic complications was a condition integral to our search for a novel hybrid treatment modality. Logically, it forced us into avoiding transseptal punctures and made us
choose a totally epicardial approach instead. In order to avoid heparinization, thus lowering the risk of these complications, we designed and implemented a hybrid setup in an operating theatre setting, combining the advantage of surgical ablation and epicardial mapping of the electrophysiologist with less-invasive surgical ablation.

The advantage of this type of surgical ablation over endocardial ablation is shown by Boersma et al in a direct comparison of surgical versus endocardial PVI\(^{5(10)}\). We believed that further developing this technique within a hybrid setup would increase the success rate. Lockwood et al showed that if completeness is the goal, it is eminently important to map extra lines. They also showed that if lines are complete, the success rate increases significantly.\(^{5(9)}\) To obtain optimal mapping results we used an epicardial mapping system in the operating theatre. Cardiologists and surgeons have to combine their expertise and skills to obtain good results and benefit for their patients by means of this approach. As we have shown, a hybrid setting seems to improve results and is consistent between different setups.\(^{5(6,7,9,11)}\) Although not randomized, in a retrospective comparison between similar patients, hybrid treatment seems to outperform non-hybrid.\(^{5(11)}\)

The autonomic nervous system

Chapter 2 explores the known data on surgical PVIs and the so-called VATS-MAZE procedure. Two hybrid setups were included, both of which performed above average. As HRS guidelines dictate, some kind of confirmation of conduction block is essential in this kind of surgery, and this is also essential in order to obtain better results.\(^{5(9)}\) It encourages us to routinely perform this kind of mapping, in particular in creating additional left atrial lines (ALAL). This procedure can only be performed as part of a hybrid approach. As these ALAL have to be created in patients suffering from other conditions besides paroxysmal atrial fibrillation, the confirmation from mapping is crucial in obtaining higher than average success rates.\(^{5(9)}\) After we present our initial results in Chapter 3, our mapping approach is documented in Chapters 4 and 5. Chapter 4 explains the variations in electrophysiological findings during surgery. As pulmonary vein isolations and rooflines were complete in most cases, they did not drive the differences in the success rate. The trigone line was only complete in two-thirds of these cases, showing no correlation with success.

We performed only a limited number of box lesion procedures, as conceptually this can reduce the transport function of the left atrium. We abandoned the inferior line because of the incapability to show completeness of the box lesion in all cases (see Chapter 5).

The difficulty of creating conduction block is a continuing and fundamental issue. Incomplete lines may give rise to even more atrial arrhythmia and may ultimately be even worse than no line at all. New mapping tools and electrodes are required in order to show the completeness
of created ablation lines more easily. By showing completeness of ablation lines, compliance with guidelines will be achieved, but, more importantly, it will result in the elimination of a substantial number of cases of arrhythmia. If in the future we are unable to show this, lines will have to be abandoned as they will result in more arrhythmia.

**Ganglionated plexi**

The various hierarchical levels of extrinsic (nuclei and axonal fields in the brain), intrathoracic (spinal cord ganglia), and intrinsic (major GP and the atrial neural network) autonomous nervous systems are interdependently connected but can function independently once disconnected. Injection of cholinergic agents into the GPs, electric stimulation of nerves, and pacing-induced AF produces proarrhythmic autonomic hyperactivity, leading to shortening of the atrial and PV APD (parasympathetic effect) and an increase in intracellular Ca\(^{2+}\) (sympathetic effect), resulting in triggered firing and induction of AF. GP stimulation also directly affects atrial myocardial electrophysiology in a proarrhythmic manner, consistent with a predominantly parasympathetic action. In dogs, disconnecting extrinsic from intrinsic cardiac innervation resulted in shortened regional refractory periods and an increased burden of AF or AT starting after 4 to 5 weeks. Thus, removing the inhibitory effect of the extrinsic on the intrinsic autonomous cardiac innervation causes proarrhythmic GP hyperactivity, which provides the rationale for GP ablation. Indeed, Katritsis et al demonstrated fewer recurrences in patients with paroxysmal AF randomized to catheter ablation of four major GP areas and Marshall’s ligament in addition to PVI compared with either treatment in isolation. Also, an anatomical approach to GP ablation conferred less AF recurrence than an evoked vagal response–based localization. Mao et al demonstrated that 8 weeks after GP ablation in dogs, APD was shorter than in sham-operated animals, and AF inducibility increased. In contrast, the acute effect of GP ablation results in APD prolongation and decreased AF inducibility but coincides with abundant reinnervation of the atrium, which may promote AF inducibility. Such reinnervation might have contributed to our findings, supported by the observation that, on Holter monitoring, increased heart rate in the GP group was no longer present after 1 year. Similarly, there is abundant clinical evidence for structural and autonomic remodeling and increased non-PV triggers in advanced and long-standing AF. Combining GP ablation with standard surgical ablation therapy seemed logical, as GPs are more easily reached.

In the AFACT trial, we randomized patients between GP ablation and no GP ablation on top of our normal VATS ablation, consisting of PVI with additional left atrial lines if the patient was in non-paroxysmal atrial fibrillation. A higher rate of freedom from AF was expected, but the outcome was dramatically different. There was no difference in freedom from atrial
Chapter 11

tachycardia but there were more complications, i.e. bleeding, conduction disorders, and sinus node dysfunction as reflected by more pacemaker implantations. The differences were equally distributed between performing surgeon and independent of time, suggesting it was not related to a learning curve. We could not find any other explanation for the higher bleeding rate and believed that it was caused by either more rigorous surgical dissection of the atrium or by a longer procedure, making it perhaps more demanding.
We could not fully explain the conduction disorders. The higher pacemaker rate and sinus node dysfunction could be a result of modulating the autonomic nervous system. The effect of modulation was strengthened by an increase heart rate after 3-6 months in the GP group.
In the recurrence group, there was a higher proportion of atrial tachycardia in the GP group than in the non-GP group. This might point to inadvertent myocardial damage within the GP group compared with the non-GP group. New and other ablation techniques could potentially avoid this but still need to be investigated. The question remains if the higher number of pacemakers and the increased risk of bleeding will persist.

Surgical boundaries

Exploring surgical boundaries is part of our practice. No progress would be made if we did not do this. Firstly, we showed that not all bleeding needs a sternotomy but in most cases can be treated minimally invasively. Of course, this depends not only on the type of bleeding but also on the skills of the surgeon. In some cases, bleeding was managed while still completing the operation. We also showed that ablation can be performed safely in a staged two-operation approach, thus preventing a sternotomy.
As our experience increased, we also explored reoperations. We showed that in selected patients, redo surgery can be performed both safely and with acceptable results. This depends on the initial operation, but also on the type of ablation that has to be done. Both the surgical management of bleeding and the possibilities in redo surgery need to be further explored.
Surgical expertise is mandatory and can only be obtained in high volume centers. It raises the question if such specialist centers should be established.

Quality of life

Although the success of the operation is measured in recurrences and medical treatment, patients have a different experience. A single recurrence after years of continuous or recurrent AF is qualified as a failure but, to the contrary, it probably feels like a great success to the individual patient. These considerations make it even more difficult to compare different
treatment modalities. In our QoL follow-up, we show that repeated recurrences and irreversible adverse events lead to a diminished score. A single episode of AF recurrence will not change therapy, and as the CHA$_2$DS$_2$VASc score drives the decision to prescribe oral anticoagulants in our patients, this will not change either. Life expectancy will not differ. Therefore, further research is mandatory, focusing on QoL and “soft” endpoints. In order to evaluate the effect experienced by patients, the monitoring of health-related QoL is becoming a standard part of the clinical care that we provide to our patients.
Chapter 11

References


General discussion and future perspectives


Summary
Nederlandse Samenvatting
Co-Authors
Abbreviations
About the Author
Publications
Dankwoord
Summary

This thesis focuses on minimal invasive rhythm surgery, for atrial fibrillation (AF) in particular, and the role of ablation of the ganglionated plexi around the heart.

Chapter 1 provides the background to this thesis. It describes how AF poses a clinical and health care problem, for which invasive interventions exist. However, although it has a reported efficacy of over 90%, due to its complexity and invasiveness the Cox maze operation has never been adopted on a large scale. On the other hand, catheter ablation of paroxysmal AF has proved successful, although often several procedures are needed before an acceptable clinical result is achieved. The efficacy of catheter ablation in patients with more advanced AF (i.e. persistent in nature, with enlarged left atria) or in whom a previous ablation procedure has failed, is modest. Wolf et al developed a minimally invasive approach to the surgical ablation of AF, which aimed to combine the efficacy of the Cox maze procedure with a less invasive approach. In turn, Yilmaz et al modified this procedure into a totally thoracoscopic procedure. The main challenges of this thoracoscopic approach are maintaining ablation line integrity to avoid left atrial arrhythmia in time, and defining additional ablation targets by the modification of the autonomous nervous system through the ablation of the ganglion plexi. An overview of how this thesis answers some of the open questions in this regard is given.

In Chapter 2 we present a review of the early publications on minimal invasive AF surgery. Twenty-three studies of minimally-invasive surgery for AF were reviewed. These compare the success rates of the standard maze procedure and of catheter ablation. On average, at one year of follow-up, freedom from AF was 69% without antiarrhythmic drugs (AAD), and 79% with AAD. Although initial results were promising, minimally-invasive surgery continues to evolve, for example, by the inclusion of electrophysiological endpoints, and by the type of additional left atrial lines (ALAL) (trigone, roof and inferior lines, box lesion). However, if any additional benefit is conferred by ganglionated plexus ablation (GP) and how hybrid collaboration with an electrophysiologist should be shaped remain to be determined.

In Chapter 3 we present the initial results of thoracoscopic surgery for AF with pulmonary vein isolation (PVI) and GP ablation. The complete absence of AF without the use of AAD was ascertained in 86% of patients, after a single procedure at one year of follow-up. The ablation strategies comprised a hybrid total epicardial approach consisting of PVI and GP ablation in patients with paroxysmal AF; and PVI, GP and ablation and additional left atrial lines in patients with persistent or longstanding persistent AF. All ablation lines were confirmed epicardially by obtaining in and exit block and pacing manoeuvres, using custom-made multi-electrodes, connected to a conventional electrophysiology amplifier. We discuss the difference
Summary

between this approach and those described by others, and speculate on the mechanisms underlying these results.

Carel Kools developed the custom-made mapping multi-electrodes for the confirmation of conduction block and for atrial stimulation at our hospital. This platform can be regarded as the modification and improvement of existing epicardial mapping tools.

Chapter 4 describes in extent the design and specific epicardial hybrid approach. It describes our joint surgical-electrophysiological protocol for confirmation of conduction block across PV isolation lines and additional left atrial ablation lines. This strategy is a feasible one, and detecting and treating residual conduction across ablation lines may contribute to the prevention of AF recurrences and improve the outcomes of thoracoscopic AF surgery.

Chapter 5 further elaborates on the evaluation of isolation of the pulmonary veins and addresses specific conceptual pitfalls related to skills, recording systems and resolution of the mapping electrode. We present a literature review and go on to describe a number of techniques for thoracoscopic mapping. Three different approaches to the periprocedural confirmation of conduction block during thoracoscopic surgery are discussed. This chapter also touches upon the potential cost effectiveness of such an approach.

Chapter 6 describes the AFACT trial, which was designed to investigate the role of ganglionated plexus ablation in the surgical treatment of atrial fibrillation. AFACT is the first randomized study on GP ablation in thoracoscopic surgery and also the largest study of minimally invasive AF surgery to date. It demonstrates that in patients with advanced AF, of whom 68% had an enlarged left atrium, GP ablation did not result in a reduction of AF recurrence. GP ablation was also associated with more major procedural complications (19% versus 8%), in particular bleeding, leading to abortion of the procedure or sternotomy, and significantly more pacemaker implantations due to sinus node dysfunction and AV block. In addition, recurrence of atrial tachycardia was more often seen in the GP group than in the control group. There was no difference in the recurrence of AF between groups during the so-called blanking period. We conclude that GP ablation should not be performed routinely in patients with advanced AF.

Most studies on AF treatment only report one year of follow-up, consistent with the HRS/EHRS/ECAS consensus report. Longer follow-up may be interesting from the perspective of both patient and caretaker, as it probably reports the effect of a particular treatment on a patient's health more accurately. We followed up the first 69 of our patients to reach 5-year follow-up. In Chapter 7 we report the 5-year follow-up in patients with advanced paroxysmal
and persistent AF who underwent thoracoscopic surgery. In 50% of these patients (67% with paroxysmal and 33% with persistent AF), there was complete absence of AF, without the use of AAD, after a single surgical procedure. After 5 years, and irrespective of recurrent episodes, 88% of patients were in sinus rhythm and 70% had discontinued AAD. Only 9% of patients had frequent AF recurrences or permanent AF. This is the first report of the 5-year outcome of thoracoscopic, electrophysiologically-guided ablation of advanced AF. Eighty-eight percent of patients returned for an outpatient appointment at 5 years. All available electrocardiographic and clinical data on 100% of the entire cohort were collected. Previous catheter ablation was a predictor for AF recurrence and exclusion of these patients resulted in the absence AF in 60% of patient’s naïve to invasive therapy at 5 years.

Freedom from AF is a clinical endpoint that can be monitored objectively. From a patient’s perspective, his or her wellbeing or quality of life (QoL), and the change therein, is probably even more important. It can help in distinguishing/choosing the treatment of choice. Additionally, as guidelines advise the prescription of anticoagulant drugs based on the risk of stroke rather than on the presumed absence of AF, and as symptoms of AF are the only approved indication for invasive therapy, change in QoL is a relevant clinical outcome. In Chapter 8, we describe the predefined sub analysis for QoL obtained from the participants of the AFACT study by short-form 36 (SF-36) questionnaire. We demonstrate an improvement in QoL in the entire cohort following thoracoscopic surgery, regardless of additional GP ablation. The most important determinant of absence of an improvement in QoL was AF recurrence. Patients who had a recurrence of AF had a lower QoL than those who did not. Also, patients with a recurrence after >6 months showed a decrease in QoL at 12 months when compared with that at 6 months. One single episode of AF recurrence appeared to decrease QoL only temporarily, as in these patients there was no difference in the SF-36 subscales or in the domains compared with patients without AF after 12 months. The QoL in patients with no or only one episode of AF recurrence increased to the level of that of the general Dutch population. Patients with complications from the procedure showed no increase in the SF-36 subscales. However, in patients in whom the procedural complications appeared reversible, the absence of QoL increase was temporary, as these patients had a QoL similar to that of patients without complications at 12 months. Conversely, in patients with irreversible complications (pacemaker implantation in particular), QoL remained at the same decreased/low level as it was before the procedure.

Over 500 thoracoscopic AF procedures have been performed at our hospital. It has made us move towards novel, more demanding techniques and therefore towards expanding surgical boundaries. Chapters 9 and 10 describe these boundaries and how we explored them.
Summary

In Chapter 9 we report two patients undergoing totally thoracoscopic PVI in whom bleeding occurred. The operations were halted and resumed approximately three weeks later. We have shown that this is a safe approach and that it prevents the necessity for sternotomy in patients undergoing totally thoracoscopic surgery for AF.

Chapter 10 describes a case series of patients who had undergone open chest cardiac surgery between 12-49 years previously or who had had a failed or aborted thoracoscopic procedure more than 1 year earlier. These cases show that it is feasible to perform a safe and successful minimally-invasive thoracoscopic ablation procedure after previous surgery at which time the pericardium was opened. In all of the patients presented in Chapter 10, the procedure was successful and there were no major complications. However, complete freedom from AF was only obtained in one patient, albeit that clinical success was achieved in 3/4 patients at longer follow-up. A longer history of AF, the inability to complete the trigone line, and a different type of atrial scarring due to previous cardiac surgery may all have contributed to this lower success rate in comparison with previous studies. It is not known whether this is indeed the case and how this may have affected the procedure and procedural outcome.

Although the rate of complete absence of AF appears low, a re-do thoracoscopic procedure may be a good alternative in selected patients who have previously undergone thoracic surgery. Evidently, a safe procedure is key, emphasizing that the surgeon should be skilled and experienced, and although tailored to the patient’s needs, the number of ablation lines, should be limited. A hybrid setup, where an electrophysiologist can confirm conduction block across lesions peri-operatively, provides the opportunity to create fewer ablation lines.
Nederlandse Samenvatting

Dit proefschrift richt zich op minimaal invasieve ritme chirurgie voor atrium fibrilleren. (AF) In het bijzonder de rol van het chirurgisch abberen van ganglion plexi rondom het hart.

Hoofdstuk 1 geeft de achtergrond van dit proefschrift. Het beschrijft hoe AF een steeds groter klinisch en gezondheidszorg probleem wordt en geeft een overzicht van de bestaande invasieve mogelijkheden. De meest efficiënte behandeling, met meer dan 90% gerapporteerde succes, de Cox-maze-operatie, is daarbij nooit op grote schaal geïmplementeerd geraakt door zijn complexiteit en invasiviteit. Aan de andere kant hebben catheterablaties voor paroxysmaal AF bewezen effectief te zijn. Wel zijn er regelmatig meerdere procedures nodig voor een acceptabel klinisch resultaat. De effectiviteit van catheterablaties in patiënten met gevorderd AF (zoals persistent of met vergrote atria) bij wie eerdere ablaties gefaald hebben, is matig.

Wolf et al. ontwikkelden een minimaal invasieve procedure voor chirurgische ablatie van AF, die beoogde de effectiviteit van de Cox maze procedure te combineren met een minder invasieve aanpak. Yilmaz et al. hebben deze procedure gemodificeerd naar een volledig thoracoscopische behandeling.

De grootste uitdaging van deze thoracoscopische aanpak is het verkrijgen van complete, transmurale, ablatielijnen. Dit is essentieel om linker atrium tachycardieën op termijn te voorkomen. Een tweede uitdaging is additionele ablatie doelen te definiëren om het autonome zenuwstelsel rondom het hart te modificeren. Hiervoor wordt een ablatie van de ganglion plexi uitgevoerd. Dit proefschrift geeft een overzicht van de relevante vragen en antwoorden inzake de uitvoering en effectiviteit van deze interventie.

In Hoofdstuk 2 wordt een review gegeven van de eerste publicaties over minimaal invasieve AF chirurgie. Er werden 23 studies over minimaal invasieve AF chirurgie beschreven. In het gehele cohort is er gemiddeld na 1 jaar een vrijheid van AF (d.w.z. geen recidieven van atriale aritmie langer dan 30 seconden) van 69%, zonder anti-aritmica (AAD), en 79% met AAD. Alhoewel de initiële resultaten veelbelovend zijn, blijft minimaal invasieve AF chirurgie verder evalueren. Voorbeelden zijn het toevoegen van elektrofysiologische eindpunten maar ook het implementeren van additionele linker atrium lijnen (ALAL). Echter, het is nog niet vastgesteld hoe er additioneel voordeel is te behalen door ganglion plexi (GP) te ableren, en hoe een hybride samenwerking tussen de electrofysioloog en chirurg er uit moet zien.

In Hoofdstuk 3 worden de eerste resultaten van onze ervaringen met minimaal invasieve chirurgie voor AF door middel van pulmonaal vene isolatie (PVI) en GP ablatie gepresenteerd. Bij 86% van de patiënten was er een jaar na een enkele procedure een volledige afwezigheid van recidieven AF zonder het gebruik van AAD. De ingreep bestond uit een hybride, volledig

Carel Kools ontwikkelde en produceerde de custom-made multi-electrode waarmee het geleidingsblock wordt gecontroleerd en atriale pacing wordt verricht. Het platform kan gezien worden als een modificatie en verbetering van reeds bestaande epicardiale mapping elektrodes.

**Hoofdstuk 4** Beschrijft in detail de specifieke epicardiale hybride aanpak binnen ons centrum. Het beschrijft tevens het gezamenlijk chirurgisch-elektrofysiologische protocol dat gebruikt wordt voor het bevestigen van geleidingsblock over de PVI-lijnen en de ALAL. Het aantonen en behandelen van residuele geleiding over de ablatielijnen kan bijdragen aan het voorkomen van recidief AF en daarmee de uitkomsten van minimaal invasieve chirurgie voor AF verbeteren.

In **Hoofdstuk 5** wordt verder ingegaan op hoe het geleidingsblock van PVI lijnen en ALAL wordt onderzocht en komen specifieke valkuilen van een hybride aanpak aan de orde. Hieronder vallen de invloed van chirurgische en elektrofysiologische vaardigheden, het mapping systeem en de invloed van de resolutie van de multi-electrode. Er wordt een overzicht gegeven van de literatuur en een aantal technieken voor thoracoscopische metingen wordt bediscussieerd. Drie verschillende benaderingen van peri-procedurele bevestiging van het geleidingsblock geïnduceerd door minimaal invasieve chirurgie voor AF worden beschreven. Dit hoofdstuk gaat ook kort in op de potentiele kosteneffectiviteit van een hybride aanpak.

**Hoofdstuk 6** beschrijft de AFACT-trial, die opgezet was om de rol van ganglion plexus ablatie in minimaal invasieve chirurgie voor AF te onderzoeken. AFACT is de eerste gerandomiseerde studie over GP-ablatie in minimaal invasieve chirurgie voor AF en tevens de grootste studie over minimaal invasieve chirurgie voor AF tot nu toe. De studie toont aan dat in patiënten met gevorderd AF, bij wie in 68% een vergroot linker atrium aanwezig was, GP ablatie geen reductie gaf in AF recidieven. GP-ablatie was daarentegen wel geassocieerd met meer majeure procedurele complicaties (19% versus 8%), in het bijzonder bloedingen, leidend tot het stoppen van de procedure of een sternotomie. Ook waren er significant meer pacemakerimplantaties door sinusknoonpdysfunctie of AV block.
Tevens trad in de GP groep meer atriale tachycardie als recidief op dan in de controle groep. Er was geen verschil in het voorkomen van recidieven van AF in de zogenaamde blanking periode, bestaande uit de eerste 3 maanden post procedureel. Onze conclusie is dat GP ablatie niet routinematig moet worden toegepast in patiënten met gevorderd AF. Verder onderzoek moet uitwijzen of er nog een rol is voor GP ablaties met andere energiebronnen of in een andere patiëntengroep.

De meeste studies over AF behandelingen rapporteren alleen de een-jaar follow-up, in overeenstemming met het HRS/EHRS/ECAS consensus rapport. Langere follow-up is van belang voor de zowel patiënt als de behandelend arts. Lange-termijn follow-up geeft naar alle waarschijnlijkheid een nauwkeurigere weergave van het effect van een specifieke behandeling op de gezondheid van een patiënt. Wij vervolgd onze eerste 69 patiënten die een thoracoscopische AF ablatie ondergingen na 5 jaar. In Hoofdstuk 7 doen we verslag van 5-jaars follow-up in patiënten met gevorderd paroxysmaal en persisterend AF die minimaal invasieve chirurgie voor AF hadden ondergaan in het AMC. Na een enkele hybride chirurgische procedure, was er in 50% van deze patiënten (67% met paroxysmaal en 33% met persisterend AF) geen enkele episode van AF, terwijl er geen AAD gebruikt werden. Na 5 jaar, onafhankelijk van of er recidieven waren, was 88% van de patiënten in sinusritme en had 70% geen AAD meer. Slechts 9% van de patiënten had frequent AF recidieven (>3 per jaar) of permanent AF. Dit is het eerste rapport van een 5 jaar follow-up van minimaal invasieve hybride chirurgie voor gevorderd AF. Achtentachtig procent van de patiënten kwamen na 5 jaar op de polikliniek. Alle beschikbare ECG’s en klinische data over 100% van het gehele cohort werden verzameld. Eerdere catheterablatie was een voorspeller voor AF recidief. Exclusie van de patiënten met een eerdere gefaald catheterablatie resulteerde in een stijging van het succes tot 60% AF recidief vrij na 5 jaar.

Afwezigheid van AF is een klinisch eindpunt dat objectief gemonitord kan worden. Vanuit een patiëntenspectifiek, is de gezondheidsbeleving of kwaliteit van leven (QoL) en de verandering daarin naar alle waarschijnlijkheid belangrijker. Inzicht in verandering van QoL kan helpen in het kiezen van de behandeling. Dit is verder zo omdat richtlijnen het voorschrijven van orale anticoagulantia baseren op het CVA risico en niet het wel of niet aanwezig zijn van AF. Omdat symptomen van AF de enige goedgekeurde indicatie voor invasieve therapie zijn, is het verschil in QoL een relevant klinisch eindpunt. In Hoofdstuk 8, beschrijven we een geprespecifieerde subanalyse van QoL, in participanten van de AFACt-studie met behulp van een short-form 36 (SF-36) vragenlijst. Wij laten, na minimaal invasieve chirurgie voor AF, een verbetering in QoL in het gehele cohort zien, ongeacht of er additioneel GP ablatie is verricht. De belangrijkste factor voor het uitblijven van een QoL verbetering was het krijgen van recidief AF. Patiënten met een recidief hadden een lagere QoL dan mensen zonder. Ook patiënten met een recidief
Nederlandse Samenvatting

meer dan 6 maanden na de ingreep, lieten een vermindering van QoL zien op 12 maanden in vergelijking met QoL op 6 maanden. Eén enkele episode van AF recidief lijkt de QoL alleen tijdelijk te verlagen, aangezien bij patiënten met niet meer dan een recidief er geen verschil was in SF-36 subschalen of domeinen vergeleken met patiënten zonder recidief op 12 maanden. De QoL in patiënten met geen of niet meer dan een enkel recidief steg tot het niveau van de (Normalised) Nederlandse populatie. Patiënten met complicatie van de procedure lieten geen verbetering zien in de SF-36 sub schalen. In patiënten bij wie deze complicaties reversibel waren, was de QoL hetzelfde als patiënten zonder complicaties na 12 maanden. In patiënten met een irreversibele complicatie (met name pacemakerimplantatie), bleef QoL op hetzelfde, verlaagde niveau als voor de ingreep.

In de afgelopen 9 jaar zijn meer dan 500 minimaal invasieve chirurgische procedures voor AF uitgevoerd in ons ziekenhuis. Het was onze missie om met onze specifieke ervaring de grenzen van de mogelijkheden te verkennen. **Hoofdstuk 9 en 10** beschrijven hoe we de chirurgisch-technische grenzen hebben opgezocht en verlegd.

**Hoofdstuk 9** Beschrijven we twee patiënten die een minimaal invasieve chirurgie behandeling voor AF ondernemen en bij wie een bloeding van het atrium ontstond. De operatie werd gestaakt en ongeveer drie weken later volledig heruitgevoerd zonder complicaties. Met deze casus tonen we aan dat tijdig onderbreken van de interventie een veilige aanpak is die een sternotomie kan voorkomen.

**Hoofdstuk 10** beschrijft een case serie van 6 patiënten die eerder een sternotomie hadden ondergaan voor hartchirurgie, 12-49 jaar eerder of die meer dan 1 jaar eerder een gefaalde of afgebroken thoracoscopische ritme procedure hadden ondergaan. Deze voorbeelden laten zien dat het mogelijk is om veilig en succesvol een minimaal invasieve thoracoscopische ablatie procedure te ondergaan na eerdere hartchirurgie waarbij het pericard was geopend. In alle patiënten beschreven in **Hoofdstuk 10**, was de procedure succesvol zonder majeure complicaties. Echter, complete afwezigheid van AF werd slechts verkregen in 1 patiënt met follow-up langeer dan een jaar. Een langere voorgeschiedenis van AF, het niet compleet transmuraal krijgen van de trigon lijn, verschillende soorten atriale littekenvorming als gevolg van eerdere hartchirurgie, kunnen allemaal hebben bijgedragen aan deze lage succeskans. Het mechanisme van het falen van deze re-interventies na eerdere hartchirurgie is niet bekend.

Alhoewel de complete afwezigheid van AF in de beschreven patiënten beperkt is, kan een re-do thoracoscopische procedure een goed alternatief zijn in geselecteerde patiënten die eerder een hartchirurgische procedure hebben ondergaan. Daarbij moet aan een aantal randvoorwaarden worden voldaan: natuurlijk is een veilige procedure daarbij een voorwaarde, de chirurg moet
ervaren en getraind zijn, en (hoewel aangepast aan karakteristieken van de patiënt), moet het aantal ablatielijnen beperkt zijn. Een hybride setting, waarbij de electrophysioloog tijdens de ingreep aan kan geven of er geleidingsblock is over de ablatielijnen kan de voorwaarden scheppen om minder ablatielijnen te maken.
Co-Authors

Aeilko Zwinderman
André Linnenbank
Arthur Wilde
Bas de Mol
Dean Chan Pin Yin
Femke Piersma
Guillaume Geuzebroek
Jacques de Bakker
Jan Leerink
Jolien Neefs
Jonas de Jong
Joris de Groot
Mark Bierhuizen
Nicolien van den Berg
Sacha Salzberg
Sébastien Krul
Sunny (Warren) Jackman
Wim Jan van Boven
Wouter Berger
**Abbreviations**

AAD: Antiarrhythmic drug  
AE: Adverse events  
AF: Atrial fibrillation  
AFACT: Atrial Fibrillation Ablation and autonomic modulation via Thoroscopic surgery  
ALAL: Additional left atrial lines  
APD: Action potential duration  
AT: Atrial tachycardia  
AV: Atrioventricular  
BMI: Body mass index  
BP: Bodily pain (SF-36 scale)  
ECAS: European Arrhythmia Society  
ECV: Electro cardioversion  
ECG: Electro cardiogram  
EF: Ejection Fraction  
EHRA: European Heart Rhythm Association  
EP: Electro physiology/physiologist  
GP: Ganglion plexus  
HFS: High frequency stimulation  
HRS: Heart Rhythm Society  
LA: Left atrial/atrium  
LAA: Left Atrial Appendage  
LAVI: Left atrial volume index  
NOAC: New oral anticoagulant  
MCS: Mental component summary (summary of SF-36 scale)  
PCS: Physical component summary (summary of SF-36 scale)  
PV: Pulmonary vein  
PVI: Pulmonary vein isolation  
QoL: Quality of life  
RF: Radio frequency  
SF-36: Short Form 36  
SR: Sinus rhythm  
TIA: Transient ischemic attack  
VATS: Video assisted thoracoscopy  
VKA: Vitamin K antagonist
About the Author


Vanaf de start werd met de afdeling Cardiologie samengewerkt op het ritme programma. Het kort ervoor door Dr. W.J.P. van Boven en Dr. J.R. De Groot opgestarte programma werd gezamenlijk uitgebouwd tot een van de grootste hybride AF programma’s wereldwijd. Dit samenwerkingsprogramma vormt de basis van onderdile dit proefschrift.

Hij is getrouwd met Annet Waaijer, samen hebben ze drie kinderen, Jan Albert, Anne Fleur en Madelief
Publications


Publications

design of the PRAETORIAN trial: a Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy. Am Heart J. 2012 May;163(5):753-760.e2.


Krul SP, Driessen AH, van Boven WJ, Linnenbank AC, Geuzebroek GS, Jackman WM, Wilde AA, de Bakker JM, de Groot JR. Thoracoscopic video-assisted pulmonary vein antrum isolation, ganglionated plexus ablation, and periprocedural confirmation of ablation lesions: first


Dankwoord

Allereerst wil ik graag mijn patiënten bedanken. Niet alleen diegenen die meegewerkt hebben aan deze onderzoeken maar ook al diegenen die ik als arts heb mogen behandelen. Het vertrouwen dat jullie als patiënt in mij stellen is immens, daarvoor dank.

Beste Joris, jou gestructureerdheid verhoudt zich geweldig tot mijn chaos. Je weet als geen ander wanneer het genoeg is of wanneer je nog kunt doorzetten. Daarmee lukt jou wel wat velen niet konden en zijn we denk ik een uniek stel. Ik heb gelukkig zo lang gewacht totdat ik jou eerste promovendus kan zijn als hoogleraar. Dank voor het vertrouwen en je geduld.

Beste Bas, geniaal, excentriek, sociaal, mens. Vooral het laatste treft me steeds weer. Dank dat je mij de kans geeft om te zijn wie ik ben.

Beste leden van de leescommissie, Wim, Mark, Lucas, Ron, Benedikt, Ruben en Arthur. Ieder van jullie representeren een gedeelte van mijn carrière en mijn ambitie. Dank voor het aanvaarden van de uitnodiging, ik hoop nog veel met jullie te mogen samenwerken.

Wim Jan, was zich liebt das neckt sich! Dank voor alle kansen die jij mij in Nieuwegein gaf, supergaaf dat je nu bij mij in het AMC zit.

Buiten alle co-auteurs, zonder wie dit natuurlijk niet gelukt was, wil ik speciaal danken Sébastien, Wouter, Jolien, Robin, Femke en auch Nicolien, Wim en Carel, zonder jullie geen patiënten, onderzoek, database, mapping tools of artikelen! En dus dit proefschrift.

Daphne, dank voor al je werk dat je verzet hebt om mijn houtje touwtje Engels toonbaar te maken!

Natuurlijk mijn directe collega’s Cardio-Thoracale chirurgie in het AMC en het OLVG maar ook de anesthesisten, cardiologen, intensivisten, chirurgen, perfusionisten, assistenten, NP’ers, VS’ers, verpleging, OK, anesthesie assistenten en anderen op beide locaties. Velen zullen het wellicht niet eens gemerkt hebben. Het zijn er ook teveel om te noemen en ik wil ook geen onderscheid maken. Zonder jullie was dit niet gelukt.

Beste collega’s in het VuMC. Ik droom al lang om in het grootste hartcentrum van Nederland te werken, defacto zijn we een. Welkom in deze gezamenlijke ster die zal gaan stralen, ik kijk daar naar uit! Ik hoop van harte dat het ons lukt samen met het OLVG en Tjark de kroon op al het werk te zetten.
Dankwoord

Ook mijn opleiders, specialisten en mede assistenten van zowel de Cardio thoracale chirurgie, chirurgie als andere disciplines in zowel het Martini als het St. Antonius, zonder hun was ik nooit Cardio-Thoracaal chirurg geworden.

Lieve Susanne, toen ik zei dat jij mijn anesthesist was, meende ik dat! Dank dat je mij zo vaak helpt als het moeilijk is.

Beste Ron, je hoort echt nog een keer genoemd te worden. Jou reflectie zorgt ervoor dat we zonder kleerscheuren naar de overkant komen. Dank je wel voor de vele uren samen op OK.

Beste Reinoud, met enorm veel plezier sta ik te kijken hou jou ster omhoog schiet. Het voelt ook een beetje van mij als ik jou backup mag zijn.

Lieve Maaike, ik blijf er van overtuigd dat we een top WPM waren, dat kwam voor het grootste gedeelte door jou!

Lieve Astrid, een rijdende trein is het lastigste om op te komen! Ik ben blij dat je je eigen draai er aan geeft. Jou doorzettingsvermogen en inzicht gaan velen te boven!

Lieve Vrienden; Vriendschap bestaat in mijn optiek voor altijd of hij bestaat niet. Ik vraag echter wel veel van jullie!

Ik weet dat velen geloven dat ik in het ziekenhuis woon. Vaak ben ik er maar half of niet, vlug ik weg of heb geen tijd. De beruchtste was wel het diner met meer dan 10 man bij ons thuis. Annet was er niet en voordat de eerste hap genomen was, was ik ook weg, een donorhart halen. Nogmaals excuus daarvoor en dank voor alle superfijne momenten.

Giuseppe, 43 jaar geleden begon een vriendschap op 50 meter en nu 1500 km verder zien we elkaar nog steeds. Zoals je zei, het voelt alsof je eigen mama verliet.....

Tim, zonder jou was ik verzopen in de Delftse Schie en nog veel meer!

Michiel en Jeroen, beide vrienden van het eerste uur, meer dan 26 jaar samen, ieder zijn eigen weg. Dank jullie wel voor de vriendschap die voor ons inderdaad onvoorwaardelijk is.

Ernst, hoe sterk vriendschap kan zijn laten wij zien!

Ellen, zonder jou.....
Dankwoord

Riccardo, Duo Penotti! Wat maar weinig door hebben is dat er weinig verschil zit tussen ons, dank je dat je naast me staat, niet alleen vandaag.

Lieve Ton, het wordt nu echt tijd voor beachclub Toni en Toni! Ik ben zo blij voor alle mooie dingen die nu gebeuren in je leven, maar ook dat je hier weer naast me staat!

Lieve Familie van Heel, de warmte thuis in Fleringen en nu in Ottersum, Amersfoort, Den Haag en Remunj zegt genoeg.

Lieve Waaijers; Annie, Corina, Pieter, Thijs, Jolanda, Abel, Bregje, Jackie, Isabelle. Maar ook Albert (†), dankbaar voor Annet maar vooral ook voor alle mooie momenten samen.

Dit dankwoord schrijf ik, kort na het overlijden van Mam. Zelden heb ik iemand meegemaakt die zich zo belangeloos wegcijfert voor anderen, niet alleen voor ons kinderen of Pap maar ook voor anderen. De enorme hoeveelheid liefde die jij gegeven hebt en jou omringde zet alles terug in perspectief.

Eric, Janneke, Olivier, Floris en Hannah ons huis is altijd open. Het is superfijn om bij elkaar te zijn.

Lisette, Jacques, Mariëlle en Jean, bij jullie ben ik pas echt wie ik ben, het kleine broertje. Dank jullie wel daarvoor, de wereld is soms wel heel groot.

Leef Pap en Mam daobaove, as ich aan uch dink, dink ich aan dit leedje: “Wengske aan wengske, saamen op 'n bengske, in de golde maoneschien. As mich is gegaeve, dan te meuge laeve, zal ik nog van dich halde euver vieftig jaor.” Ich zal altied van uch blieve haje.

Lieve Jan Albert, Anne Fleur en Madelief, jullie zijn het mooiste wat mama en ik hebben in ons leven. Wat hou ik veel van jullie.

Lieve lieve Annet, op het bandje staat “Ik heb wat stille woorden, die ik jou nooit heb gezegd… ik heb ze bewaard héél héél zorgvuldig, voor dit moment…

met jou ben ik in Utopia!
Dankwoord
Minimally Invasive Surgical Management of Atrial Fibrillation, The Role of Ganglionated Plexuses

Antoine Driessen

UITNODIGING
Voor het bijwonen van de openbare verdediging van mijn proefschrift

Minimally Invasive Surgical Management of Atrial Fibrillation, The Role of Ganglionated Plexuses

Vrijdag 16 maart 2018, te 10:00 uur in de Agnietenkapel Oudezijds Voorburgwal 229 - 231 1012 EZ Amsterdam

Na afloop van de promotie bent u van harte welkom bij de receptie ter plaatse.

Antoine Driessen
Stationstraat 12
1591 GN Abcoude
a.driessen@amc.uva.nl

PARANIMFEN

Riccardo Cocchieri
r.cocchieri@olvg.nl

Ton Heestermans
a.a.c.m.heestermans@nwz.nl