Keynote Lecture Series

Surgical options for treatment of atrial fibrillation

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If we want to improve the outcomes, increase the success and reduce the complication rate of existing treatment strategies in concomitant and stand-alone atrial fibrillation (AF) procedures, we will have to increase our understanding of the pathophysiology, and of the disease, the limitations of current energy sources and ablation catheters, the different possible lesion sets, as well as improve communication between the electrophysiologist and cardiac surgeon. The technical limitations of percutaneous endocardial ablation procedures and the empirical techniques in surgical AF procedures necessitate new and innovative approaches. Surgeons should aim to improve the quality of the lesion set and minimize the invasiveness of existing techniques. The Maze procedure remains the basis upon which most of the more limited concomitant ablation procedures are and will be designed, but in stand-alone patients, recent progress has directed us towards either a single-step or sequential combined percutaneous endocardial procedure with a thoracoscopic epicardial procedure on the beating heart. A dedicated team of electrophysiologists and cardiothoracic surgeons can now work together to perform AF procedures. This can guide us to determine if there is an additional value of limiting the lesion set of the Maze procedure in concomitant surgery, and of an epicardial access in the treatment of stand-alone AF on the beating heart. If so, we will better understand which energy sources, lesion sets and surgical techniques are able to give us a three-dimensional knowledge and a three-dimensional treatment of AF. As a result, we can expect to obtain a higher single procedure long-term success rate with an acceptable low complication rate.

Keywords: Atrial fibrillation (AF); concomitant surgery; stand-alone atrial fibrillation; hybrid

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What are the indications and the surgical options for treatment of concomitant or lone atrial fibrillation (AF)? The 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation recommended that it is appropriate to consider all patients with symptomatic AF undergoing other cardiac surgery for AF ablation (1). The indications for concomitant surgery according to this consensus statement are class IIa level of evidence C. According to the same consensus statement, stand-alone AF surgery should be considered for symptomatic AF patients who prefer a surgical approach, who have failed one or more attempts at catheter ablation, or who are not candidates for catheter ablation. The indications for lone AF surgery according to this consensus statement are class IIb level of evidence C.

The difficulty with the treatment of AF is the understanding of the underlying pathophysiology. The onset and maintenance of AF requires an event (trigger) that initiates the arrhythmia and the presence of a predisposing substrate that perpetuates it. Additional factors may also cooperate as modulators in facilitating initiation or continuation of AF. Triggers and substrate can be found both in the left and right atrium, but are usually located in the pulmonary veins (PVs) and/or left atrium (LA) (2-5). Haïssaguerre and colleagues published in 1998 that paroxysmal AF often originates from ectopic beats in the PVs (6). This was explained by the anatomical transition from PV endothelium to left atrial endocardium and the observation that juxtaposed tissues with different electrical properties may potentiate development of AF (6,7). The strategy of percutaneous catheter ablation of the posterior LA, including the antra surrounding the PVs, has proven effective at treating both paroxysmal and permanent AF (7-9). Other anatomical structures that may initiate AF are the superior caval vein, the vein of Marshall, the musculature of coronary sinus and the posterior wall of the LA. However, for AF to become sustained, the presence of an atrial substrate of sufficient mass capable of maintaining re-entrant circuits is necessary. The LA-PV junction and the posterior wall of the LA are critical structures in this regard (10). Electrophysiological and electro-anatomic mapping have increased our insights into the nature of abnormalities within the atria predisposed to AF. Loss of atrial myocardium characterized by atrial dilation and lower mean atrial voltage, conduction abnormalities characterized by prolongation of conduction times, increased effective refractory period and impaired sinus node function are contributing factors to AF (11).

Another important modulating factor is the autonomic cardiac innervation. Four major ganglionated plexi are located near the PVs, which are a primary location for entry of vagal nerves into the LA (12,13). Imbalance of autonomic nerve activity has been implicated in the initiation of AF (14). Parasympathetic nerves (slowing the heart rate) and sympathetic nerves (increasing heart rate) can both initiate AF, due to shortening of the atrial effective refractory period and to changes in intracellular calcium cycling (3,15). On this basis, it has been suggested that selective elimination of ganglionic plexi might diminish the occurrence of AF.

Some of the important questions we have to ask when we are considering a patient for treatment of AF include:

(I) Do we have an understanding of the exact pathophysiological mechanism of the disease?
(II) What is the optimal ablation approach?
(III) What are the choices of the lesion set?
(IV) Which energy source should we use?
(V) How to improve communication between the electrophysiologist and the cardiac surgeon?

In 1987, Dr. James Cox, in collaboration with cardiologist John Boineau and physiologist Richard Schuessler, pioneered an open-heart surgical procedure to treat AF (16-19). Multiple "blind alleys" were made in both atria by creating scar tissue, thereby directing the electrical impulse from the sinus node to the AV node. This allowed for coordinated electrical activation of the atrial myocardium. The procedure was modified to improve the results and to simplify the operation, culminating in the Cox-Maze IV technique (20). Key components of the Maze procedure are isolation of the PVs and excision of the left atrial appendage (LAA). These features are maintained in most of the operations designed to treat AF.

The Cox-Maze III procedure did not gain widespread acceptance for the treatment of lone AF because of its complexity and technical difficulty. New ablation tools have been marketed to replace the "cut-and-sew" technique and facilitate surgical ablation of AF. These catheters rely on energy sources to create long, continuous, linear lesions that block conduction. They differ mainly in the way by which they transfer energy to the tissue and how deep that energy is conducted into the tissue. Their ability to create a transmural lesion on the non-beating and beating heart from either the endocardial or epicardial surface is still not guaranteed. They can be organized in two major groups: unipolar and bipolar. The unipolar energy sources (mostly cryo and unipolar radiofrequency energy) radiate either heat or cold from a single unfocused source. When used on the epicardial surface on the beating heart, these energy sources have difficulties in creating transmural lesions. Bipolar radiofrequency energy has the potential to overcome this shortcoming (21-23). Since energy is delivered between two closely positioned electrodes, the tissue conductance between the two electrodes can be more accurately measured. Algorithms have been developed to better predict lesion transmurality and to adapt the energy delivery to the physiological characteristics of the tissue being ablated.

These new tools often allow for less invasive surgery, but this surgery is mostly done with a more limited lesion set.

How do we decide upon the lesion set? What is the theoretical design upon which the Maze procedure has been developed? Since AF mapping data was ambiguous and difficult to analyze, the Maze procedure was developed as a salvage procedure. It was designed as an anatomic procedure that eliminated all potential reentrant circuits that could rotate around the thoracic veins and valve annuli, subdivided large areas of contiguous tissue, and left a pathway for the sinus node to activate both atria and the AV node (24).

In both concomitant and stand-alone AF, PV isolation is the cornerstone of most ablation strategies. Performed two by two, or as an encircling lesion of the LA anterior of the ostium of the PVs, a so-called "box lesion". Many atria will have a substrate outside the PVs. Therefore, linear lesions connecting the PVs, towards the mitral annulus and the ostium of the LAA, and lesions in the right atrium can be necessary to improve the outcome of the ablation procedure. Mapping and ablation of complex fractionated electrograms could be part of the treatment strategy in the stand-alone population. The decision to perform a given lesion set on the beating or arrested heart will depend upon the ability to obtain a permanent continuous transmural lesion with existing ablation tools. Since the risks for thrombo-embolic events are increased, exclusion or excision of the LAA should be considered in patients with AF.

The 2009 consensus statement by the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) stated that the different lesion sets, the managing of the LAA and the various energy sources in use (cryotherapy, radiofrequency, cut-and-sew) still need to be compared prospectively (25).

What is the available literature on concomitant AF in cardiac surgery? There have been 16 randomized controlled trials (RCTs) published between 2002 and 2012 (26-41). In these studies, a total of 1,082 patients were included, 607 of whom were treated with an ablation. In seven studies, more than 50 patients were included, fourteen mitral valve surgeries were performed. In eight studies, data on patients undergoing coronary artery bypass grafting were reported. The energy sources used were radiofrequency in seven studies, cryo in three, microwave in two and cut-and-sew in four. Sinus rhythm at discharge was significantly higher in the ablated group: 62.7% *vs*. 26.6% for the non-treated group. Sinus rhythm at ≥12 months for the ablated and non-ablated groups was reported as 66.7% and 26.1% respectively. Thirty-day all-cause mortality was not significantly different between both groups: 5.3% *vs*. 3.8% respectively. There were no significant differences in neurological events (4.9% *vs*. 5.8%) and in pacemaker implantations (5.8% *vs*. 8.3%). Surgical ablation is a viable treatment for AF during concomitant cardiac surgery without increased mortality or risk of morbidity. We can conclude from these RCTs that short-, mid- and long-term SR prevalence are significantly improved in patients who undergo surgical ablation. Interestingly, subgroup analysis of the different ablation techniques showed no significant difference affecting SR outcomes. Furthermore, from 10 RCTs (735 patients), no significant difference was found in terms of neurological events between both groups.

How can we improve communication between the electrophysiologist and the cardiac surgeon? Basic concepts in AF treatment are obscured by different strategies in cardiac surgery and electrophysiology, leading to conflicting trends and misunderstandings. One of the major weaknesses of endocardial catheter-based ablation techniques is their inability to guarantee longlasting transmurality of the lesions. Ablation of the PVs with proof of an acute bi-directional electrical isolation is the cornerstone of most EP ablation strategies. This is the reason why recurrent AF after endocardial ablation is often associated with PV reconnection because of technical difficulties during energy delivery. The current limitations of energy delivery in the left and right atrium with a percutaneous approach are the major concern for this approach. Modern surgical AF ablation techniques are less confronted with incomplete lesions but are still empirical. The cardiac surgeon lacks the ability to define the specific properties of the underlying atrial electrical substrate in order to customize the subsequent ablation strategy. A Cox-Maze procedure on the arrested heart with no electrophysiological confirmation of the effect and quality of the lesion set is still the basis of a successful surgical AF procedure.

The benefits of a multi-disciplinary approach, combined with real-time visualization and mapping of the ablated tissue in both atria, will improve the accuracy of controlled power delivery to targeted cardiac tissue. Surgery for stand-alone AF has not achieved the same impact as surgery for concomitant AF. A sternotomy and cardiopulmonary bypass are invasive procedures with substantial associated morbidity, which most patients and cardiologists wish to avoid for treatment of lone AF. Indeed, the traditional sternotomy approach has, despite its efficacy, not achieved widespread application. Instead, percutaneous catheter-based procedures are used for lone AF. In 2007, only 700 procedures for lone AF were reported for that year in the Society for Thoracic Surgeons database (42).

In patients with stand-alone AF, the type of AF, duration of AF, the left and right atrial sizes will influence the success rate of an ablation procedure. The group of Allessie demonstrated in a goat model that AF begets AF (43). We could assume that in humans the moment AF begets AF, catheter ablation begets catheter ablation, since recurrence of AF is higher in atria with a more important substrate modification. A possible solution to avoid repeat catheter ablations could be a thoracoscopic epicardial radiofrequency ablation on the beating heart. New technologies have simplified creation of transmural lesions on the beating heart through a less invasive, thoracoscopic procedure. This allows for PV isolation, isolation of the posterior wall, ganglionic plexi evaluation and destruction, and LAA exclusion. In order to improve the durability of the lesions and to decide upon the lesion set, the epicardial approach can be combined with a percutaneous endocardial mapping and touch-up ablation strategy as a single-step or sequential procedure.

Why would a cardiologist or electrophysiologist refer a patient with lone AF for a surgical approach? A recent EP wire done by the European Heart Rhythm Association showed that the indications were failed catheter ablation in 30%, longstanding persistent AF in 24% of cases, the wish to exclude the LAA in 15%, preference of the patient in 16%, and 12% because of a shorter waiting list (44). These surgical procedures are effective in restoring permanent sinus rhythm, but transmurality of a lesion set cannot be guaranteed with current ablation catheters on the beating heart. In an attempt to limit the shortcomings of an endo- or an epicardial technique, a hybrid approach has recently been introduced. This approach is based on a close collaboration between the surgeon and the electrophysiologist, employing a patient-tailored procedure which is adapted to the origin of the patient's AF and takes into consideration triggers and substrate. A combined endocardial and epicardial procedure for the treatment of AF could be a way the cardiac surgeon and the electrophysiologist can explore as a team, to achieve a superior long-term cure rate.

A catheter ablation is more likely to be transmural when the energy from the catheters can be delivered on the endocardial and epicardial surfaces of the atrial wall. The single-step or sequential hybrid procedure combines minimally invasive surgical techniques with the latest advances in percutaneous ablation, and allows creation of transmural lesions on a beating heart through alternative, less-invasive approaches. Recently, a review has been published on hybrid procedures for the treatment of lone AF (45). Inclusion criteria were studies with >10 patients, and follow-up of >3 months. This review helps us to summarize and discuss results from published articles about hybrid thoracoscopic and transvenous catheter ablation for the treatment of stand-alone AF, and to establish the efficacy and safety of this procedure. The hybrid studies were published between 2011 and 2013, were observational in nature, single center, and none was randomized. The total number of patients included was 335 (range 15-101). Mean age ranged from 55.2 to 62.9 years. One hundred and fourteen patients (34%) had undergone one or more previous percutaneous catheter ablations. A total of 69 patients (20.6%) had paroxysmal AF, 104 (31.0%) had persistent AF and 162 (48.4%) had long-standing-persistent (LSP) AF. Mahapatra *et al.* (46) employed a sequential approach combining minimally invasive surgical ablation followed 3 to 5 days later with a planned endocardial catheter ablation, while Muneretto *et al.* (47) and Bisleri *et al.* (48) performed a staged catheter procedure 30-45 days after the surgical ablation. The other authors described a single-step approach with the catheter ablation following the surgical ablation during the same procedure. Three studies (47-49) employed a right thoracic monolateral approach, four a bilateral thoracic approach (46,49-52), one a subxiphoideal approach (53) and one a subxiphoid approach (54).

Four authors (46,50-52) employed bipolar radiofrequency, five (47-49,53,54) used monopolar radiofrequency as ablation source. One hundred and two patients (30.4%) underwent excision/ligation of the LAA. PV isolation was performed in all cases and additional left atrial lesions are reported in all studies. All papers defined the primary efficacy endpoint of surgery by current guidelines. Six studies (47-52) reported ≥12-month AAD-free success rate. The success rate ranged from 85.7 % to 92 % in papers employing bipolar RF and from 36.8 % to 88.9% in those utilizing monopolar RF. Mahapatra *et al.* (46) showed that the sequential approach compared favorably to a control group of patients who underwent repeat catheter ablation in terms of freedom from any atrial arrhythmias either off AAD (P=0.04) or on ADD (P=0.01). La Meir and co-workers (51) compared early results of a hybrid versus a standard minimally invasive approach. The hybrid group yielded better results in LSP-AF (P=0.01) whereas freedom from AF-off AAD was significantly higher in persistent and paroxysmal AF (both P=0.04).

There were three early deaths (0.8%) in the monopolar ablation group related to an atrio-esophageal fistula. Three patients (0.8%) required conversion to sternotomy in the bipolar ablation group. The complication rate was 4.1% (n=14), which is comparable to the results published by Cappato *et al.* for catheter ablations (55). Importantly, no thrombo-embolic complication was reported. No patient died during the follow-up.

A more extensive lesion set beyond PV isolation is often necessary (mainly in persistent and LSP-AF) to diminish the left and right atrial triggers and substrate. Interestingly, the only standard lesion applied to all hybrid patients was PV isolation and all energy sources used were radiofrequency. Theoretically-a hybrid approach allows completion of mitral and cavotricuspid lines, but these lesions were created in only a relatively small percentage of patients. Since it is not clear which lesions or lesion sets are needed and what the best end points for this procedure are, we can make no predictions about the need for a standard technique which can be applied to most patients and performed by all operators. Furthermore, it is not clear if it would be preferable to perform a simultaneous surgical/EP procedure or to perform a sequential procedure after maturation of the epicardialy created lesions. For some authors (56,57), simultaneous epicardial/endocardial procedures may be associated with false negative results (such as acute demonstration of a bidirectional block which could be transient due to edema), as well as the difficulties of early inducible arrhythmias. Nevertheless, a hybrid thoracoscopic and transvenous catheter ablation resulting from close collaboration between the surgeon and the electrophysiologist has a higher AAD-free success rate than isolated thoracoscopic or percutaneous procedures. The bilateral approach utilizing bipolar bidirectional devices showed a higher success rate independently of the AF type and seems to be the better choice for the hybrid procedure.

Patients with AF have a higher risk for thrombo-embolic events, with oral anticoagulation as the first choice of therapy to reduce systemic embolization. For those patients for whom anticoagulation is contraindicated, there is a need for alternative therapeutic approaches. It is assumed that 90% of clinically apparent embolisms in patients with AF originate from the LAA (58). Obliteration of the LAA could play an important role in stroke prevention in this patient population. Indeed, LAA amputation has been part of the Maze procedure since the beginning of concomitant AF surgery. There are several therapeutic options for LAA closure. The least invasive consists of a percutaneous transcatheter delivery of a LAA occlusion device. Currently two devices are widely used: the Watchman LAA system and the Amplatzer Cardiac Plug. Both devices have shown that all-cause stroke and all-cause mortality outcomes were not inferior to warfarin therapy (59,60). However, blood clots may still develop on these devices necessitating warfarin therapy (61,62). Surgical LAA occlusion, a more invasive procedure, can be achieved on the beating heart without the need for extracorporeal circulation by thoracotomy or thoracoscopy. It provides an epicardial mechanical closure of the LAA, avoiding the potential emboligenic risk of intracardiac foreign material. A second important difference is the electrical isolation of the LAA due to mechanical clamping or resection (63). Di Biase *et al*. suggested that in 27% of redo AF cases, the LAA was the site of origin (64) and therefore excision or clipping of the LAA eliminates this potential mechanism of AF.

What about the long-term follow-up of the hybrid procedure? Fifty-six patients underwent a hybrid procedure at the University Hospital Maastricht between May 29, 2008, and September 5, 2011. Twenty-nine patients had paroxysmal AF, 25 patients had persistent AF, 2 had LSP-AF. Eighteen patients had at least one previous catheter ablation for AF; in only one patient the PVs appeared to be isolated at the start of the hybrid procedure. The mean follow-up period was 1,084±363 days (range: 90 to 1,826 days). In all patients, block of all the PVs was confirmed during the procedure. In 8 patients with severe chronic obstructive pulmonary disease, a thoracoscopic epicardial isolation of the PVs was done only on the right side, and the left PVs were isolated endocardially using a cryothermal energy balloon catheter (Arctic Front; Cryocath, Montreal, Quebec City, Canada). In nine patients, AF was not inducible after PV isolation only. In 11 patients, a cavotricuspid line was made, and in 45 patients, a roofline was deployed, resulting in conversion to normal sinus rhythm (NSR) in five patients. In 42 patients, a box lesion was created epicardially by adding an inferiorline. In 6 patients, this resulted in a mitral isthmus-dependent atrial flutter which was successfully ablated. Thirty patients converted to NSR after creation of the box lesion. After endocardial touch-up in 9 patients (16%), endocardial entrance and exit block in the box during sinus rhythm was confirmed in 42 patients (75%). In one patient, an epicardial left fibrous trigone linear lesion was made. Four patients were still in AF at the end of the procedure and were cardioverted, and subsequently developed arrhythmia recurrence during follow-up. In the group of 53 (95%) patients who reached 2-year follow-up, 3 patients (5%) were lost to follow-up. At two years, 49 of 53 patients (92%) were in NSR, with no episodes of AF, atrial flutter or atrial tachycardia lasting longer than 30 seconds on office follow-up, Holter monitoring or pacemaker interrogation. Thirty-six (97%) of 37 patients were in NSR at three years of follow-up. Twenty patients reached the longest follow-up of four years, and 19 (95%) of them were in NSR. Two-year success, defined according to the Heart Rhythm Society, European Heart Rhythm Association and European Cardiac Arrhythmia Society consensus statement (freedom from AF, AFL and AT off AADs), was 82% for patients with paroxysmal AF and 88% for patients with non-paroxysmal AF. At four-year follow-up, this was 75% and 87% respectively. A total of 9 (16%) patients underwent CA for recurrence of supraventricular arrhythmia after the hybrid procedure, with 8 (15%) of 53 patients by two-year follow-up had undergone catheter ablation and 4 (20%) of 20 patients doing so by four-year follow-up.

Conclusions

AF is a serious disease which still necessitates multicenter

RCTs. For the hybrid procedure that targets a population of patients with long-standing persistent AF, it is necessary to establish whether this approach may become a standard treatment for lone AF.

To improve the long-term success rate, we need to search for solid endpoints and a better understanding of which patients benefit most. Since success is not only reflected by the percentage of sinus rate, we need to reduce complications and develop single procedures which eventually will lead to a higher cost efficacy of AF ablation.

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