Catheter ablation of atrial fibrillation (AF) has evolved over the past 20 years from being a novel, unproven procedure to a commonly performed procedure. Triggers are important for the initiation of AF and a suitable substrate is important for perpetuation of AF. Remodeling, including electrical and structural remodeling, is common in patients with persistent AF. Therefore, targeting the remodeled atrium is a critical issue during persistent AF ablation. However, ablation outcomes remain suboptimal despite aggressive substrate modification. Empirical linear ablation is not recommended because of the difficulty in achieving complete linear block and it is recommended only if macroreentrant tachycardia develops during the procedure. Complex fractionated atrial electrogram (CFAE) ablation is recommended in the Heart Rhythm Society Consensus Document but efficacy has been limited in long-term follow-up studies. Rotor ablation is controversial. A combined approach using CFAE, similarity and phase mappings with rotor identification may be helpful in searching for AF sources and subsequent substrate ablation. Nevertheless, more prospective randomized studies are required to validate efficacy and safety. (Circ J 2016; 80: 306–313)

Key Words: Ablation; Atrial fibrillation; Mapping; Rotor; Substrate

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and the prevalence will at least double in the coming 5 decades because of aging populations. Since Haissaguerre and Chen first reported the pathogenic role of pulmonary vein (PV) triggers as an important mechanism of AF, catheter ablation has been a therapeutic option for these patients. Percutaneous catheter ablation is now widely used as an interventional tool for non-pharmacological AF rhythm control, particularly in those who are refractory to antiarrhythmic medications. The natural history of AF is characterized by a progression from paroxysmal to persistent and then to permanent AF over time. As AF progresses from the paroxysmal to persistent type, atrial remodeling increases the disease complexity. Therefore, ablation of persistent AF is more challenging and the outcome is not satisfactory. Substrate modification is usually required in order to improve the outcome, in addition to PV isolation. Here, we will review the advantages and disadvantages of different substrate modification techniques in catheter ablation of persistent AF.

Pathophysiology of AF

The mechanism of AF is not completely understood. It represents a final common presentation of multiple disease pathways. There have been 2 theories since the early era in the 1950s: AF is caused by either a rapid firing focus or multiple reentrant wavelets. The studies by Scherf et al supported the concept of a rapid firing focus initiating AF. By administrating aconitine on the atrium, both rapid, regular atrial rhythm and rapid irregular atrial rhythm could be initiated. Goto et al and Azuma et al reproduced similar findings and found the mechanism was secondary to enhanced automaticity. Currently, we understand that reentry, automaticity, and triggered activity are all possible causes of a rapid firing focus initiating AF.

Later, Moe et al proposed the multiple reentrant wavelet hypothesis as a mechanism of AF. Random reentry, different from regular reentry caused by circus movement, could lead to AF development. AF consisted of a critical number of randomly distributed reentrant wavelets, which could collide and divide, or change in size and velocity. The hypothesis is now widely accepted and Allessie et al further reported their experimental results of the hypothesis. Multiple reentrant wavelets are separated by functional conduction block lines. In real-world practice, sometimes ablation terminates AF early during ablation before compartmentalization of the atrium. In contrast, some patients receive extensive ablation with little acute effect. Therefore, both a focal trigger and multiple wavelet reentry perpetuate AF.

Most of the AF triggers originate from the PVs. Therefore, the PVs are important for the initiation of AF. Coordinated, regular atrial activity is replaced with disorganized rapid excitations. The possibility of conversion and maintenance of
sinus rhythm decreases as the AF duration increases. This pathophysiologic adaptation to fibrillatory conduction has been named “remodeling”. The remodeling process has both electrical and structural components. Electrical remodeling develops as early as the first week of AF, with shortening of the atrial refractoriness and slowing of the conduction velocity. Structural remodeling is the second factor that facilitates the maintenance of AF in the following months. Inhomogeneous conduction, electrical uncoupling, and enlargement of the atrium cause the progressive remodeling of the atrium and therefore, it can accommodate more circulating electrical wavefronts and stabilize the AF. The dilated atrium may show pronounced structural abnormalities, including interstitial fibrosis, cellular hypertrophy, and degeneration, and thickened basement membrane. Both remodeling processes are advanced in patients with persistent AF. Therefore, not only trigger elimination, but also substrate modification is important during the catheter ablation procedure.

Catheter Ablation Strategy for Persistent AF

In the 2014 AHA/ACC/HRS guidelines for the management of patients with AF, catheter ablation is a Class IIa indication and is reasonable for symptomatic persistent AF refractory or intolerant of at least one Class 1 or 3 antiarrhythmic medication, and it is indicated as a Class IIb indication before any medical therapy. In the guideline from the European Society of Cardiology, catheter ablation for persistent AF is also considered as a Class IIa indication in symptomatic AF that is refractory to antiarrhythmic therapy. But in those patients with minimal or no organic heart disease, the treatment strategies and risk-benefit ratio of catheter ablation are less established. In the updated 2012 HRS/EHRA/ECAS Consensus Document, catheter ablation is a Class IIa indication and reasonable for persistent AF in those refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication. In this Consensus, catheter ablation is also recommended as a Class IIb indication before any medical therapy.

In the HRS/EHRA/ECAS Consensus Document, PV isolation is still the cornerstone of treatment for the patients with persistent AF. However, the ablation target and endpoint are ill-defined, and there is no consensus on the optimal ablation strategy in these patients. Because of the substantial recurrence rate observed in patients with persistent AF who undergo PV isolation alone, continued efforts are underway to identify additive strategies to improve the long-term outcome. As mentioned, advanced substrate remodeling develops in the patients with persistent AF, so additional substrate modification is usually required after encircling the 4 PVs. There are 2 methods that are more definitive and recommended in the Consensus Document for modifying the atrial substrate: linear ablation or ablation of complex fractionated atrial electrograms (CFAEs). Recently, some have also reported that voltage map guide modification or rotor ablation could be an alternative for modifying the atrial substrate.

Advantages and Disadvantages of Different Substrate Modification Strategies

Linear Ablation Approach

The roof and mitral isthmus of the left atrium (LA) are the most commonly preferred sites for substrate modification using linear ablation. In the prospective randomized study conducted by Willems et al., PV isolation alone was insufficient in the treatment of persistent AF, and additional LA linear lesions increased the success rate significantly. Early AF relapses were associated with a negative outcome after PV isolation alone, but not following additional linear ablation. Miyazaki et al reported that PV isolation followed by biatrial substrate modification with a predetermined order of linear ablation is a feasible approach to ablation. AF termination occurred in 51% of the patients and the AF-free rate was 74% after 1.7 procedures in a 1.5-year of follow-up. Matsuo et al reported that in patients with persistent AF, PV isolation with LA linear ablation diminished the CFAE area in regions remote from the ablation sites. Pak et al proposed that linear ablation along the LA anterior wall results in a better clinical outcome in persistent AF patients, with a higher rate of bidirectional block compared with lateral mitral isthmus ablation.

However, linear ablation is a double-edged sword because proarrhythmic atrial tachycardias can be created secondary to an incomplete block line. It is difficult to achieve a durable complete bidirectional conduction block across these lines. Morady et al reported that during a repeat procedure, up to 90% of atrial tachycardias after AF ablation (including linear ablation in the index procedure) were reentrant, and the mitral isthmus, roof, and septum accounted for 75% of the ablation targets for the macroreentrant atrial tachycardia. In the study by Sawhney et al, more patients developed LA flutter after PV isolation plus linear ablations, compared with segmental PV isolation alone. In our recent study of patients who received multiple AF ablation procedures, the incidence of atypical flutter or atrial tachycardia was approximately 30% after a second procedure. It is possible that linear ablation used in a stepwise ablation strategy in the index procedure is proarrhythmic during long-term follow-up. Although linear lesions may be helpful in eliminating AF at initial ablation, incomplete linear lesions may be proarrhythmic, and even complete lines can also promote reentry. The risk-benefit ratio of such linear lesions is always controversial. Recent studies demonstrated that a more extensive ablation strategy with a linear approach, in addition to PV isolation, provided no further benefit for persistent AF patients. Empirical and anatomically defined lines do not address individual localization of the fibrotic atrial substrate. Therefore, we should reconsider the role of linear lesion ablation and it should be reserved for those with macroreentry atrial flutter developed after PV isolation during the index or recurrent procedure. Line completeness should also be demonstrated by mapping or pacing maneuvers.

CFAE Ablation Approach

Ablation targeting CFAEs is popularly used during a stepwise ablation approach in persistent AF and is recommended in the HRS Consensus Document. Near 50% of Task Force members routinely apply CFAE-based ablation as part of their strategy during persistent AF ablation. Nademanee et al reported that the areas of the CFAEs represented a defined electrophysiologic substrate and are ideal sites for ablation to eliminate AF and maintain normal sinus rhythm. However, the true mechanism of CFAEs detected during ablation is still not fully understood. The percent area of CFAE increases and the mean CFAE cycle length shortens as the LA undergoes advanced remodeling. CFAEs are strongly associated with the areas that have adjacent structures in contact with the LA (eg, ascending aorta, vertebrae) with a very low voltage electrogram during sinus rhythm. A study of a noncontact mapping system revealed different activation patterns in the repetitive and continuous fractionated CFAEs. Non-PV ectopy are also found to be located at the same sites as the CFAEs, and targeting those CFAEs can effectively eliminate
AF, 25% of CFAEs, and 57% of those in the right atrium, are related to non-PV triggers after PV isolation. Figure 1 shows an example of coronary sinus ostial non-PV ectopic triggers initiating AF that manifests a continuous CFAE. Ablation terminated this non-PV initiating AF. The cardiac intrinsic autonomic activity also contributes to the fractionated atrial electrogram activities. Ablation of the ganglionated plexi can attenuate CFAE activity.

Although some studies have shown better outcomes for termination of AF by supplemental CFAE ablation in addition to PV isolation, some recent reports revealed no clinical benefit of CFAE ablation in patients with persistent AF. Nevertheless, AF procedural termination is still considered as a good predictor of a favorable long-term outcome in persistent AF. The limitations of targeting CFAEs with ablation has been the extensive amount of ablation needed. It is not easy to differentiate “culprit” from “bystander” CFAEs during the procedure. Although Nademanee et al reported a definition of CFAE in their first study, the specificity of the different types of CFAEs is still unclear. The definition of CFAE is also inconsistent among the different laboratories. Our recent study demonstrated that in the patients with persistent AF who fail to achieve AF termination after PV isolation, targeting continuous CFAE (fractionated interval <60 ms) could be considered as an initial ablation strategy because of the lower incidence of recurrent atrial flutter and better reverse remodeling of the LA, and better outcome with freedom from any atrial arrhythmia after 2 procedures. Figure 2 illustrates cases of extensive CFAE or limited CFAE ablations and Kaplan-Meier curves demonstrating sinus rhythm maintenance after 2 procedures. Additionally, it is not uncommon for AF to organize into macroreentrant or focal atrial tachycardia during targeting of CFAEs. The major mechanism of those tachycardias is macroreentry around large anatomic obstacles.

In summary, it is important to know that improved outcomes with CFAE ablation in patients with persistent AF have not yet been uniformly reported and the scientific basis of CFAE ablation is not universally accepted. Careful selection of patients, avoiding empirical extensive defragmentation, and complete lesion creation while CFAE are being ablated are recommended in order to prevent the proarrhythmic side effect.

Voltage Map-Guided Ablation Approach
Atrial structural remodeling involves fibrosis and scarring of the atrium and it is important in AF pathogenesis. The scarring can be detected by delayed enhancement MRI and correlates well with the reduced electrogram amplitudes recorded by endocardial voltage maps. The low voltage areas are extensively distributed in the patients with persistent AF, compared with those with the paroxysmal type. The low voltage areas can be demonstrated in approximately every third patients with persistent AF, and less often in patients with
Substrate Modification: Advantages and Disadvantages

Rotor Ablation

The concept of rotor ablation was first reported by Jalife and colleagues in the ventricular muscle and then supported by evidence from optical mapping in isolated animal preparations. Rotor is a phase singularity; that is, spiral waves radiate at a high speed into the surrounding tissues. Clinically, we can observe a rotor in a repetitive, cyclic activation around a core. There are 2 forces from a rotor: one is rotational force with curvature, the other is divergence force with peripheral fibrillatory conduction. As mentioned earlier, a cycle length-based linear analysis is not good enough to differentiate culprit CFAEs from bystanders. By using a 64-pole basket catheter in the LA, Narayan et al proposed panoramic contact mapping, incorporating phase analysis, repolarization, conduction dynamics, and oscillation at AF rate, hypothesizing that AF may be sustained by electrical rotors and focal impulses. Ablation

Figure 2. Different substrate modification methods: limited and extensive approaches to CFAE ablation. Kaplan-Meier curves of freedom from any atrial arrhythmia recurrence after the first ablation procedure (A) and after 2 procedures (B) over long-term follow-up. CFAE, complex fractionated atrial electrogram; LA, left atrium. (Reproduced with permission from Lin YJ, et al.)
of such sources (FIRM: Focal Impulse and Rotor Modulation) has been shown to improve ablation outcome compared with conventional ablation alone. Recently, nonlinear analysis of the fibrillatory electrogram similarity and phase mapping to be applied in AF ablation have also been proposed by Lin and colleagues. A higher similarity index has been reported to predict sites of AF procedural termination and long-term outcome in retrospective studies. In the extended follow-up of the CONFIRM trial, Narayan et al claimed rotors or focal sources were observed in 97.7% of the patients during AF. After more than 2 years of follow-up with 1.2 ablation procedures, 78% of the patients maintained free from AF.

Unfortunately, that result cannot be reproduced in other laboratories. Studies from the UCLA group using the FIRM technique to guide AF ablation found that rotor sites did not exhibit the quantitative atrial electrogram characteristics expected from rotors and did not differ from the surrounding tissue. In addition, the basket catheter used in constructing the FIRM map covers the LA incompletely. The rotational activation found in 3D electroanatomical mapping systems was also not visualized in the FIRM map. Therefore, AF termination or organization was only observed in 17% of the patients. After a 1.5-year follow-up, only 37% of patients were free from documented recurrent AF, indicating poor efficacy of the FIRM ablation outcome. The Bourdeaux group used an array of 252 body surface electrodes and noncontrast computed tomography scan to obtained accurate biatrial geometry. They found that in the early months of persistent AF it is predominantly maintained by unstable reentry drivers with meandering, and periodic occurrence, also different from Narayan’s temporary stable rotors.

There are some pitfalls in the FIRM map-guided ablation. In the FIRM map, rotor is neither clearly defined nor truly identified. Second, the delicate electrogram recordings along the reentry pathway are not available because of the wider interelectrode distance. Third, the curvature of the core and the divergence force are not evaluated in the system. The study by Lin et al demonstrated that rotor was only identified in a limited number (15%) of patients with persistent AF.

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Figure 4. Examples of phase mapping at CFAE sites. (A) Continuous, regular rapid repetitive CFAE with a high SI at the LA roof. Ablation at this location terminated the AF. (B) Continuous CFAE with a low SI at the LA septum. Ablation targeting this CFAE did not change the AF cycle length. AF, atrial fibrillation; CFAE, complex fractionated atrial electrogram; LA, left atrium; SI, similarity index.

Table. Summary of Advantages and Disadvantages of Different Substrate Modification Approaches

<table>
<thead>
<tr>
<th>Approaches</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Linear ablation</td>
<td>· Recommended by 2012 HRS Consensus Document</td>
<td>· Difficulty in achieving durable complete conduction block across the line</td>
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<td></td>
<td>· Connecting 2 anatomical obstacles empirically</td>
<td>· Gap-related sustained proarrhythmias</td>
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<td></td>
<td>· Time-saving without advance mapping procedure</td>
<td>· Empirical and anatomically defined lines do not address individual localization of the fibrotic substrate</td>
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<tr>
<td>CFAE ablation</td>
<td>· Recommended by 2012 HRS Consensus Document</td>
<td>· Mapping procedure is required</td>
</tr>
<tr>
<td></td>
<td>· Some evidence showing favorable outcomes</td>
<td>· Unclear specificity of different types of electrograms</td>
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<tr>
<td></td>
<td>· Eliminating parts of non-PV triggers</td>
<td>· Variable definitions of CFAE</td>
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<td></td>
<td>· Modification of GP activities</td>
<td>· Extensive targets, difficult to differentiate culprit from bystander CFAEs</td>
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<tr>
<td>Voltage map-guided ablation</td>
<td>· Homogenization of heterogeneously scarred atrial tissue</td>
<td>· Limited reports and lack of long-term outcome studies</td>
</tr>
<tr>
<td></td>
<td>· Block pathway for left atrial macroreentry tachycardia</td>
<td>· Difficulty in application in advanced fibrotic left atrium (strawberry left atrium)</td>
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<td></td>
<td></td>
<td>· Small channels or gaps cause proarrhythmias</td>
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<tr>
<td>Rotor ablation</td>
<td>· Identify fibrillatory activation maintaining AF source</td>
<td>· Mechanism and definition of rotor are unclear in clinical AF</td>
</tr>
<tr>
<td></td>
<td>· Some evidence showing favorable outcomes</td>
<td>· Limited reports with variable results</td>
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AF, atrial fibrillation; CFAE, complex fractionated atrial electrogram; GP, ganglionated plexi; HRS, Heart Rhythm Society; PV, pulmonary vein.
other continuous CFAE sites and ablation did not terminate AF during radiofrequency application at low similarity sites.

**Best Substrate Modification Strategy in Persistent AF: Taipei Approach to Rotor Ablation**

The Table summarizes the advantages and disadvantages of the different substrate ablation approaches. Although the conclusion from STAR AF II was a negative result after additional linear or CFAE substrate modification,29 many centers still believe that an adequate substrate ablation strategy is definitely required. How to select and perform this approach in persistent AF on top of PV isolation is still disputed. Based on the available evidence, we performed CFAE mapping and identified the location of continuous CFAEs after PV isolation.40 Then, regional analysis is suggested, using a high-density multi-electrode mapping catheter (ie, circular catheter or Penta-ray™ catheter), followed by real-time phase mapping using a nonlinear method at the continuous CFAE sites.48 Areas with a similarity index higher than 0.57 are selected for quantification of the rotor curvature and divergence forces. Rotor ablation is applied after identification of these sites. If AF still persists, right atrial CFAE mapping with rotor identification and ablation is then performed. If AF still persists after biatrial substrate modification, electrical cardioversion is required. How to select and perform this approach in persistent AF remains as a controversial topic.29,30 Activation mapping is recommended at any stage if AF transforms into organized tachycardia. Non-inducibility of sustained AF has not been tested in our laboratory in patients with persistent AF.

**Conclusions**

Accumulating data have demonstrated the importance of eliminating AF sources and should be the goal in ablation of persistent AF. Ensuring complete PV isolation is still the cornerstone in the initial step of AF ablation. Empirical linear ablation is not recommended because of the difficulty in achieving complete linear block. It is recommended only during macroectomy tachycardia that develops during the procedure. CFAE ablation is recommended in the HRS Consensus Document but efficacy is limited in recent long-term follow-up studies.39,49 Rotor ablation is controversial. A combined approach using CFAE, similarity and phase mapping with rotor identification may be helpful in searching for AF sources and subsequent substrate ablation. Whether or not those substrate modifications will be beneficial in the long term in persistent AF requires more prospective studies with randomization to validate efficacy and safety.

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**Conflict of Interest Disclosures**

None of the authors have conflicts of interest to declare.

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