Electrophysiological Evaluation of Thoracoscopic Pulmonary Vein Isolation

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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.

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. 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. 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%.

The cornerstone of catheter ablation is isolation of the pulmonary veins from which the arrhythmogenic triggers arise. 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. 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. 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.

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. A number of mostly small studies with minimally invasive surgery for AF have recently been reviewed. 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. As with catheter ablation of AF, recurrences after thoracoscopic surgery have been ascribed to reconnection of the pulmonary veins or incomplete left atrial lines. 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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{27,30}

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{32,34} Krul et al. describe the initial experience with an entirely epicardial procedure.\textsuperscript{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 trigue line connecting the superior line to the left fibrous trigone at the level of the aortic annulus, functioning as a mitral isthmus line.\textsuperscript{42} 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).\textsuperscript{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.\textsuperscript{33} Sequentially a roof line, 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).\textsuperscript{44} 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.\textsuperscript{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.\textsuperscript{39,42}

**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.\textsuperscript{27,45} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 remodeled 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 perse better in paroxysmal AF and suggesting a relation between the rate of bidirectional block and the chance of recurrence.\textsuperscript{46}

Lockwood et al. described 14 patients in whom, after application of minimally invasive surgery for AF employing the Dallas lesion set,\textsuperscript{41} 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.\textsuperscript{47} Kron et al. investigated the mechanism of arrhythmia recurrence in 13 patients.\textsuperscript{25} 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.\textsuperscript{26} 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.
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 thoroscopic 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, Nademanee et al have to be credited for bringing the role of continuous fractionated atrial electrograms (CFAE) to our attention as a mechanism of AF perpetuation. Recently, ablation of rotors with use of the TOPERA 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 pacemaker 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 transcutaneously 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.

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 reliable 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...
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.

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 is 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...
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 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.

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 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).

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
Liu et al demonstrated that atrial tachycardia after thoracoscopic surgery for AF was caused by macroreentry through iatrogenically 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.

References:


