

# CATHETER-BASED MANAGEMENT OF ATRIAL FIBRILLATION

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## INTRODUCTION

The management of atrial fibrillation has undergone radical changes over the past decade. Although our understanding of the mechanisms underlying this common arrhythmia is still incomplete, with multiple overlapping and controversial theories, catheter ablation has rapidly become part of the standard of care as recognized in the latest version of the ACC-AHA-HRS guidelines.<sup>1</sup>

What follows is a brief overview of the rationale, techniques, results, pitfalls and challenges of catheter-based treatments of atrial fibrillation.

### MECHANISMS OF ATRIAL FIBRILLATION: A BRIEF ACCOUNT

Lacking a full understanding of a disease has never been an obstacle for designing and testing many successful therapies, and in fact it may seem that proposed mechanisms stem from therapies. For example, shortly after the electrocardiogram was described, researchers proposed several hypotheses regarding the mechanisms of atrial fibrillation, none of which are universally accepted. Prinzmetal et al. proposed that a single, rapidly firing focus could lead to fibrillatory activation patterns.<sup>2</sup> Afterward, Moe and Abildskov reported that multiple self-perpetuating wavelets could lead to fibrillation in the presence of dispersion of refractoriness and in the absence of organized reentry or focal activations.<sup>3</sup> This multiple wavelet hypothesis was the prevailing paradigm for more than four decades.

In the last decade, however, experimental and clinical data have questioned this understanding. Haissaguerre et al. demonstrated that in patients with paroxysmal atrial fibrillation, the initiating atrial ectopic beat could be mapped most commonly at the pulmonary veins, and that ablation of these foci abolished atrial fibrillation in 62% of patients.<sup>4</sup> Thus a paradigm in which a focal trigger initiates fibrillation was proposed.

Multiple mapping studies have shown that there is a gradient activation rate

between the left and right atrium during atrial fibrillation. Jalife and collaborators combined simultaneous optical recordings of left and right atrium and found that activations in the left atrium were consistently faster, more regular, and with more beat-to-beat propagation pattern consistency than activations in the right atrium, which were slower, more irregular, and showed more variable spatial activation patterns. They proposed the mother rotor paradigm,<sup>5</sup> which posits that there is a stable reentrant source, usually in the left atrium, from which propagations emanate to neighboring tissues. Such neighboring tissues, however, cannot sustain 1:1 propagations, and ensuing wavebreaks generate irregular activation patterns seen in the electrocardiogram. This paradigm concurs with data showing a left to right frequency gradient. Mapping studies have demonstrated the perivenous left atrium's ability to sustain such rotors, which have been correlated with the complex fiber architecture of the

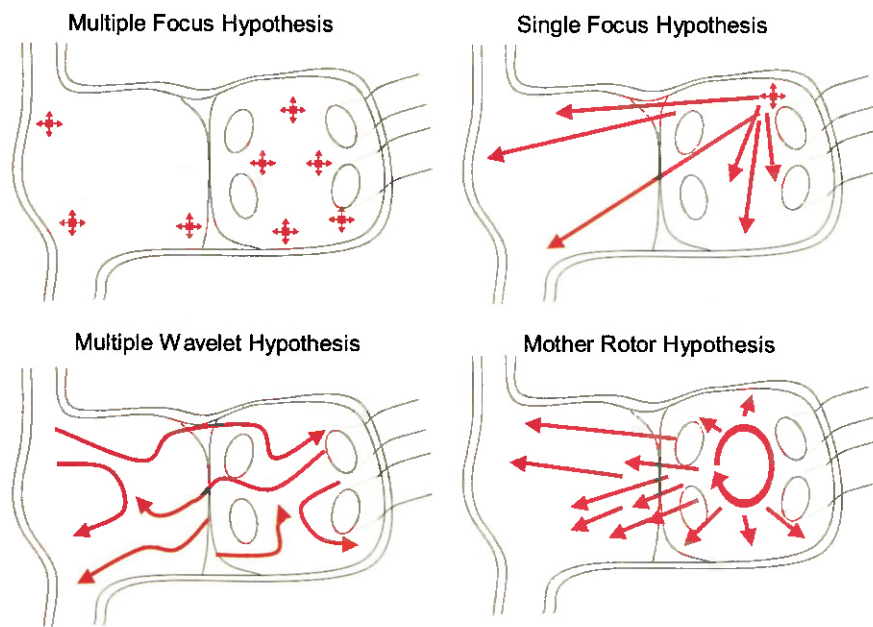
pulmonary veins leading to anisotropic reentry. However, more recent work from Peng-Sheng Chen<sup>6</sup> and Jeffrey Olgin<sup>7</sup> suggest that focal beats can also originate from the pulmonary veins.

The role of the autonomic nervous system in initiating and maintaining atrial fibrillation has long been the source of clinical and basic research. It is well known that cholinergic influences tend to shorten action potential duration and enhance the ability of atrial myocytes to sustain rapid activation rates. Both vagal and sympathetic nerve endings are abundant in the pulmonary veins, and a recent hypothesis posits that the simultaneous discharge of both sympathetic and parasympathetic nerves initiates focal activations via early afterdepolarizations, created by sympathetically induced calcium overload combined with parasympathetically induced shortening of the action potential. Focal activations in the presence of complex anisotropic structure around the pulmonary veins

#### Modalities of catheter-based treatment of atrial fibrillation:

1. Pulmonary vein isolation
2. Circumferential (wide area) pulmonary vein ablation
3. Antrum isolation
4. Complex and fractionated atrial electrogram ablation
5. Vagal denervation

**Table 1.** A summary of catheter-based treatments for atrial fibrillation.



**Figure 1.** Proposed mechanisms of atrial fibrillation

can lead to reentry formation. Figure 1 summarizes the proposed mechanisms of atrial fibrillation.

### **THE BEGINNING: SURGICAL MAZE**

The procedure pioneered by Cox et al. included a set of surgical incisions across the right and left atrium to divide atrial tissue in smaller segments, thus limiting the amount of tissue to which a given electrical propagation had access.<sup>8</sup> Although the procedure has significant reported success (sinus rhythm in 81-95% of the patients) and very low reported incidence of stroke (less than 0.1 % per year), the need for cardiac surgery, frequent requirement of pacemaker implant due to sinus node dysfunction (up to 15%), and frequent loss of atrial transport function (7%)<sup>8</sup> have made the surgical approach a less desirable first option for the nonpharmacologic management of atrial fibrillation.

### **CURRENT INVASIVE APPROACHES TO TREATMENT**

Encouraged by results of the surgical procedure, cardiac electrophysiologists

attempted to emulate the surgical lesion set using a catheter-based approach to deliver radiofrequency energy, replicating the linear incisions of the maze procedure. Schwartz and Haisaguerre<sup>9</sup> reported rather disappointing results with this approach due to their inability to complete the full lesion set and frequent discontinuities in the lines of ablation, which lead to atrial flutters and the need to repeat the procedure. Figure 2 illustrates the current catheter-based approaches for ablation of atrial fibrillation. The following sections describe the various catheter-based modalities for the treatment of atrial fibrillation (Table 1).

#### *Pulmonary vein-based strategies*

In their now classic study, Haissaguerre et al. found that initiation of paroxysmal atrial fibrillation could be mapped to pulmonary veins in the overwhelming majority of the cases. Furthermore, focal ablation of these sites resulted in a 62% elimination of atrial fibrillation at eight months follow-up.<sup>4</sup> While the results were rapidly replicated by several groups, they found that focal ablation at these sites was inferior to complete electrical isolation using a multipolar catheter. The proce-

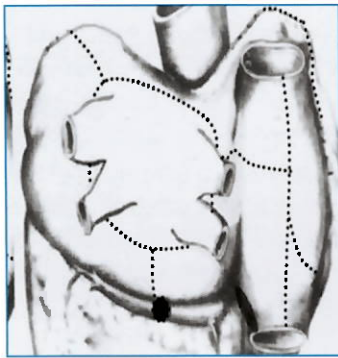
cedure evolved to include insertion of a circular catheter in the pulmonary vein ostia to record local pulmonary vein potentials. Radiofrequency ablation was then performed proximally, aiming at eliminating such potentials in the circular catheter to obtain pulmonary vein isolation. These results have been reproduced by different groups, oscillating between 50-85% success in eliminating atrial fibrillation. Results were consistently better in patients with paroxysmal (~70-80% success) compared to chronic (20-50%) atrial fibrillation.<sup>10</sup>

In 2000, Pappone et al. introduced a procedural variant whereby circular lesions were created around the circumference of each pulmonary vein ostium to decrease the local electrogram amplitude at each site. This variant obviated the need for the circular catheter and a second transeptal puncture but required the use of a three-dimensional mapping system to track lesions in space and to achieve complete encircling of the pulmonary veins.

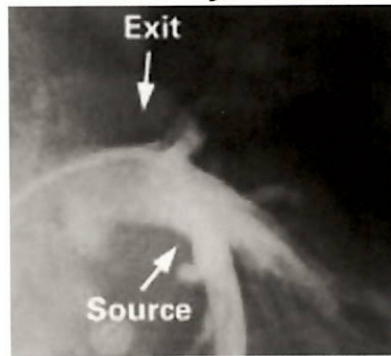
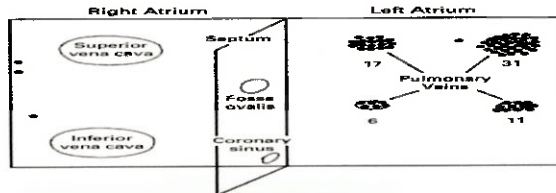
Furthermore, the initial success rates in patients with chronic forms of atrial fibrillation seemed to be more comparable to those with paroxysmal forms (85% vs. 68%, respectively).<sup>11</sup> This approach was later modified by moving the circumferential lesion set towards the body of the left atrium, away from the ostium of the veins. From the mechanistic standpoint, it no longer meant isolation of pulmonary vein foci, and it was understood as a "substrate modification." Following the description of this procedural variant (often called circumferential pulmonary vein ablation), the results were reproduced by several groups, with success rates between 40-90% for paroxysmal atrial fibrillation and 50-70% for chronic.<sup>10</sup>

It has been hard to compare the efficacy of these two procedural variants. Two studies that compared their efficacy head-to-head yielded opposite results. Oral et al. showed superiority of the circumferential pulmonary vein ablation (88% vs. 67%),<sup>12</sup> whereas

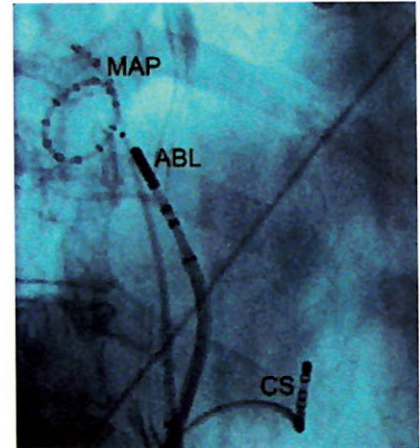
**Figure 2.** Invasive therapies for atrial fibrillation.



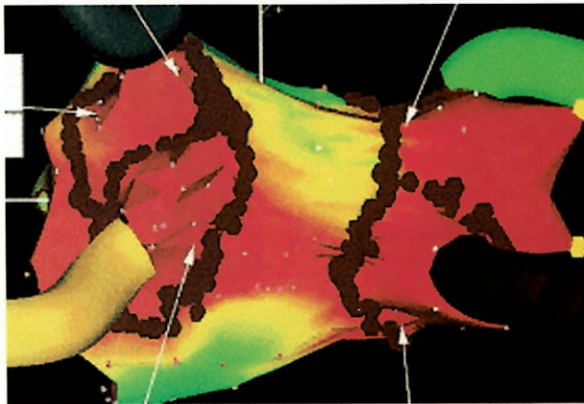
**A.** The maze procedure<sup>8</sup>



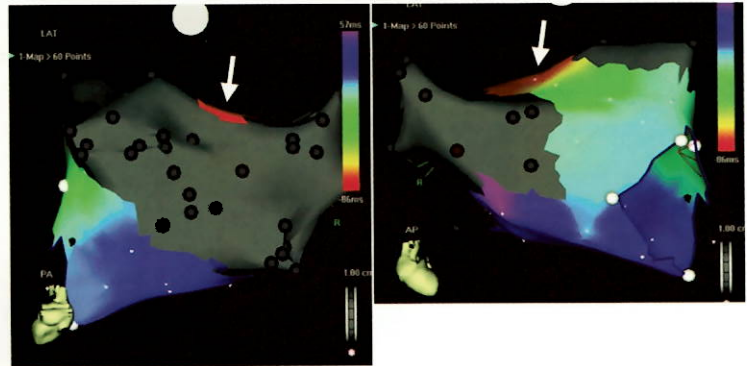
**B.** Ablation of pulmonary vein foci.<sup>4</sup>



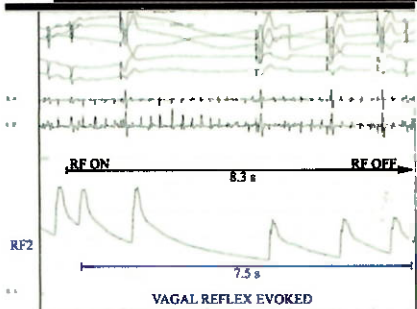
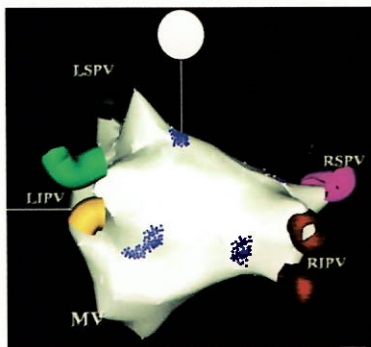
**C.** Pulmonary vein isolation



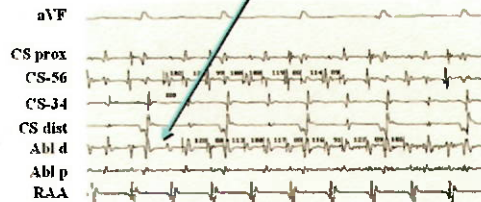
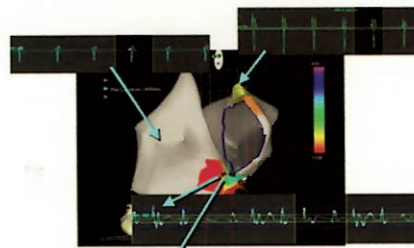
**D.** Circumferential pulmonary vein wide area ablation.<sup>11</sup>



**E.** Antrum isolation.<sup>14</sup>



**F.** Ablation of vagal ganglia.<sup>15</sup>



**G.** Ablation of complex and fractionated potentials.<sup>16</sup>



Karch et al. showed 82% symptom-free survival with pulmonary vein isolation versus 54% for circumferential ablation.<sup>13</sup>

An alternative approach, proposed by the Cleveland Clinic and labeled antrum isolation, entails ablation of all atrial tissue surrounding the entrance of the pulmonary veins into the left atrium. Such variant requires extensive lesions in the ~2cm cuffs of atrial tissue proximal to the pulmonary veins and almost the entire posterior wall of the left atrium. The procedural endpoint is elimination of all atrial electrograms in these areas, which requires thorough radiofrequency applications guided by a circular multielectrode mapping catheter. In the hands of the Cleveland Clinic group, this procedure surpasses other procedural modalities in efficacy and safety, with reported success rates oscillating between 75-95% depending on patient characteristics.<sup>14</sup>

#### *Nonpulmonary vein strategies*

As a result of lesions delivered in the left atrium with the attendant creation of substrates for reentry, left atrial flutters were reported as a common complication. The addition of adjunctive linear ablation lesions between the pulmonary veins in the posterior wall and in the mitral isthmus (from the mitral annulus to the left pulmonary veins) was shown to help prevent such flutters.

Given the obvious fact that pulmonary veins are part of the normal anatomy whereas atrial fibrillation is not part of normal physiology, it follows that their role is at most permissive and that other factors also must play a role in initiating and maintaining atrial fibrillation. The autonomic nervous system is an attractive candidate, since it is well-known that some paroxysms of atrial fibrillation are triggered by either parasympathetic (e.g. postprandial, nocturnal) or sympathetic (exercise) influences.

The group at the University of Oklahoma has done extensive research in the role of parasympathetic ganglia as promoters of atrial fibrillation and

found a common colocalization of these ganglia and the pulmonary vein ostia and coronary sinus. Not surprisingly, these areas can be targeted during the ablative strategies previously outlined. Indeed, Pappone et al. have shown that vagal reflexes can be triggered during ablation of pulmonary veins and that abolition of these reflexes (implying destruction of the vagal ganglia) leads to an incremental outcome benefit.<sup>15</sup> As of today, vagal ganglia ablation is not part of the routine ablation strategies and remains investigational.

One additional strategy described by Nademanee et al. is ablation of complex fractionated electrograms during atrial fibrillation throughout atrial tissue.<sup>16</sup> This approach does not entail a particular spatial distribution of the lesion set but rather directs radiofrequency application to specific sites in the atria that exhibit particularly rapid, fractionated, or complex electrograms. Although no specific spatial patterns of lesions can be described a priori, common locations of complex potentials included the pulmonary veins, interatrial septum, coronary sinus ostium, cavotricuspid isthmus, and inferolateral right atrium. Using this approach, 91% of the patients were free of atrial fibrillation after one year.

The procedure, in any of its variants, requires a high level of skill and training, including competence with the transeptal puncture, dexterity in manipulating catheters, an accurate three-dimensional understanding

of cardiac anatomy, and experience interpreting intracardiac electrograms. Adjunctive tools to guide ablation such as intracardiac echocardiography and 3D mapping systems (Figure 3) have become standard and require training and experience. Prompt recognition and treatment of complications such as tamponade (with pericardiocentesis) require additional expertise. The technical sophistication of the procedure keeps growing, and remote magnetic-based or robotic navigation systems are likely to be incorporated.

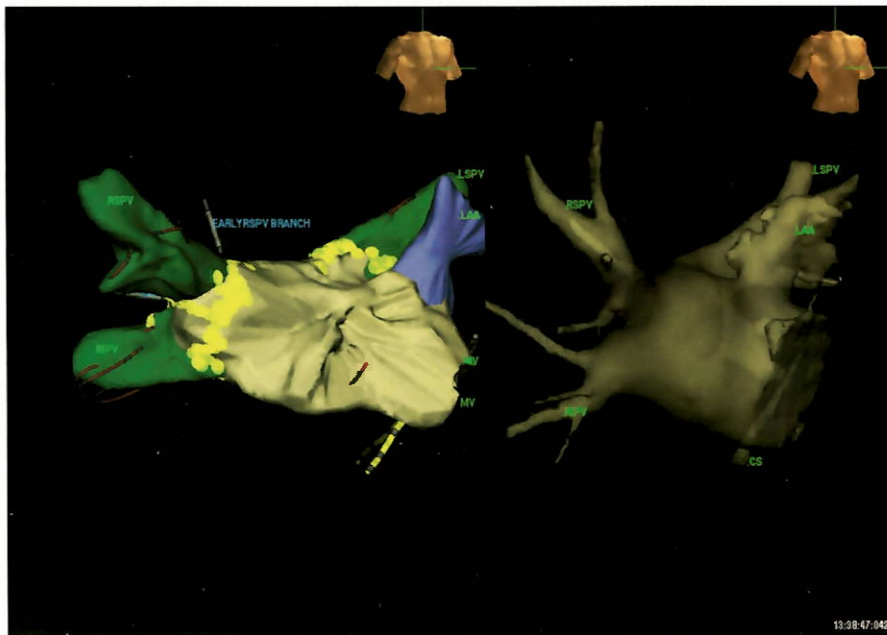
### **PATIENT-BASED SELECTION OF A PROCEDURE STRATEGY**

Atrial fibrillation literature is plagued with confusing, reiterative, and contradictory information regarding the relative merits of different ablation strategies. A reasonable aspiration would be to find the right procedure for each patient. Several groups have attempted a stepwise approach to ablation that minimizes complications and delivers only the necessary lesions. It seems reasonable to attempt pulmonary vein isolation in young patients with normal hearts and paroxysmal atrial fibrillation while possibly using more extensive ablations in patients with chronic atrial fibrillation or structural heart disease. However, the patient's epidemiological anatomical characteristics may not be the sole determinants of the response to

#### **Criteria for patient selection.**

1. Patients' expectations: symptom relief, freedom from anticoagulation, freedom from antiarrhythmic therapy, resolution of tachycardia-induced myopathy
2. Failure of prior antiarrhythmic therapy or prior procedures
3. Pattern of atrial fibrillation: paroxysmal vs. chronic
4. Presence of structural heart disease: left atrial size, left ventricular dysfunction, hypertrophic cardiomyopathy
5. Duration of atrial fibrillation

**Table 2.** Relevant factors in patient selection for ablation of atrial fibrillation.



**Figure 3.** Adjunctive role of cardiac imaging guiding ablation of atrial fibrillation. **Left:** Real-time three-dimensional reconstruction of left atrial geometry (gray), pulmonary veins (green), and left atrial appendage (blue). Yellow dots mark locations of radiofrequency ablation. **Right:** Three-dimensional rendering of the patient's left atrium by CT scan.

ablation. Oral et al. and Jaïs et al. have reported on the efficacy of guiding the number and extent of ablation lesions based on mapping characteristics<sup>17</sup> and inducibility<sup>18</sup> of atrial fibrillation, respectively.

### PATIENT SELECTION

Although initial reports of atrial fibrillation ablation included patients with paroxysmal atrial fibrillation, our use of the procedure has been expanded to patients with chronic forms of atrial fibrillation—both persistent (those that do not revert to sinus rhythm spontaneously and require chemical or electrical

cardioversion) and permanent (refractory to cardioversion). Table 2 lists important factors to consider when indicating the procedure. It is critical to discuss realistic expectations with the patient before embarking on a long procedure that has significant risks. Atrial fibrillation impacts patients' health because of a) symptoms of palpitations due to unpleasant irregularly irregular rapid beats, b) risk of thromboembolism, and c) tachycardia-induced myopathy or worsening of heart failure.

At this point, the literature solidly supports that symptoms of atrial fibrillation can be ameliorated by ablation.

Observational data support that discontinuation of anticoagulation can be safe in younger patients with  $\leq 2$  risk factors for stroke,<sup>19</sup> but this remains to be confirmed. At this point, performing an ablation with the promise of warfarin discontinuation in high-risk patients does not seem prudent. Similarly, improvement of left ventricular (LV) function has been reported in patients with heart failure and atrial fibrillation subjected to ablation. However, this has to be confirmed in larger trials, and it remains to be proven that catheter ablation is indicated in patients with atrial fibrillation and heart failure for the sole purpose to improve their LV function.

In general, most ablations are performed in patients who have failed prior antiarrhythmic therapy since this is often a reasonable and safe first-line therapy for atrial fibrillation. Many patients exhibit bouts of atrial fibrillation in the first two to three months post-procedure; while these bouts often resolve, temporary antiarrhythmic therapy is frequently required and is most acceptable if patients have been exposed to it prior to the procedure. Although initial strategies were more effective in paroxysmal forms of atrial fibrillation, ablation of chronic atrial fibrillation can now achieve comparable cure rates.<sup>20</sup>

Structural heart disease is not an independent predictor of ablation failure in published reports. The feasibility and efficacy of ablation in patients with significant LV dysfunction has been reported. However, patients in this study did not have severe left atrial enlargement. Indeed, a left atrium diameter  $< 55$  mm has been associated with greater chances of ablation success, while the presence of left atrial scarring has been associated with decreased success. Longer duration of chronic atrial fibrillation may also be associated with decreased success rates.

Severe comorbidities, presence of multiple risk factors for stroke, severe atrial enlargement, valvular atrial fibrillation, and the inability to take warfarin

### Complications of atrial fibrillation ablation

- Tamponade (~1%)
- TIA/Stroke (~0.5 – 1%)
- Atrio-esophageal fistula (~0.01%)
- Phrenic nerve paralysis (~0.1%)
- Pulmonary vein stenosis (~0.5%)
- Laryngeal nerve paralysis
- Vascular access complications (~0.5-1%)
- Gastroparesis

**Table 3.** Complications of atrial fibrillation ablation.

for three months after the procedure are accepted contraindications.

### CHALLENGES, RE-DO PROCEDURES AND COMPLICATIONS

In any of its variants, the reported need of repeat procedures is about 30-50% due to recurrences or failures. There is a delicate balance between providing adequate lesions to achieve the desired procedural endpoint while also avoiding unnecessary lesions. Further understanding of the individual mechanisms of atrial fibrillation should help delineate the right approach for each patient.

Complications are listed in Table 3. Some can be serious and even lethal. While some are linked to the unavoidable fact that lesions are created in thin atrial tissue in the presence of heavy anticoagulation (e.g. tamponade), others, such as atrio-esophageal fistula and pulmonary vein stenosis, are preventable if the operator is cognizant of the anatomical relationships of the atria and avoids making lesions near the esophagus or deep inside pulmonary veins.

At this point, catheter ablation demands a high level of skill and training, carries a substantial risk of complications, and often requires multiple procedures to achieve results comparable to published data. However, these results remain superior to any anti-arrhythmic therapy available. Future developments are likely to solidify the role of catheter ablation in the treatment hierarchy for atrial fibrillation.

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