Atrial fibrillation (AF) is an arrhythmia associated with increased morbidity and mortality. Since the first report of catheter ablation curing AF, numerous techniques have evolved, from linear ablation to segmental pulmonary vein (PV) isolation, to extensive encircling PV isolation, to left atrial (LA) linear ablation, to ablation of complex fragmented atrial electrograms (CFAEs) and ablation of ganglionated plexi. A new approach for complete isolation of the posterior LA, including all PVs, is box isolation. PV isolation is associated with a high clinical success rate in paroxysmal AF. However, in persistent AF or longstanding persistent AF, PV isolation only may not be sufficient, so additional ablation at sites with CFAEs is needed to improve the clinical outcome. A hybrid approach of combining PV isolation plus CFAE ablation is highly effective in the majority of patients with persistent AF or longstanding persistent AF. Thus, AF ablation is an effective and established treatment for AF that offers an excellent chance of a lasting cure. It is about time that AF ablation became a first-line therapy for selected patients with AF.  

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Electrophysiology of the PV

As early as the 1960s, detailed conduction and arrhythmic properties in the thoracic veins and their junctions with the atria were described by Japanese investigators. Despite these early observations, investigation of the anatomic and electrophysiologic properties of the PVs remained limited, until the importance of PV triggers in the development of AF was appreciated. PV focal firing by abnormal automaticity and triggered activity may trigger AF or act as a rapid driver to maintain AF. Other experimental studies have provided evidence that suggests the PVs and the posterior LA are also preferred sites for reentrant arrhythmias. My group also demonstrated that the PV–LA junction has heterogeneous electrophysiologic properties capable of sustaining reentry in humans. In a clinical study using basket catheter mapping, a PV–LA unstable reentrant circuit involving the exit and entrance breakthrough points at the PV–LA junction was observed. The different conduction properties of the exit and entrance sites, depending on the site of discharge, may contribute to reentry formation. The presence of anisotropic structures at the PV–LA junction may be critical for reentry. Thus, the PVs play a critical role in both triggering and maintaining AF.

PV Isolation

The goals of AF ablation procedures are to prevent AF by either eliminating the trigger that initiates AF or by altering...
the arrhythmogenic substrate. A recent consensus of world-renowned experts in AF ablation states that PV isolation is a cornerstone of catheter ablation of AF, and most laboratories perform PV isolation as the primary approach for patients with AF. Earlier studies of electrophysiology-guided segmental ablation at the ostial level suggested that PV disconnection could be achieved with minimal ablation by targeting specific breakthrough points between the PV and LA. Complete electrical isolation was typically achieved after ~50% of the circumference of the PV ostium was ablated. However, PV ostial ablation may result in PV stenosis. Therefore, most operators have moved toward ablation away from the PV ostium toward the level of the antrum. The antrum blends into the posterior wall of the LA. To encompass as much of the PV structure as possible, ablation needs to be performed around the entire antrum, along the posterior LA wall. The circumferential lesions may also alter the arrhythmogenic substrate by eliminating tissue located near the PV–LA junction that provides a substrate for reentrant circuits that may generate or perpetuate AF, and/or by reducing the mass of atrial tissue needed to sustain reentry.

A recent meta-analysis of 31 studies including 2,800 patients found that the single-procedure success rate of PV isolation of all types of AF without antiarrhythmic drugs was 57% (50–64%). An analysis of 34 studies enrolling a total of 3,481 patients shows that the success rate without antiarrhythmic drugs increased to 71% (65–77%) after multiple procedures. However, examining data from 6 pioneering centers with greater experience in AF ablation, the success rate without antiarrhythmic drugs was 81% (71–88%) in 1,039 patients followed up for a period of 6 months to 2.4 years.

**Box Isolation**

Both the PVs and the posterior LA develop from the sinus venosus, where there are many pacemaker cells with spontaneous rhythmic activity in the early embryonic heart. The discrete site of high-frequency periodic activity is localized most often to the posterior LA, including the PV, during AF in sheep hearts. Non-PV foci originated mainly from the PV ostium or from the posterior LA, and the posterior LA and the LA roof serve as a substrate for maintenance of AF in patients with AF. It has been proposed that the surgical procedures for isolating the posterior LA and PVs could cure AF in 93% of patients with lone AF and 86% with chronic AF. These findings support that isolation of not only the PVs but also the whole posterior LA can result in a much better cure rate in the patients with paroxysmal and persistent AF. Therefore, a new approach for complete isolation of the posterior LA, including all PVs, has been developed, namely, box isolation (Figure 1). In the posterior LA, there are many arrhythmogenic substrates for AF, including the triggers, reentries, and ganglionated plexi. Box isolation can contain these abnormal substrates in the posterior LA. There is increasing recognition of the importance of atrial autonomic ganglia in AF maintenance and the value of targeting them in AF ablation procedures. The lesion set of box isolation may interrupt sympathetic and parasympathetic denervation from the autonomic ganglia, which have been identified as potential triggers for AF.

**Techniques and Endpoints for Box Isolation**

Box isolation is performed by my group as the primary approach for patients with all types of AF. Radiofrequency energy is delivered with a power of 30W using an irrigated-tip ablation catheter. The temperature is limited to 40°C. The operator should pay atten-
Ablation of AF

Figure 2. Isolation of pulmonary veins (PV). (Left) Tracings of electrograms during ablation. Lasso 1 is positioned in the left superior PV (LSPV) and Lasso 2 in the left inferior PV (LIPV). (Right) Inside view of the left PVs. In this case the left PVs were not isolated by only anterior lines. Segmental ablation of the breakthrough points at the carina created simultaneous isolation of the left ipsilateral PVs.

Figure 3. Entrance block of the box lesion. Lasso 1 is positioned in the LSPV (yellow) and Lasso 2 is positioned at the posterior wall within the box (green). Ablation of a gap at the mid floor line (Lasso 6) created the entrance block of the box lesion during atrial fibrillation. LSPV, left superior pulmonary vein.

tion to ablating the esophageal aspect of the floorline by decreasing the power and duration of RF energy application. Therefore, the luminal esophageal temperature is monitored with a catheter in the esophagus close to the tip of the ablation catheter. During the ablation at the posterior LA close to the esophagus, cooling water through a tube just above the catheter is infused into the esophagus and the ablation is performed at a maximum power of 20W and a temperature of 40°C. If the esophageal temperature is higher than 38°C, RF applications are interrupted. Radiofrequency energy is delivered for 30s at each point.

Continuous lesions at the anterior portion of the ipsilateral...
superior and inferior PVs are initially created under guidance of double Lasso catheters and a 3D mapping system. Ablation is started at the superior wall and continued around the anterior and inferior venous perimeter. There is no vertical lesion line created at the posterior portion of the PVs along the esophageal aspect of the posterior LA. However, when the PVs are not isolated by only anterior lines, segmental ablation at the breakthrough points is performed (Figure 2). After complete isolation of all PVs, ablation of the LA roof is then performed by creating a contiguous line of ablation lesions joining the superior PVs. Finally, ablation of the LA floor is performed by creating a contiguous line of ablation lesions joining the inferior PVs to isolate the posterior LA.

Entrance block of the box lesion is confirmed by lack of potentials in the box during AF or sinus rhythm (Figure 3). Exit block of the box lesion is confirmed during sinus rhythm. Gaps along the ablation lines are detected and closed using high voltage (10 V) pace mapping through the ablation catheter. With lack of left atrial (LA) capture (yellow), the line was considered as complete at this location. In the case of LA capture (pink), a gap was suspected and RF energy was delivered simultaneously while pacing from the tip of the ablation catheter. (Right) Ablation at the site with LA capture was continued until there was a lack of LA capture.

**Ablation of CFAE**

PV isolation or box isolation alone is effective for treating paroxysmal AF, but is not enough for curing persistent AF or longstanding persistent AF. Nademanee et al have provided a new electrogram-guided approach by mapping and targeting areas of CFAE defined as fractionated electrograms composed of 2 or more deflections with a mean cycle length ≤120 ms. CFAE may indicate slow conduction, pivot points of wave fronts, reentries and drivers. Also, there is a close relationship between autonomic ganglionated plexi activity and CFAE.

Nademanee et al showed that AF was terminated in over 85% of patients, and reported that after CFAE ablation, 93% of the patients with paroxysmal AF, 87% of patients with persistent AF and 78% of patients with longstanding persistent AF were arrhythmia-free, including 11% of the patients taking antiarrhythmic drugs. However, their results were not fully reproduced by others. Oral et al performed ablation of CFAE in patients with chronic AF and in their study, only 12% of the patients had AF converted to sinus rhythm during the ablation and 4% converted to atrial flutter. Only 33% of the patients were in sinus rhythm without antiarrhythmic drugs after a single procedure and 57% of the patients were in sinus rhythm after a second procedure. Although it is unclear what are the factors underlying the differences in outcome between the 2 studies, several reasons may explain them, including additional right atrial ablation, the power and duration of RF energy, and the study endpoint.

CFAE are sometimes recorded over a diffuse area and numerous ablation applications are often necessary to eliminate all CFAE or to terminate AF. It is also difficult to distinguish culprit CFAE (eg, CFAE associated with perpetuating AF) from bystander CFAE. Although the most robust endpoint may be termination of AF, this generally requires a very long procedure time. Furthermore, extensive ablation is associated with procedural complications, proarrhythmia, stroke risk, and
compromise of atrial mechanical function.\textsuperscript{38} Nademanee et al\textsuperscript{37} used intravenous ibutilide to highlight the CFAE associated with perpetuating AF after CFAE ablation, if the patient remains in AF despite elimination of all visible CFAE. They demonstrated that ablation of CFAE resulted in termination of AF in 95% of patients; however, 28% required concomitant ibutilide treatment.\textsuperscript{37}

### Long-Term Efficacy of AF Ablation

Recently, 2 5-year follow-up studies reported that single-procedure success rates without antiarrhythmic drugs were 47% in patients with paroxysmal AF\textsuperscript{39} and 29% in patients with all types of AF,\textsuperscript{40} and after a repeat procedure, the success rates increased to 80% and 63%, respectively.

At the Heart Rhythm Center, 513 patients, including 353 with paroxysmal AF, 73 with persistent AF (<1 year, mean 5±2 months), and 87 with longstanding persistent AF (>1 year, mean 5±4 years) underwent box isolation, after which, CFAE ablation was performed in 34 (47%) patients with persistent AF, and 70 (80%) patients with longstanding persistent AF. After a single ablation procedure, AF recurred in 70 (20%) patients with paroxysmal AF, 20 (27%) patients with persistent AF, and 31 (36%) patients with longstanding persistent AF. In the patients with AF recurrence, antiarrhythmic drugs were re-administered. A second ablation procedure was performed in 39 (11%) patients with paroxysmal AF, 13 (18%) patients with persistent AF, and 26 (30%) patients with longstanding persistent AF, including atrial tachycardia or flutter in 3% of the patients. During the second session, recovered conduction gaps along the lines were found in 88% of the patients and re-box isolation was performed. Additional ablation was performed in 74% of the patients, including CFAE in 48%, superior vena cava isolation in 30%, mitral isthmus in 26%, focal atrial tachycardia in 24%, cavotricuspid isthmus in 20%, and gap-related flutter in 11%.

After a follow-up period of 24±8 months, 328 (93%) patients with paroxysmal AF, 65 (89%) patients with persistent AF and 74 (85%) patients with longstanding persistent AF were free of AF, of whom 297 (84%) patients with paroxysmal AF, 58 (79%) patients with persistent AF, and 63 (72%) patients with longstanding persistent AF were without antiarrhythmic drugs.

### Procedure Complications

Catheter ablation of AF is associated with significant complications,\textsuperscript{41,42} which include vascular complications secondary to venous access, cardiac perforation/tamponade, valvular injury, embolic stroke or systemic embolism, PV stenosis, esophageal injury, and proarrhythmia resulting from reentrant tachycardias occurring from incomplete ablation lesions. The incidence of complications depends on operator experience.

At the Heart Rhythm Center, cardiac tamponade has occurred in 5 of 513 patients (1.0%) and was managed by percutaneous drainage; 1 patient had homonymous hemianopsia; 1 patient had phrenic nerve injury, but recovered fully within 3 months; 1 patient had gastric hypomotility, but recovered fully within 2 weeks. No cases of atrio-esophageal fistula, significant PV stenosis or procedure-related death occurred.

### Indication of AF Ablation

Ablation should be considered for patients with symptomatic paroxysmal AF that has failed treatment with one or more antiarrhythmic drugs, with normally sized or mildly dilated atria, and normal or mildly reduced ventricular function. Ablation may particularly benefit younger patients with lone AF who are frequently symptomatic and for whom very long-term antiarrhythmic and anticoagulation therapy has higher risks and costs.

It has been shown that good success of ablation can be achieved in patients with left ventricular dysfunction,\textsuperscript{43,44} previous cardiac surgery or valvular heart disease,\textsuperscript{45} and advanced age.\textsuperscript{46} Patients with heart failure benefit from AF ablation because the ejection fraction and functional endpoints such as exercise tolerance may significantly improve.\textsuperscript{44,47} Considering the potential of AF ablation to achieve rhythm control in symptomatic patients with paroxysmal AF and minimal or no organic heart disease, and the relative safety of the technique when performed by experienced operators, ablation may be considered as an initial therapy in selected patients.

There are several factors for determining the indication of AF ablation: the stage of atrial disease (ie, AF type, LA dimensions, duration of AF), the presence and severity of organic heart disease, age and the severity of symptoms, and patient preference. In symptomatic paroxysmal and persistent AF in patients with relevant organic heart disease, successful ablation is more difficult to achieve. In addition, little information is yet available about the late success of ablation in patients with heart failure and other advanced structural heart disease.\textsuperscript{48} Ablation of persistent and longstanding persistent AF is associated with variable but encouraging success rates, but often requires several attempts.

In clinical practice, many patients with AF may be asymptomatic but seek catheter ablation as an alternative to long-term anticoagulation. Although retrospective studies have demonstrated that discontinuation of oral anticoagulation therapy after ablation may be safe over the medium-term in some subsets of patients, this has never been confirmed by a large prospective randomized clinical trial and therefore remains unproven.\textsuperscript{49,51} Furthermore, it is well recognized that symptomatic and/or asymptomatic AF may recur during long-term follow-up after an AF ablation procedure. Therefore, discontinuation of anticoagulation therapy post ablation is generally not recommended in patients who have a CHADS score ≥2. A patient’s desire to eliminate the need for long-term anticoagulation by itself should not be considered an appropriate selection criterion.

### Meta-Analysis and Randomized Trials of Ablation vs. Antiarrhythmic Drugs

Meta-analyses of studies performed mostly in patients with paroxysmal AF have confirmed the superiority of catheter ablation compared with antiarrhythmic medication.\textsuperscript{52–56} However, there is no evidence so far that successful AF ablation will result in reduced mortality, but a large prospective worldwide trial is already underway: catheter ablation vs. antiarrhythmic drug therapy for AF (CABANA). It is conceivable that AF ablation embedded in a comprehensive rhythm control intervention is most effective and beneficial when performed early during the course of disease.\textsuperscript{57}

### Conclusions

AF is an arrhythmia associated with increased morbidity and mortality. Current therapies, especially antiarrhythmic drugs, not only are ineffective but can threaten a patient’s quality of life and even longevity. AF ablation is an effective, safe, and established treatment that offers an excellent chance of a last-
ing cure. Therefore, it is about time that AF ablation became a first-line therapy for selected patients with AF in terms of efficacy and safety when performed by experienced operators. AF ablation requires operator skills in manipulating catheters, understanding all facets of clinical electrophysiology, and treating procedure-related complications.

The present reality will gradually develop, and advances such as robotically controlled catheters and real-time MRI or CT imaging will help electrophysiologists to become more proficient in the task. AF ablation should be performed in centers that are well-equipped with an advanced mapping system and an experienced team to achieve the excellent outcomes.

References


