Box Isolation for Atrial Fibrillation

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Since the first report of catheter ablation curing atrial fibrillation (AF), numerous techniques have evolved, from linear ablation to segmental pulmonary vein (PV) isolation, extensive encircling PV isolation, LA linear ablation, ablation of complex fragmented atrial electrograms (CFAE) and stepwise ablation. We developed a new approach for complete isolation of the posterior LA including all PVs, namely box isolation. 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. Box isolation is associated with a high clinical success rate in paroxysmal AF. However, in persistent AF or longstanding persistent AF, only box isolation may not be sufficient, therefore, additional ablation at sites with CFAE outside the box area is needed to improve the clinical outcome. A hybrid approach of combining box isolation with CFAE ablation is highly effective in the majority of patients with persistent AF or longstanding persistent AF. Thus, AF ablation is an effective and safe treatment for AF that offers an excellent chance for a lasting cure.
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Introduction

It is well accepted that the development of atrial fibrillation (AF) requires both a trigger and arrhythmogenic substrate. The goals of ablation are to prevent AF by either eliminating the trigger that initiates AF or by altering the substrate. Haissaguerre et al.1) first found that most focal AF is initiated by premature beats from the orifices of the pulmonary veins (PVs) or from the myocardial sleeves inside the PVs, and catheter ablation of triggered foci has been shown to cure AF. This discovery started a new era in the treatment of AF. The initial approach was focal ablation of the culprit PV identified as the triggering site initiating AF. However, detecting the exact focus is often difficult when atrial premature beats are infrequent, or each extrasystole may induce AF, thus necessitating repeated defibrillation. For these reasons, Haissaguerre et al.2) provided an alternative approach that simply seeks to electrically isolate the PVs from the left atrium (LA) at electrophysiological breakthroughs from the LA to the PV.

Rationale of PV Isolation

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 paroxysmal AF. The dominant rotors in AF are localized primarily at the PV-LA junction, as demonstrated by several investigators. Moreover, vagal inputs may be very important in both triggering and maintaining AF, and many of these inputs are clustered close to the PV-LA junction. We also demonstrated that the PV-LA junction has heterogeneous electrophysiological properties capable of sustaining reentry. In our study using basket catheter mapping, unstable reentrant circuits were observed in response to single extrastimulus and repetitive focal activities in the PV. These reentrant circuits were short lived (i.e., were unstable). Furthermore, a PV-LA reciprocating reentrant circuit involving the exit breakthrough point and the entrance breakthrough point at the PV-LA junction was observed. A wave front from a focal discharge in the PV goes through the nearest exit breakthrough point and re-enters to the PV from the entrance site, forming a reentrant circuit. The different conduction property of the exit and entrance sites depending on the site of pacing or discharge may contribute to the reentry formation. Wave fronts traveling to and from the LA may play an important role in the formation of unstable reentrant wave fronts. The presence of anisotropic structures at the PV-LA junction may be critical to form reentry. Thus, the PVs play a critical role in both triggering and maintaining AF. Therefore, the goal of present AF ablation is to electrically disconnect the PVs from the rest of the atrium by ablating around the origin of the PVs. The circumferential PV isolation may alter the arrhythmogenic substrate by elimination of tissue located near the PV-LA junction that provides a substrate for reentrant circuits that may generate or perpetuate AF, and/or by reduction of the mass of atrial tissue needed to sustain reentry.

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. According to the reports from several groups using ablation of all 4 PVs outside the tubular portion, the success rate without antiarrhythmic drugs is much more consistent, at 75 to 95%. A further 10 to 20% of patients may become responsive to previously ineffective antiarrhythmic drugs. Some variation remains, partly because of differences in the precise end point used and operator experience.

**Advantages of Box Isolation**

Both PVs and the posterior LA are developed 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 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 PVs but also the whole posterior LA can result in a much better cure rate in the patients with paroxysmal and persistent AF. Therefore, we developed a new approach for complete isolation of the posterior LA including all PVs, namely box isolation. In the posterior LA, there are many arrhythmogenic substrates for AF, including the ganglionated plexi, reentries and triggers. Box isolation can contain these abnormal substrates in the posterior LA. A big difference between box isolation and extensive two by two PV isolation is the line design of the posterior LA. The total length of two horizontal lines in box isolation is shorter than two vertical lines in two-by-two continuous circular lesions. Although the total length of lines in box isolation is shorter than in extensive PV isolation, box isolation can isolate the posterior LA wider than two-by-two continuous circular lesions. Thus, box isolation can minimize lesions and maximize the success rate.

**Techniques and Endpoints for Box Isolation**

We perform box isolation as the primary approach for patients with all types of AF. Radiofrequency energy was delivered with a power of 30 W using an irrigated-tip ablation catheter. The temperature was limited to 40 °C. Although only a part of the floorline crosses close to the esophagus, the transverse width of the esophagus in contact with the posterior LA...
may be shorter than its vertical length and therefore the floorline would be safer for the esophagus than the posterior vertical line. However, the operator should pay attention to ablation of the esophageal aspect of the floorline by decreasing the power and duration of RF energy application. Therefore, we monitor the luminal esophageal temperature with a catheter in the esophagus at a position 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 was infused into the esophagus and the ablation was performed at a maximum power of 20 W and a temperature of 40°C. If the esophageal temperature was higher than 38°C, RF applications were interrupted. Radiofrequency energy was delivered for 30 seconds at each point.

Continuous lesions at the anterior portions of the ipsilateral superior and inferior PVs were initially created under guidance of double Lasso catheters and the 3D mapping system. Ablation was started at the superior wall and continued around the anterior and inferior venous perimeter. There was no vertical lesion line created at the posterior portions of the PVs along the esophageal aspect of the posterior LA. However, when PVs were not isolated by only anterior lines, segmental ablation at the breakthrough points was performed (Figure 4). After complete isolation of all PVs was created, ablation of the LA roof was then performed by creating a contiguous line of ablation lesions joining the superior PVs. Finally, ablation of the LA floor was performed by

**Figure 1** Advantages of box isolation
Classical one-by-one PV isolation can be complicated by occurrence of PV stenosis. Two-by-two PV isolation can decrease the risk of PV stenosis and improve the success rate, but esophageal injury is a potential complication. In contrast, box isolation can decrease the risk of PV stenosis and esophageal injury, and increase the success rate.

**Figure 2** Difference between box isolation and extensive 2-by-2 PV isolation in total length of lines
The total length of two horizontal lines in box isolation (84 mm) is shorter than two vertical lines in two-by-two PV isolation (99 mm). LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein, RSPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein

**Figure 3** Difference between box isolation and extensive 2-by-2 PV isolation in isolated area
Total isolated area in box isolation (22.1 cm²) is wider than that in two-by-two PV isolation (17.5 cm²).

**Figure 4** After complete isolation of all PVs was created, ablation of the LA roof was then performed by creating a contiguous line of ablation lesions joining the superior PVs.
creating a contiguous line of ablation lesions joining the inferior PVs to isolate the posterior LA.

Entrance block of the box lesion was confirmed by lack of potentials in the box during AF or sinus rhythm (Figure 5). Exit block of the box lesion was confirmed during sinus rhythm. Gaps along the ablation lines were detected and closed using high voltage (10 V) pace mapping through the ablation catheter (Figure 6). With lack of LA capture, the line was considered as complete at this location. In case
of LA capture, a gap was suspected and RF energy was delivered simultaneously while pacing from the tip of the ablation catheter. The endpoint of box isolation was defined as bidirectional conduction block, that is, both lack of potentials in box and lack of LA capture. This is important to prevent a recurrence of gap-related atrial flutter.

**Ablation of CFAE**

PV isolation or box isolation alone is effective for treating paroxysmal AF, however, not enough for cure of persistent AF or longstanding persistent AF. To improve the clinical outcome, extensive ablation, including multiple linear lesions and/or ablation of complex fractionated atrial electrograms (CFAE), has been widely adopted, particularly in patients with 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 two or more deflections with a mean cycle length ≤120 ms. CFAE may indicate slow conduction, pivot points of wave fronts, reentries, drivers, and ganglionated plexi. They showed that AF was terminated in over 85% of the patients, and reported that after CFAE ablation, 93% of the patients with paroxysmal AF, 87% of the patients with persistent AF and 78% of the 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. 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 underlying factors may be attributed to the differences in outcome between the two studies, several reasons may explain the differences, including additional right atrial ablation, power and duration of RF energy, and endpoint.

**Hybrid Approach of Combining Box Isolation with CFAE Ablation**

In our previous study, with box isolation alone, 73% of the patients with persistent AF and 46% of the patients with longstanding persistent AF were arrhythmia-free without antiarrhythmic drugs. In
these successful patients, CFAE ablation was not necessary even if CFAE was present. In the remaining patients who show recurrence of AF, CFAE ablation may improve the success rate. However, it is difficult to identify patients who require additional CFAE ablation. CFAE are sometimes recorded in 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 (e.g. CFAE associated with perpetuating AF) from bystander CFAE. Although the most robust endpoint may be termination of AF, this generally requires very long procedure time.

Furthermore, extensive ablation is associated with procedural complications, proarrhythmia, stroke risk, and compromise of atrial mechanical function. Nademanee et al. 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 the patients; however, 28% required concomitant ibutilide treatment. We used antiarrhythmic drugs before CFAE ablation in 60 patients, including 38 with longstanding persistent AF and 22 with persistent AF who underwent box isolation. After box isolation, CFAE maps were created before and after infusion of a pure Na⁺ blocker, pilsicainide (1 mg/kg), in 30 patients or a pure Iₖ blocker, nifekalant (0.3 mg/kg), in 30 patients. Nifekalant had a greater effect on AF termination than pilsicainide (33% versus 7%). Both pilsicainide and nifekalant similarly decreased degree of LA fractionation and reduced CFAE (Figure 7A). Ablation of CFAE localized by pilsicainide and nifekalant terminated AF in 20% and 27% of the patients, respectively (Figure 7B–D). Endpoint of ablation was defined as the elimination of CFAE or termination of AF. After a single ablation procedure, 17 patients (28%) had a recurrence of AF; patients in whom AF was terminated by minimal CFAE ablation had a lower recurrence rate than those in whom AF was not terminated despite extensive CFAE ablation (19% versus 35%). A second ablation procedure was performed in 14 patients (23%) who showed recurrence of AF. At 17 ± 7 months after the last ablation procedure, 55 patients (92%) were free of AF; 47 (78%) without antiarrhythmic drugs and 8 (13%) with antiarrhythmic drugs. Our procedure can achieve a success rate as high as that of CFAE ablation without antiarrhythmic drugs. Therefore, additional ablation of CFAE may not be necessary when antiarrhythmic drugs terminate AF after box isolation, and ablation of only CFAE localized with antiarrhythmic drugs may be sufficient for clinical efficacy. Thus, a hybrid approach of box isolation combined with ablation of CFAE localized with antiarrhythmic drugs is feasible and effective for decreasing the unnecessary ablation of bystander CFAE.

Long-term Clinical Outcomes

At our own institution, 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 box isolation, 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 the box isolation procedure was repeated. Additional ablation was performed in 74% of the patients, including CFAE in 48% (Figure 8), superior vena cava isolation in 30%, mitral isthmus in 26%, focal atrial tachycardia in 24%, cavo-tricuspid isthmus in 20%, and gap related flutter in 11%.

After the 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

Cardiac tamponade occurred in 5 patients (1.0%). This was managed by percutaneous drainage. One patient had homonymous hemianopsia. One patient had phrenic nerve injury, but recovered fully within three months. One patient had gastric hypomotility, but recovered fully within two weeks. No atrioesophageal fistula, significant PV stenosis or procedure-related death occurred.
Conclusions

AF is an arrhythmia associated with increased morbidity and mortality. Current therapies, especially antiarrhythmic drugs, not only are ineffective but also present a threat to patient quality of life and even longevity. AF ablation is an effective, safe, and established treatment for AF that offers an excellent chance for a lasting cure. Therefore, it is about time that AF ablation could be considered a first-line therapy for selected patients with AF in terms of efficacy and safety when performed by experienced operators. AF ablation requires operator skill in

Figure 7 Termination of AF by the ablation of localized CFAE with pilsicainide
A: Regional distribution of CFAE in the LA before and after pilsicainide and the corresponding bipolar electrograms during AF. CFAE mapping revealed multiple CFAE sites (white color), including the LA septum, LA anterior wall, and near the mitral annulus region. Before pilsicainide, both sites A and B showed CFAE, but after pilsicainide only site B still showed CFAE. B: Ablation of localized CFAE with pilsicainide. A Lasso catheter was positioned in the LA appendage. Ablation (#7) of CFAE at the LA appendage was performed.
Figure 7 Termination of AF by the ablation of localized CFAE with pilsicainide

C. Ablation (#10) of the CFAE at the LA appendage was performed. D. Ablation (#10) of the last CFAE at the LA appendage resulted in the restoration of sinus rhythm.
Figure 8 Ablation of CFAE during second session
Tracings of electrograms during second session in a patient with longstanding persistent AF. A Lasso catheter was positioned in the left atrial appendage. During second session, complete box isolation had been created, ablation of CFAE was then performed. A: CFAE was observed at the mitral annulus (red square). Mean AF cycle length of coronary sinus was 128 msec. B: Ablation of CFAE at the mitral annulus eliminated all CFAE in the LA and prolonged AF cycle length from 128 to 143 msec.
Figure 8  Ablation of CFAE during second session
C: CFAE in the RA was then mapped. Severe CFAE were observed in the right atrial appendage (RAA). AF cycle length at the high RA (HRA) was shorter than that at the coronary sinus (CS) or left atrial appendage. D: Ablation of CFAE in the RA converted AF to atrial tachycardia (AT) with a cycle length of 248 msec.
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 will help electrophysiologists to become more proficient to the task. AF ablation should be performed in centers that are well-equipped with an advanced mapping system and an experienced team to achieve excellent outcomes.

**Figure 8** Ablation of CFAE during second session

E: The mechanism of AT was focal AT originated from the posterior RA. F: Ablation of the focus terminated AT.
References


