Atrial fibrillation ablation: evolution of the curative approach

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The morbidity and mortality of atrial fibrillation (AF) makes the search for a curative approach one of the main quests in modern electrophysiology. After the groundbreaking steps of surgery for AF, recognition of the pulmonary veins’ (PVs) role in triggering AF, followed by the PV isolation (PVI) technique brought new hope for catheter ablation for AF. Safety and success were progressively improved in parallel with improvements in technological tools. The mechanistic heterogeneity of AF, enhanced in the chronic form, may explain the limited success of PVI alone in long-standing AF. This complex environment needs multiple approaches to extend the success rate to the whole spectrum of AF. Increase in mechanistic knowledge and technology may result in broader indications.

Introduction

Atrial Fibrillation (AF) is not only the commonest arrhythmia encountered in everyday clinical practice but the most challenging to manage. Pharmacologic therapy has largely been ineffective and several studies have questioned the benefits of sinus rhythm maintenance given the risk related to antiarrhythmic medications. Although the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial did initially suggest that maintenance of sinus rhythm with antiarrhythmic therapy is no better than ventricular rate control, a subsequent substudy of enrolled patients indicated that patients in sinus rhythm had better long-term prognosis.¹ This is not surprising given the significant morbidity and mortality associated with AF, which includes thrombo-embolic risk and impaired quality of life. New surgical techniques in the middle of the last decade² and catheter ablation³ have emerged as an alternative to pharmacologic treatment offering the potential for cure of AF. Paroxysmal AF can be effectively treated with pulmonary vein isolation (PVI) with high success rates of the order of 85–90%. Many groups have now demonstrated proof of concept in extending catheter ablation to patients with persistent or permanent AF, achieving medium term (1–2 years) success rates of 70–95% with an acceptable procedural risk in their hands.⁴–⁶ This review focuses on evolution of curative ablation therapy for the wide variety of patients in the clinical spectrum of AF.

Theories of atrial fibrillation

Although the mechanism of AF remains unclear, several hypotheses have been suggested. In 1963, Moe et al.⁷ proposed a theory of AF based on a multiple reentrant wavelets hypothesis, Computer modelling revealed that perpetuation of AF was related to a number of multiple wavelets depending on conduction velocity and refractory period. In a series of experiments based on this theory, Allessie and co-workers.⁸ demonstrated that a
minimum of between four and six reentrant wavelets was required to sustain AF. Since then, multiple mechanisms contributing to initiation and maintenance of AF have been described, including triggers of pulmonary venous,3 non-pulmonary venous origin,9 rotors10 and cardiac autonomic nerve activity.11 Observations that ectopics arising from the PVs could initiate AF, heralded an era of catheter-based ablation therapy.3,12 Jalife et al.10 described the ‘Rotors’ theory based on anatomical heterogeneities in cardiac muscle and so-called drivers responsible for perpetuating AF. The mother rotor concept is consistent with spectral analysis studies revealing regions of dominant high frequency activities that may be crucial to maintenance of AF.13 Importance of vagal input in patients with idiopathic AF and sympathetic tone AF in those with structural heart disease lend support for the role of autonomic nervous system. This is further supported by the findings and presence of autonomic ganglia near PVs.11 However, the impact of an ablation procedure purely based on ganglionic plexi remains to be demonstrated.

This mechanistic heterogeneity may explain why no single predetermined ablation scheme is effective across the entire spectrum of AF and also why strategies, which were previously recognized as quite distinct, have developed important areas of common ground.

### Evolution of surgical atrial fibrillation therapy: lessons for catheter ablation

Catheter ablation of AF, during its dawn, was guided by experience from surgical therapy for AF. In the 1980s, Williams et al.14 proposed isolation of the left atrium LA following his successful experiment in dogs, and Guiraudon et al.15 in 1985 developed the corridor procedure where incisions were made to create a path between the sino-atrial node and atrio-ventricular node with the hope of restoring regular rhythm to the ventricles. At that time, the only non-surgical technique available was the fulguration of His reported by Scheinman et al.16 in 1982 in order to isolate the atrium electrically from the ventricles.

All these three early techniques had similar drawbacks; they minimize the burden to the ventricles but the atrial tissue kept fibrillating without improving the atrial transport mechanisms and risks of thromboembolism.

Cox2 was the first to show that termination of AF was possible, in experiments on canine hearts. It was later found in human studies that including a lateral incision at the level of the mitral annulus, a medial incision from the PV to the inter-atrial septum posterior to the superior vena cava orifice and across the anterior limbus of the fossa ovalis down to the level of the tendon of Todaro converted AF to a right atrial (RA) flutter. The flutter was eventually terminated by a medial left incision to the RA, between the cava veins and then to the right free wall tricuspid annulus. Unfortunately, efficacy of this procedure was low and was extremely time consuming. Surgical modifications in attempt to improve success resulted in the Maze procedure, which has continued to evolve into the current Maze III procedure. The Cox-Maze III procedure includes: PVI, with a left-sided lesion made to connect to the LA appendage (LAA) and to the mitral annulus, a septal lesion, cryolesions in the coronary sinus (CS), an RA isthmus lesion, and finally excision of the LAA. The published 8-year follow-up of >90% restoration of sinus rhythm was impressive with a mortality rate of 2% and stroke risk was virtually eliminated. Short periods of post-operative AF were reported in 38% of the patients but restoration of the atrial transport function occurred in 80%. A major drawback was sinus node dysfunction requiring pacemaker implantation in 5–10% of the patients.

With the clinical evidence about the importance of PVI in AF, a modified procedure was developed to isolate the veins with an additional lesion connecting the line around the veins with the mitral annulus. This procedure resulted in >90% freedom from AF after 12 months.17

Surgical treatment has continued to evolve with new alternative energy sources (radiofrequency, microwave, ultrasound, laser and cryotherapy) replacing the cut-and-sew technique, reducing procedure time and bleeding risks, but at the cost of reducing the likelihood of transmural lesion contiguity. In practice, surgery for AF is performed mostly in patients undergoing concomitant cardiac surgery such as mitral valve surgery.18

### History of catheter ablation

Early attempts at catheter ablation of AF were largely inspired by the success of the Maze surgical procedure in treating both paroxysmal and persistent AF. The initial attempt to reproduce Maze procedure by catheter ablation was performed by Schwartz et al.19 in the LA, and Haissaguerre et al.20 in the RA in 1994. Linear ablation of the LA, in 18 patients with chronic AF, resulted in acute termination in 50% and long-term drug-free success in 78% but the procedures were long and redo procedures were performed in 39%. Early studies involving linear ablation confined only to the RA showed symptomatic improvement in only 53% of the patients, but when the ablation was extended to the LA significant improvement was observed.21 Recognition of the importance of PV ectopy as initiators of AF21,12 and subsequent demonstration that paroxysmal AF could be cured by PVI cemented this approach as the cornerstone strategy of catheter ablation for AF. (Figure 1).

### Evolution of strategies for catheter ablation

#### Pulmonary vein isolation

PVI confirmed by absence or dissociation of PV potentials following ablation is the key technique used in many centres for treatment of paroxysmal and persistent AF. The technique is based on electrical isolation confirmed by the use of circular mapping catheter pioneered by Haissaguerre et al. However to find the culprit vein by inducibility protocols is not reliable and recurrence may occur, caused by others veins, leading to repeated
procedures. In consideration of the foregoing, empirical isolation of all veins became the standard technique. In experienced hands, isolation of all veins can now be achieved in almost 100% of patients.

Although electrical isolation is used as the endpoint, variations in techniques have been reported such as double Lasso (Ouyang et al.,21) targeting one vein at a time or encompassing two veins simultaneously, wide area circumferential ablation, and PV antrum ablation. Regardless of the technique, the primary aim remains isolation of the PVs. However, there is a consensus now to favour lesions placed in the atrium rather than at the PV ostia to prevent PV stenosis and to increase the success rate. Following PVI and adjunctive LA ablation, success rates of 90–95% have been reported in patients free of antiarrhythmic drugs at 18 months follow-up.22,23 Additional cavotricuspid ablation has also been shown to improve outcome in patients with typical atrial flutter following successful PVI.24,25

In patients with paroxysmal AF, recurrences of atrial fibrillation following successful PVI are uncommon and typically focal, originating from reconnected pulmonary venous ostia.26 However for patients with persistent AF, PVI alone is inadequate for restoration and maintenance of sinus rhythm.27 Additional linear lesions at the roof and mitral isthmus have been shown to improve the outcome of ablation in persistent AF. Willems et al.28 achieved sinus rhythm in 69% of patients (off antiarrhythmic medication) who underwent PVI plus ablation at the roof and mitral isthmus in comparison with only 20% of patients who underwent PVI alone.

Wide encircling left atrial ablation

Pappone and co-workers6 described the electroanatomic-guided technique in which encircling lesions are created around each PV with a further ablation line connecting both the superior and inferior PVs and a mitral isthmus line to reduce the incidence of post-ablation atrial flutter. The aims consisted of PVI, elimination of anatomical anchors for rotors, ablation at sites of non-PV triggers, interruption of interatrial communication, atrial debulking, and PV vagal denervation which all contribute to the success of their technique in both paroxysmal and persistent AF. Although difficult to validate, sinus rhythm can be achieved and maintained following a single circumferential ablation procedure in up to 88% of patients with paroxysmal AF off antiarrhythmic drugs29 and in 83% of patients with chronic AF,6 following a repeat procedure in 32% of the latter group.

Ablation targeting fractionated potentials

Nademaneet al.30 demonstrated that both chronic and paroxysmal AF could be effectively treated by targeting areas of continuous fractionated electrical activity (CFAEs) without specifically targeting the LA–PV junction. CFAEs are fractioned electrograms (more than 2–3 deflections) with very short cycle length (CL) (≤120 ms) and usually of low voltage (0.05–0.25 mV). These potentials could be recorded at the interatrial septum, the PVs, the LA roof and the proximal CS. At 1 year of follow-up, sinus rhythm was present in 91% of a combined population of paroxysmal and persistent AF, with continued antiarrhythmic medication in 9% of patients and after a second ablation in 26%.

Similarly, Oral et al.31 demonstrated that incorporation of complex electrograms as an ablation target in patients with paroxysmal AF, in addition to selective PVI, resulted in freedom from AF in 77% of patients (off antiarrhythmic medication) at 11 months follow-up. In patients with persistent AF and amiodarone pretreatment, they have also shown that LA linear ablation incorporating complex electrograms in the LA roof, septum, anterior wall, mitral isthmus, and atrial aspect of the mitral annulus gave similar results to a PVI strategy in terms of restoration and maintenance of sinus rhythm (60% vs. 68% off drugs respectively).32

Linear lesions

The rationale of the linear lesions is to interrupt macroreentrant loops participating in AF maintenance and to ablate macro-reentrant circuits observed in the course of or after AF ablation. Linear lesions at the roof and mitral isthmus in addition to PV isolation achieved sinus rhythm in 69% of patients with persistent AF in comparison with only 20% of patients who underwent PVI alone.28

The incremental benefit that an LA line brings to AF is higher in persistent AF but has also been demonstrated in selected paroxysmal AF patients. At 18 months follow-up, 91% of patients with paroxysmal AF were free of arrhythmia when adjunctive linear ablation was performed, guided by the presence of persisting or inducible AF following PVI.53 However, linear lesions can be technically challenging and incomplete block may be proarrhythmic.

Ablation of non-pulmonary vein triggers

Some reports describe initiation of paroxysmal AF by non-PV triggers, this incidence, according to the series, may vary much (3.2–47%). Even after previous PV...
Sequential ablation strategy: a novel concept

Whilst PVI procedures can potentially cure patients with paroxysmal AF, no single ablation strategy has been shown to be as effective in patients with long-lasting AF. There is growing recognition that the approach taken should be tailor made to individual patients. Combination approaches were required to achieve high procedural success rates defined as termination of AF by radiofrequency ablation. Our approach consists of:

(i) PVI;
(ii) electrogram-based ablation of the LA targeting regions with rapid atrial activity, continuous fractionation, and centrifugal atrial activation;
(iii) linear ablation;
(iv) RA ablation.

Before the beginning of the procedure and after each step, simultaneous recording of atrial fibrillatory cycle length (AFCL) at both LA and RA appendages (LAA/RAA) were performed to monitor the impact of ablation. In our experience conversion to sinus rhythm or atrial tachycardia is preceded by progressive increase in AFCL to a critical level of 180–200 ms.33

Using this ablation strategy, 153 patients with chronic AF (mean duration: 22 months), underwent catheter ablation, AF was terminated in only 5% of patients by PVI but when electrogram-based ablation and linear ablation were added the rate of termination was 60 and 84%, respectively. Multivariate analysis incorporating LA dimensions and structural heart disease demonstrated that AFCL was the strongest independent predictor of procedural AF termination,34 with the baseline AFCL cutoff of less than 140 ms indicating reduced probability of procedural AF termination (Figure 2).

At follow-up, repeated ablation for recurrent arrhythmia was performed in 53% of the patients who had AF termination and in 71% without AF termination (P < 0.01) recurring in the form of atrial tachycardia in the former compared with AF in the latter (P < 0.001). After 20 ± 10 months, 95% of the patients with AF termination were in sinus rhythm against only 50% without AF termination. This observation indicates the importance of AF termination as an important endpoint during CAF ablation.

Before the importance of the PVs was discovered, attempts to cure AF through ablation in the RA were unfruitful. We came to know that sometimes the RA might have crucial importance. During the sequential ablation of CAF, if we carefully follow the CL at the LAA and RAA, there is a simultaneous increase in both atria until conversion. However, in a small proportion of cases, the RAA maintains a short CL despite the increase in the LAACL. This useful marker indicates the perpetuation of AF by the RA. Targeting the RA through the same electrogram-based approach used in the LA, resulted in termination of CAF, clearly indicating a role of the RA in continuing AF.

Guidelines currently recommend ablation for persistent AF only after failure of at least one antiarrhythmic drug and severe symptoms, despite rate control.35

Safety of atrial fibrillation ablation

As AF ablation involves extensive lesions in the atria, one should anticipate a level of complications higher than in other common ablation procedures (Table 1). That is actually true; some complications should be expected, recognized, and if possible prevented. The incidence of complications has decreased significantly since the dawn of AF ablation. More than 10 years ago, it was around 20% now the global incidence is about 6% and in experienced centres less than 4% (Figure 1). The technical development, operator experience, and new ablation energies (e.g. cryoenergy) will further increase the safety of AF ablation.35

Technological adjuncts

Image integration with magnetic resonance or computer tomography into 3D mapping systems has been shown to reduce radiation exposure and facilitate anatomically based ablation performed in some centres.36 Other techniques such as the use of intracardiac echocardiography (ICE) have been advocated.37 ICE provides real time intracardiac anatomy and may be extremely useful in difficult situations where transseptal puncture is difficult due to anatomic variations but may also be used to monitor microbubble formation during radiofrequency application. Furthermore, ICE monitoring has been proposed as a means to reduce procedural related injury to atrial structures. However, the cost efficacy remains a major impediment to widespread use of this technology.

Expanding indications for catheter ablation

Established indications for catheter ablation consist of paroxysmal AF patients with drug-refractory symptoms. However, it is anticipated that recommendations for catheter ablation will be broadened to include subsets of patients likely to benefit from maintenance of sinus rhythm. This includes patients with structural heart disease, that when associated with AF, is complicated by clinical heart failure or when heart failure precipitates AF implying a worse prognosis for all those, who have one condition and subsequently develop the other. Restoration of sinus rhythm by catheter ablation of AF in patients with heart failure has been shown to improve cardiac function, symptoms, exercise capacity, and quality of life.38 If this apparent benefit is confirmed, by large prospective trials, catheter ablation may become an important therapeutic option for these patients. Currently it is thought that only select patients with heart failure should be referred for catheter ablation.35
Figure 2 Impact of sequential approach ablation in the prolongation of cycle length (CL) recorded at left and right atrial appendage (LAA and RAA). (A/B) Patient with procedural termination during left atrial ablation. AF converted to atrial tachycardia (AT) during anterior LA ablation (star). ‘A’ demonstrates the nearly simultaneous prolongation of both LAACL and RAACL at each ablation step in the LA as shown in ‘B’. (C/D) Patient with conversion of AF to AT during RAA ablation (star). ‘C’ After extensive LA ablation, the curve demonstrates disparate prolongation of LAACL compared with RAACL during LA ablation, shorter RAACL justified ablation in the RA as shown in ‘D’, which was associated with AF termination. EGM, electrogram-based ablation; PVI, pulmonary vein isolation. Black thick lines – PVI lesions and linear lesions and grey dots – electrogram (EGM) sites targeted during sequential approach.

Table 1 Complications during atrial fibrillation ablation

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<th>Prevalence</th>
<th>Cause</th>
<th>Prevention</th>
<th>Treatment</th>
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<tr>
<td>Cardiac tamponade</td>
<td>1.2-6%</td>
<td>‘Pops’, catheter manipulation</td>
<td>Limit power, careful manipulation, operator experience, proper anticoagulation.</td>
<td>Percutaneous drainage, reversal of anticoagulation.</td>
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<tr>
<td>Pulmonary Vein stenosis</td>
<td>0-38%</td>
<td>Proximal ablation, high power</td>
<td>Limit power, ablate distal to vein.</td>
<td>Angioplasty/stent</td>
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<tr>
<td>Atrio-oesophageal fistula</td>
<td>0.25%</td>
<td>Relation of post wall and oesophagus, high power</td>
<td>Limit power, move catheter when close to oesophagus; oesophageal probe</td>
<td>Surgical repair/stent as an emergency</td>
</tr>
<tr>
<td>Phrenic-nerve injury</td>
<td>0.48%</td>
<td>Thermal injury (more common to the right phrenic)</td>
<td>High output pacing at ablation sites, monitor respiratory movements, cryoenergy</td>
<td>Stop application as soon as recognized may reverse injury; reversible in most cases</td>
</tr>
<tr>
<td>Thrombo-embolism</td>
<td>0-7%</td>
<td>Intra-cavitary thrombus, vascular sheath, char</td>
<td>Proper anticoagulation, sheath irrigation, open irrigation ablation catheter</td>
<td>Vascular surgery, thrombolysis</td>
</tr>
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Other potential patient groups include those with AF related complications such as thromboembolism, contraindications to long-term anticoagulation therapy and perhaps elderly patients.

Data concerning mortality benefit of AF ablation over conventional therapy are still missing. A multicentre, randomized study including a broader sample of the population (elderly, permanent CAF, structural heart disease) will allow a better selection of patients for ablation.

Future evolution in technology

The standard energy for catheter ablation, radiofrequency, is unfortunately, far from being perfect. Alternate forms of energy (cryoenergy, ultrasound and laser) and new forms of delivery (balloons) may increase safety, lesion continuity and permanence decreasing complications and recurrences.

An important improvement would be to monitor tissue temperature or lesion formation during ablation to ensure persistent lesions without compromising safety from perforation or extracardiac damage. Contact intensity is probably another important parameter to be considered in the future.

The mapping and image technology are progressively merging, providing a better real time relation between arrhythmia mechanism and anatomical location. The future will certainly optimize this relation allowing faster decision-making during the procedure, increasing safety and success.

Conclusions

Cure for AF represents one of the greatest quests of modern electrophysiology; the last decade was very profitable in the understanding of mechanisms and invasive treatment. The progressive increase in knowledge of catheter ablation technology and safety has turned AF ablation into a common daily procedure in many centres. The lack of success of PVI in permanent CAF needs an adaptation of approach to the complex environment, which exists. Incorporation of different approaches and targets is necessary to increase the success. The future will rely on wider ablation and global mapping. New tools will be required to shorten the procedure time while preserving or improving safety.

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References


