Ablation therapy for atrial fibrillation (AF): Past, present and future

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Abstract

Atrial fibrillation, the most common arrhythmia, is frequently disabling and drug resistant. Non-pharmacological approaches including surgery and catheter-based ablation have been developed for the most symptomatic patients. These new treatment strategies have dramatically increased our knowledge of the pathophysiology of this arrhythmia but most importantly demonstrated that atrial fibrillation is curable. These approaches are far from being perfect but good enough to be offered in routine practice to selected patients in experienced centers. The importance of pulmonary veins in the initiation of AF has clearly been demonstrated and their role in maintaining AF is likely. Most of the curative approaches are therefore based on their isolation. Future technical improvements based on presently applied concepts are likely to widen the indications for ablation therapy of AF. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Ablation; Arrhythmia (mechanisms); Atrial function; Supraventricular arrhythmia; Veins

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is increasing in prevalence [1,2]. From a scientific point of view, the arrhythmia and the newer developments in our understanding of the pathophysiology and treatment are fascinating. For patients and physicians it remains frequently disabling, responsible for extra cost, morbidity and probably mortality, and often very frustrating [2–8]. Although there is much that remains unchanged in the treatment of AF, particularly related to initial treatment strategies of AF, there is much that is new. We have learned a lot in the past 10 years from surgical and catheter-based treatment for AF.

The number of centers involved in a surgical or catheter-based approach is dramatically increasing to the benefit of the most symptomatic patients affected by this problematic and challenging arrhythmia.

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2. Lessons from the past

2.1. Mechanisms of AF

In 1959 Moe et al. demonstrated, using a computer model, that AF was sustained by the presence of multiple reentrant wavelets propagating simultaneously in the atria [9]. This mechanism was further demonstrated by Allessie et al. both in animals and in humans [10,11]. These data were derived from surgical mapping of ongoing AF in patients. Although the multiple wavelets reentrant hypothesis fits quite well for explaining AF maintenance, it does not explain how AF is initiated. This is because these patients were studied during induced AF and also because of the absence of spontaneous initiation in animal models. The old concept [12] that a rapid rhythm may drive the atria fast enough resulting in fibrillatory conduction recently resurfaced in patients and animal models [13–15]. In fact, we have learned from the past 10 years that the role of foci is prominent in AF, not only for initiation but
probably also for maintenance of the arrhythmia. A focus may initiate AF, and arrhythmia may become sustained because of multiple reentrant wavelets (Fig. 1). The focus may also be fast enough to create fibrillatory conduction in the atria, therefore being responsible for initiation and maintenance of the arrhythmia. But the most important finding is that these foci are not randomly located anywhere in the atria. They are significantly clustered within pulmonary veins (PVs) where 80 to 95% of foci are identified [14–21] (Fig. 2).

2.2. Insight from surgical procedures

Various surgical approaches have been developed during the past 10 years (Fig. 3 and Table 1). Based on the multiple wavelet reentry hypothesis, Cox’s group pioneered a surgical curative approach, called the Maze operation, targeting the anatomic structure of both atria on the basis that this represents the arrhythmia substrate [22]. Long linear obstacles and isolation of the posterior LA aimed to reduce the mass of electrically continuous atria below the critical threshold required for AF maintenance. The placement of these linear obstacles was modified from Maze I to III, mainly to decrease associated complications, particularly the need for pacemaker implantation due to sinus node dysfunction [23]. It is interesting to note that PVs and posterior LA isolation has consistently been retained in each modification of the Maze procedure [23–27]. The Maze procedure and its variants are probably the most widely performed curative surgical interventions for AF. While the long-term success rate is good, 80% and up to 99% with AAD, these surgical techniques remain complex and are associated with a significant increase in cardiopulmonary bypass time, morbidity and mortality. In order to preserve a more physiologic atrial transport function, Cox’s group have developed a new concept of surgical treatment for AF, the radial approach [28,29]. However, results in humans have not been reported so far.

Another surgical approach intended to produce LA isolation resulted in restoration of sinus rhythm in the right atrium in 71% of cases [30,31]. Notably, the left atrium remained fibrillating in more than half, suggesting the dominant role of this chamber for initiation and maintenance. In the same fashion, the corridor operation of Guiraudon achieved a high success rate in converting the RA corridor to sinus rhythm (85%) but the left atrium continued to fibrillate [32]. The aim of corridor surgery was not to decrease the critical mass of atrial tissue

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Fig. 1. This 12 lead ECG shows typical AF initiation due to a burst from the right superior pulmonary vein (arrow).
Fig. 2. Endocardial recordings showing trains of rapid discharges inducing AF from left superior (LS) and right superior (RS) pulmonary veins. Star, venous extra systole; dotted line, beginning of extra-systolic P wave.

perpetuating AF but rather to maintain conduction of sinus impulses to the ventricles and achieve physiological chronotropy. The major limitations of this concept are the absence of mechanical function of the atria and the persistent risk of thromboembolic events. The long-term results were disappointing and the procedure was abandoned in 1992. Finally, atrial transection proposed by Lin had a 71% success rate when performed in the left

Fig. 3. Schematic representation of various LA surgical lesion strategies (dotted lines) for AF. PV, pulmonary veins; LAA, left atrial appendage; MA, mitral annulus.
Table 1
A synopsis of the results of surgical treatment of chronic (CAF) and paroxysmal (PAF) atrial fibrillation from various groups

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<th>CAF</th>
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+AAD±RF represents long-term success (>3 months) with AAD and/or additional transcatheter RF ablation. IHD, intra-hospital death; PM, pacemaker requirement after surgery; MI, MII, MIII, Maze I, II and III.

2.3. Insight from catheter ablation

A similar evolution can be observed for the catheter ablation technique of most electrophysiology laboratories. For safety reasons linear lesions were initially placed in the right atrium [40,41]. The analysis of published series using this approach shows that less than 20% of patients with paroxysmal AF can be cured. In some series, initial results were better but subsequent follow up showed significant attrition of results. Extension of linear lesions to the left atrium [42–48] (Fig. 4) was demonstrated to be much more effective even in chronic AF patients, particularly in the initial report of Swartz [42]. However, most published series showed significant complications as well as long procedure times. The production of complete linear lesions in the left atrium remains challenging even using irrigated tip catheters [44]. Several problems have become evident. The creation of the ablation line may be difficult because the manipulation of the catheter does not allow completion of the desired line, and this may happen despite the use of various curves and combinations of long sheaths [42]. Lesions may not be continuous and/or transmural [49,50]. The use of navigation systems has been proposed [45,46,51] but the additional benefit is usually limited as the difficulty is usually not to localize already created ablation lesions but rather to create transmural lesions. For this purpose, irrigated tip catheters are more effective and safer as the limited temperature of the ablation electrode prevents clot formation and charring.

Once the ablation line is achieved, its completeness has to be demonstrated. Several options are available for this purpose. Navigation mapping systems like Carto Biosense are of interest but assessment using a conventional catheter recording double potentials all along the line, associated with differential pacing maneuvers is much faster and as accurate. Various complications have been described, some
being dramatic like strokes or death. Their prevalence is limited (0 to 10% [42–46]) but remains unacceptable. Using this catheter-based linear ablation approach a success rate ranging from 0 to 60% has been reported without adjuvant antiarrhythmic drug administration. These results were even better when previously ineffective drugs were reintroduced. Interestingly, Ernst et al. [45] elegantly demonstrated that they were able to achieve a complete isolation of the lateral part of the right atrium (showing a slow independent rhythm) without modifying AF. Though similar isolation of parts of the LA has rarely been observed after linear ablation of chronic AF, this observation further supports the driving role of left atrium for maintaining AF.

Once again, the most significant clinical observation has been the recognition of the importance of pulmonary veins for the initiation of AF [14]. In contrast to the slow dissociated rhythm (incapable of driving the atria into fibrillation) observed after isolation produced by atrial linear ablation, an extremely rapid (cycle length as short as 115 ms in our experience) and dissociated rhythm can be observed in PV myocardium isolated by proximal RF ablation. It is evident that such a rapid rhythm conducted to the atria would rapidly initiate AF. This supports the hypothesis that instead of modifying the substrate responsible for maintenance of AF we could cure AF just by preventing its initiation [15]. The initial strategy was therefore the elimination of foci that initiate AF within pulmonary veins, superior vena cava and/or non-venous foci. Several groups have reported that many patients, perhaps the majority, with paroxysmal AF have identifiable foci which may be amenable to catheter ablation. The initial approach comprised mapping the earliest activity responsible for AF initiation followed by ablation of this focus [14–20]. Limiting factors were rapidly identified. First of all, this approach supposes AF initiation at the time of the EP study and this is difficult to obtain for a capricious arrhythmia like AF. In addition to mapping difficulties, the elimination of one focus in one pulmonary vein did not prevent another focus from the same vein or from elsewhere firing at a later time and inducing AF again.

Provocative maneuvers were used in order to increase foci identification and ablation but they frequently resulted in long lasting AF requiring DC shock.

At the present time most EP labs have modified their approach and now pursue a pulmonary vein disconnection-based procedure [20,21].

3. The present procedure

3.1. Pulmonary vein disconnection

This procedure is now much easier to achieve using specific mapping catheters developed for pulmonary veins.
Three different models are currently available on the market. They share the same concept. Multiple electrodes are placed on the distal circular part of the mapping catheters in order to map the ostia of pulmonary veins perpendicular to the axis of the vein. The most interesting finding using these catheters has been that pulmonary veins are not homogeneously activated (Fig. 5). The activation from the atrium to the vein always begins in one point of the vein considered to be one input or one connection. Two catheters placed transseptally in the left atrium are required to disconnect the PVs from the atrium. Once the atriovenous input has been identified by locating the earliest venous activity by some form of circumferential mapping, the ablation catheter is placed proximal to the mapping catheter within the first millimetres of the ostium in front of the electrodes that record the input. RF energy is delivered at this segment and may result in a change in the activation sequence displayed by the mapping catheter or in disappearance of all venous potentials. Usually at least two segments of the ostium have to be ablated to achieve a complete disconnection. If the activation has changed after the ablation of the first segment, the new earliest site is then targeted and so on until complete disconnection. In 80% of cases the total length of segmental ablation does not exceed 50% of the circumference of the vein. It is probably important to disconnect the vein using the minimum required number of applications in order to reduce as far as possible, the risk of pulmonary vein stenosis.

In some centers, the ablation is limited to proven arrhythmogenic pulmonary veins. This was our initial strategy but because of significant numbers of AF recurrences due to initiation from spared veins, we now systematically disconnect all pulmonary veins during the first ablation procedure. The risk for PV stenosis has to be very low to justify this systematic approach. Several points have to be mentioned to reduce as much as possible the incidence of PV stenosis. At the beginning of our experience, the use of powers ranging from 40 to 50 W were associated with pulmonary vein stenosis in 5% of cases. By decreasing the power limit to 20 to 30 W, this complication has been reduced to about 1%. Very proximal lesions (at the very edge of the venous ostia) are more effective and safer than distal lesions as they are delivered.

Fig. 5. This figure illustrates the usual approach in our lab for AF ablation. Direct angiography of the four PVs is systematically performed to define the position of the ostium (of the LSPV in this example). The Lasso catheter is then introduced within the first centimetre and the activation sequence after ablation of the superior input is displayed—in panel 2. The bow shaped (arrows) activation pattern of venous potentials shows the earliest activity in bipolar 5–6, corresponding to the inferior part of the ostium. The ablation catheter is placed proximal to the circular mapping catheter (panel 3 lower part) and records a continuous activity bridging the interval between left atrial appendages (LAA), far field potentials (star) and venous activity (arrows). RF delivery at this site resulted in complete disappearance of all venous potentials, but as expected, far field activity from LAA remained unchanged.
at the maximum diameter of the vein. Lastly, the use of circular mapping allows an accurate localization of atriovenous inputs and therefore decreases the risk for stenosis by preventing unnecessary RF applications.

Disconnection is ideally performed during sinus rhythm for right pulmonary veins or during pacing from the distal coronary sinus or the lateral part of the left atrium in order to clearly distinguish atrial and venous potentials recorded by the mapping catheter placed in the left pulmonary veins. The end-point is the disappearance or the dissociation of venous potentials. Atrial far field potentials are still recorded after successful ablation in left pulmonary veins. This far field activity is usually due to left appendage activation but may also be caused by activation in the posterior part of the left atrium. In the right pulmonary veins, far field activity may be recorded that originates in the right atrium. The signal is therefore synchronous with the first part of the P wave. Pacing at various atrial locations is extremely useful to distinguish venous activity from atrial far field signals.

Once the four pulmonary veins are disconnected, the identification and ablation of non-venous foci is performed if required. In the absence of spontaneous extrasystoles or spontaneous AF initiation, Isoproterenol can be infused with a target heart rate of 120–140 bpm. Burst atrial pacing in order to induce post pause initiations may also be used.

Seventy percent of patients with symptomatic drug-resistant paroxysmal AF remain free of arrhythmias after a mean of 1.45 ablation procedures during a follow-up of 1 year. The incidence of PV stenosis in our experience is reasonable (<1%) [52] though an incidence ranging from 0 to 42% has been reported [15–22]. The management of symptomatic or severe PV stenosis was found to be problematic, sometimes requiring PV stenting [53]. The risk for thromboembolic events is lower than 0.5% as is the risk of tamponade. To the best of our knowledge, no deaths have been reported in more than 2000 PV isolation procedures. At the present time it has not been demonstrated that curative ablation affects the prognosis and outcome. Further studies are required to demonstrate that the effect is more important than a simple disappearance of symptoms even if this is of major interest for patients. As a consequence, the indication for catheter-based AF ablation should be restricted to symptomatic patients in whom AAD treatment fails to control arrhythmia. In our series, patients with at least one episode of AF every 10 days in spite of having tried ≥2 AAD of class I, II or III have been included. Amiodarone was unsuccessful in 74%.

Most clinical series suggest that paroxysmal AF is more frequently curable using this approach as opposed to chronic AF. The only study to report discordant results was from Pappone et al. [22]. For this reason, we consider patients with chronic AF for catheter-based ablation only in case of symptomatic and complicated AF, because of poor hemodynamic tolerance, suspicion of tachycardio-myopathy, and or thromboembolic events. The procedure in this situation involves a combination of long linear lesions placed in the posterior LA drawing an inferiorly incomplete (to avoid isolation) rectangle bounded by the PV ostia. To prevent perimital reentry the rectangle is extended to the lateral mitral annulus at the level of the LIPV. High power (50–60 W) is usually required to create a complete connecting line anchored to the mitral annulus because of the thickness of the atrial wall at this level.

As previously mentioned, focal ablation of one arrhythmogenic point in one vein has been abandoned as it is unable to prevent initiation from other parts of the same vein. This is also true for the superior vena cava which was reported to be arrhythmogenic in up to 23% of Asian patients [54]. However, this punctiform ablation is still used for atrial foci mostly originating from the LA but sometimes also reported to be localized in the RA [55]. A more specific approach has been reported for foci originating from the remnant of the left superior vena cava, the ligament of Marshall. Ideally, direct angiography and mapping of the vein of Marshall is performed if the vein is patent. A purely endocardial approach is probably safer [56].

A variant of the PV-based procedure has been reported [57]. The aim is to encircle the four PVs with RF lesions as based on a 3D electroanatomical reconstruction of the LA. Good results with very few side effects have been reported both for paroxysmal and chronic AF. One of the limitations is the absence of a procedural endpoint, i.e. there is no demonstration of PV disconnection as a result of ablation. However, safety/efficacy ratios are excellent and in fact among the best reported.

### 4. Future of catheter ablation for AF

#### 4.1. Concept

AF probably requires triggers for initiation, a favorable substrate for maintenance, and also favorable autonomic tone. This last point has not really been investigated, as we do not currently have the capability to consistently and durably modify it. This may theoretically be a potential target.

Another hypothesis was formulated by Allessie suggesting that in association to initiators (from pulmonary veins for example) the activity had to reach perpetuators [58]. These perpetuators are areas of slow conduction located in close proximity to the ectopic source. They will promote the transformation of ectopic activity to reentrant circuits or rotors. However, at the present time, this concept is purely speculative without evidence that the ablation of these areas could cure AF.

Another attractive concept could be to improve conduc-
ion velocity so as to favorably alter the wavelength, particularly at sites of slow conduction for example at the junction between the vein and the left atrium. Conceptually it looks more attractive than RF ablation, which eliminates these areas instead of normalizing them. We are, of course, far from this good activity.

4.2. Improvements of the present procedure

The Achilles’ heel of the present procedure is the not insignificant recurrence rate of AF after the index procedure. Recovery of conduction to the PVs, arrhythmogenic manifestations from unablated (pulmonary and non-pulmonary vein) tissue as well as from atrial myocardium altered by RF and/or inflammatory reaction may all be responsible for recurrent AF. Conduction recovery to the PVs can easily be verified by remapping and transiently arrhythmogenic atrial foci tend to spontaneously disappear within the first month after ablation. Foci from other arrhythmogenic non-pulmonary veins (superior vena cava, ligament of Marshall, coronary sinus, persistent left superior vena cava and exceptionally inferior vena cava) can be just as effectively neutralized. The most difficult challenge is to locate and ablate persisting atrial foci. Several strategies are being considered for this purpose.

- The use of computerized mapping with Basket catheters (with the limitation that not the entire surface of the atria may be mapped).
- Surface ECG-based localization strategies hampered by low voltage signals and lower resolution.
- Non-contact mapping which is conceptually well suited to identify infrequent foci immediately initiating sustained AF, however, with a presently low spatial resolution. There may also be practical limitations to its use in the LA.

In order to widen the indications of AF ablation based on the same concept, several points could be improved.

- Different navigation systems have been developed. For AF they have not been shown to be critical. However, anatomical imaging of the ablation catheter in relation to known cardiac structures should be of importance. Computer assisted manipulations of the catheter allowing to control exactly the contact with the endocardium should also be a significant improvement. Imaging based evaluation of the lesions (continuity, transmurality) would also be desirable.
- Ablation catheter: the ablation catheter currently used has been developed for very focal targets like WPW. They are relatively satisfying for segmental ablation to disconnect pulmonary veins but the creation of long linear lesions using these devices remains challenging.

Different prototypes have been assessed in order to facilitate the creation of long linear lesions without being successful so far. Many prototypes have also been used for pulmonary vein disconnection. Balloons or other expandable devices have not been very convincing but this could change in the near future.

- Energies. Radiofrequency has the advantage of an enormous background and probably combines the best efficacy and safety so far [15,18,44,45,22]. Ultrasound has been used via balloon catheters without being very convincing so far. In the report of Natale [59] using the Atrionix balloon, 66% of patients were cured without antiarrhythmic drugs. However, 1 to 29 applications were required to isolate PV. This was not entirely attributable to the energy, as the balloon was found quite difficult to manipulate. The results achieved in German centers participating in the initial evaluation of the ultrasound device were more disappointing. Laser and microwave are also interesting alternatives but their potential interest has not yet been confirmed [60]. Cryoablation is probably the most advanced alternative to RF. It has been widely used by surgeons. The most significant advantage is that it creates homogeneous lesions of muscular cells sparing the collagen and therefore leaving the architecture of the tissue intact. The chronic scar is made of dense fibrotic tissue without tendency to rupture. It also has the advantage to spare the endocardium and is therefore believed to carry a very low risk for thromboembolic events [61]. The lesions are not always transmural, however, and it is impossible for the surgeon to be sure that the lesion is complete and transmural as the lesions are not directly visible to the human eye. Another potential problem is that the duration of the applications are much longer than with RF energy.

Finally, it would be desirable to supplement catheter-based ablation procedures with complete linear lesions of appropriate length in order to reduce the critical mass and to prevent macroreentry. The successful delivery of such lesions with a similar safety profile to the present strategy may allow a curative approach for the full spectrum of AF including persistent or chronic AF.

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