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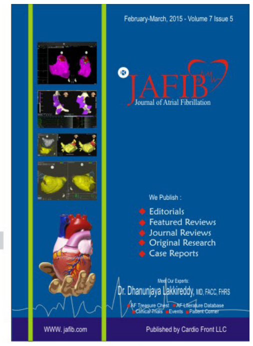

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Elimination Of Triggers Without An Additional Substrate Modification Is Not Sufficient In Patients With Persistent Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is a multifactorial disease with complex pathophysiology. Although restoring sinus rhythm delays the progression of atrial remodeling, non-pharmacologic intervention, such as radiofrequency catheter ablation (RFCA), should be done based on the background pathophysiology of the disease. While circumferential pulmonary vein isolation (CPVI) has been known to be the cornerstone of AF catheter ablation, a clinical recurrence rate after CPVI is high in patients with persistent AF (PeAF). Step-wise linear ablation, complex fractionate atrial electrogram (CFAE)-guided ablation, rotor ablation, ganglionate plexus ablation, and left atrial appendage isolation may improve the ablation success rate after CPVI. But, there are still substantial AF recurrences after such liberal atrial substrate ablation, and current ablation techniques regarding substrate modification still have limitations. Therefore, more understanding about AF pathophysiology and early precise intervention may improve clinical outcome of AF management. Keeping in mind "more touch, more scar," operators should generate most efficient substrate modification to achieve better long-term clinical outcome.

Introduction

Radiofrequency catheter ablation (RFCA) is an effective rhythm control strategy for patients with atrial fibrillation (AF), and it has become a standard procedure for anti-arrhythmic drugs (AAD)-resistant AF in current guidelines for AF management.[1] The main target of AF catheter ablation is the pulmonary vein (PV) antrum, and complete durable circumferential PV isolation (CPVI) is the cornerstone of this procedure.[2] However, radiofrequency catheter ablation remains challenging in patients with persistent AF (PeAF) and long-standing PeAF.[3]

As evidenced by a substantially high recurrence rate, CPVI alone is considered insufficient in catheter ablation for PeAF.[4] To overcome this limitation, various ablation strategies have been attempted, including additional linear ablation, complex fractionate atrial electrogram (CFAE) guided ablation, right atrial (RA) ablation, non-PV foci ablation, and rotor ablation. Despite the various ablation strategies for PeAF, the success rate of a single procedure has ranged between 20 and 60%.3 When 1.3~2.3 additional procedures are performed, long-term AF control rate becomes 72~79% with or without AAD.[5] Although RFCA for L-PeAF significantly reduces AF burden, this procedure still has limitations even when it is performed with current technology at world-class, highly experienced institutions. Here, the mechanism and limitations of RFCA for PeAF are reviewed based on the recent clinical studies.

Key Words:

Persistent Atrial Fibrillation, Catheter Ablation, Pulmonary Veins.

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Pathophysiology of Persistent AF

AF is a progressive disease and the mechanism for generation of AF is not yet fully understood.[6,7] Coumel[8,9] suggested that trigger factors or trigger foci initiate AF, and an arrhythmic substrate leads to its persistence. It is known that 70~90% of AF triggers exist around PVs in patients with paroxysmal AF, but non-PV foci are more common in those with PeAF.[10-12] Generally, PV isolation at the level of PV antrum is the mainstay of catheter ablation for AF,[13-15] but PV isolation may not be enough for PeAF with multiple non-PV triggers (Figure A). Verma et al[16] considered complex fractionated atrial electrogram (CFAE)- guided ablation to be well-suited for non-PV substrate and trigger ablation, and Lemery et al[17] found CFAE map to co-localize with cardiac autonomic ganglionate plexi detected by nerve stimulation. Another factor to consider in the mechanism of PeAF is AF progression and structural remodeling. AF is a progressive disease associated with increased atrial size,[18] histological change,[19] higher number of co-morbid factors,[20] and more frequent overall cardiovascular events.[21] Significant structural remodeling has atria susceptible to a continuous wavebreak and the maintenance of fibrillation by increasing critical mass.[22] Antifibrillatory effects of critical mass reduction have been proved with RF energy delivery,[21,23] cut and sew operation,[24] pharmacologic effect,[30] and pacing effects[25] in ex-vivo and in vivo animal model as well as human heart models.[26,27] Therefore, the reduction of atrial critical mass can be one potential anti-arrhythmic mechanism of linear AF catheter ablation for PeAF patients with significant atrial remodeling.

Role of Circumferential PV Isolation (CPVI) in PeAF

In 1993, Schwartz initially described a catheter-based technique for linear ablation of PeAF [AHA abstract, Circulation.1993;90:335]. In 1998, Haissaguerre et al.13 reported the importance of PV triggers elimination in patients with paroxysmal AF. Afterward, catheter ablation of AF, a much less invasive procedure compared to the maze operation, was accepted as an effective rhythm control strategy. The efficacy of CPVI has been well established and considered to be the cornerstone of RFCA for AF.[28] In patients with PeAF, however, it is associated with a high recurrence rate due to extensive atrial substrate remodeling and atrial dilatation.[10, 25] However, it still remains the most important step of ablation for PeAF for the following reasons:

1) AF triggers frequently arise from PVs;[29]

2) cardiac autonomic nerves reach the heart mainly along the PV antral area;[10, 30, 31] and

3) CPVI itself reduces about 15~17% of left atrial critical mass. In other words, CPVI is effective in elimination of PV triggers,[32, 33] cardiac autonomic denervation,[34] and substrate modification in both paroxysmal AF and PeAF.

Stepwise Approach for PeAF Ablation: Linear Ablation

A stepwise approach of adding linear ablations to CPVI has been known to be effective for AF substrate modification and improving the clinical outcome.[35,36,37] This stepwise AF ablation was first introduced by Haissaguerre et al.[35] and is an important strategy to terminate PeAF or macro-reentrant atypical atrial tachycardias. The benefit of linear ablation in addition to CPVI has been reported in multiple clinical studies,[5, 36, 38-40] and a recent meta- analysis (OR 0.22; 95% CI 0.1-0.49; $p<0.001$).[41] As AF ablation was performed, AF frequency spectra were organized as increments of linear ablation lesions and were finally terminated. The organization of AF into atrial tachycardia might be a sign suggesting a stepwise reduction of atrial critical mass during RFCA. However, there are several limitations in linear ablation in addition to CPVI:

1) the achievement of complete bidirectional block of linear ablation is sometimes very difficult;

2) incomplete block or reconnection of linear ablation is a major reason for recurrence and aggravates macro-reentrant tachycardia;

3) confirming bidirectional block of linear ablation by differential pacing maneuver[42-44] is not always accurate, especially in patients with significant substrate remodeling and conduction delay; and

4) excessive ablation to achieve bidirectional block may increase the risk of collateral damage. The anatomical location for linear ablation is also variable depending on the operators. While there is a general consensus for high bidirectional block rate, efficacy, and safety of roof line,[40,42] left lateral mitral isthmus line showed variable bidirectional block rate between 32% and 92%.[40,45-47] It also frequently requires coronary sinus ablation,[44, 45] and long-term maintenance of bidirectional block is doubtful. We previously reported that the anterior linear ablation connecting mitral valve annulus in 12 o'clock direction to the roof line was more effective in achieving bidirectonal block and lowering clinical recurrence rate after PeAF ablation than left lateral mitral isthmus ablation (Figure B).[47] However, linear ablations are still limited in producing a long-lasting transmural bidirectional block. In our institution, the bidirectional block rates for roof line and anterior line were 90% and 68%, respectively. During the redo-ablation procedure for recurred patients, previously blocked roof line and anterior line were maintained in only 67% and 37%, respectively (unpublished data).

Complex Fractionated Atrial Electrogram (CFAE) Guided Ablation

CFAE was initially introduced by Konings et al. as an electrogram showing high frequency and irregularity that were recorded by high density mapping of AF at right atrium.[48]

Afterward, Nademanee et al. reported that CFAE area recorded by a bipolar catheter represented an electrophysiologic substrate of AF and an ideal target for ablation to eliminate AF.[49] Clinically, CFAE is known to play a role in maintaining AF,[50, 51] co-localize with the autonomic ganglionate plexi,[17] and act as a target for AF catheter ablation.[49, 51] However, CFAE-guided ablation has its limitations: it

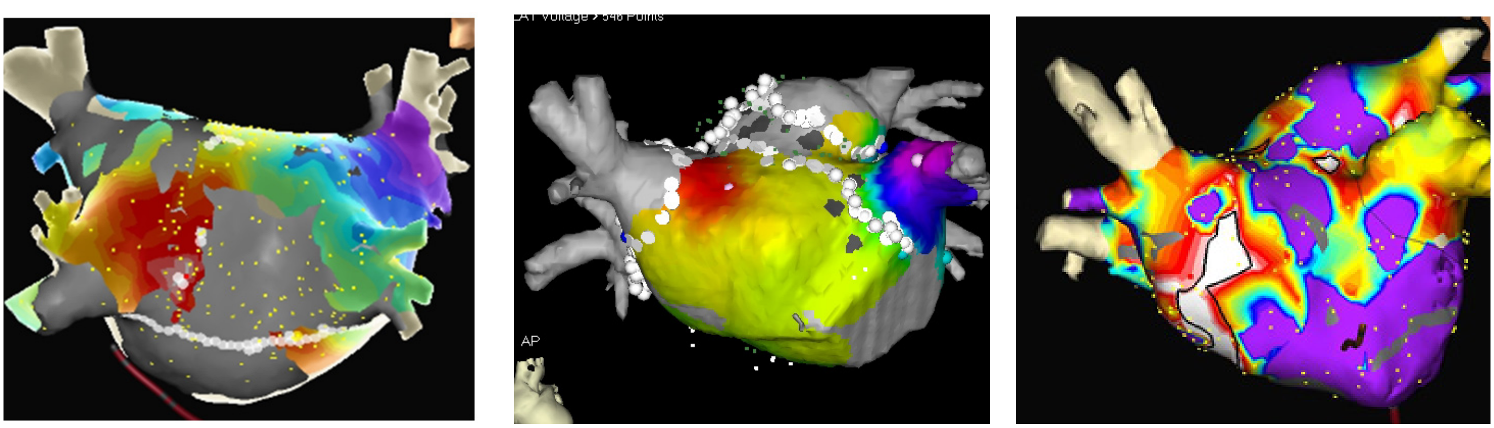

Figure 1: A. Mapping and ablation of post-procedural frequent atrial premature beats originated from non-PV focus utilizing 3D activation map. Quick activation mapping by multipolar catheter revealed non-PV foci located on LA posterior wall (white dots) and conduction gap at posterior inferior linear ablation site. B. The example of anterior linear ablation. Anterior line connects from 12 o' clock direction of mitral valve annulus to roof line and blocks peri-mitral reentry, septal to posterior wall reentry, and reentry around left atrial appendage. C. CFAE map guided catheter ablation. Automated 3D-CFAE map localizes low CFAE cycle length area, generally deposited on left atrial septum and base of left atrial appendage

is somewhat subjective and is based on uncertain pathophysiology. Although Nademanee defined CFAE as fractionated electrograms with a very short cycle length (<120ms), composed of two deflections or more, and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10 second recording period,[49] CFAE can be affected by catheter configuration and direction. The mechanism of CFAE is still controversial as CFAE can be generated by anatomical factors (such as complex anisotrophy),[35,49,52,53] histologic factors (focal myocardial fibrotic scar),[54] or functional reentries.[55-58] We previously reported that CFAE is primarily located in the area of low voltage and conduction velocity, surrounded by high voltage areas,[59] and that CFAE cycle length is longer in patients with remodeled atrium (Figure C).[60] All these factors can result in an abrupt change of AF cycle length, wave-wave interaction, and wave-break, forming pivotal points of multiple reentries.[50, 61] However, CFAE includes both the active driver of AF and passive wave breakers, and extensive CFAE-guided AF ablation has the risk of unnecessary cardiac tissue damage. Verma et al[16] considered CFAE ablation after CPVI to be favorable for non-PV substrate and trigger ablation, and reported low recurrence rate of AF in patients with PeAF. However, Oral et al.[62] reported that an additional ablation of CFAE after CPVI did not improve clinical outcome of RFCA. It may be because the definition of CFAE is variable depending on investigators, subjects, and the setting of softwares used for analysis.[61, 63-68] In a recent meta-analysis, CFAE ablation in addition to CPVI did not show significant reduction of clinical recurrence rate compared to that with CPVI alone (OR 0.64 95% CI 0.35~1.18, p=0.15).[41]

Ablations for Left Atrial Appendage, Right Atrial Ablation, Ganglionate Plexi, or Rotor

Di Biase et al. reported that left atrial (LA) appendage is an arrhythmogenic structure and that electrical isolation of LA appendage reduces AF recurrence after catheter ablation.[69] CFAE area is commonly accumulated at the base of LA appendage and is related to the location of ligament of Marshall and gaglionate plexus. However, the risk of stroke should be considered after LA appendage isolation, because intra-cardiac thrombus is commonly formed in LA appendage.

During the stepwise approach in PeAF ablation, it is often necessary to ablate RA in addition to LA, because previous biatrial mapping has demonstrated multiple biatrial sources of tachycardia in human AF.[70, 71] A divergent prolongation of AF cycle length after LA ablation may suggest that the main driver of AF maintenance exists in RA.[72] In fact, Kim et al. reported over 50% chance of AF termination by additional RA CFAE ablation when LA ablation alone was not successful in patients with longstanding PeAF.[73] A random study on routine RA CFAE ablation did not show incremental efficacy compared with LA ablation,[74] but RA inter-caval linear ablation and superior vena cava (SVC) isolation improved clinical outcome of PeAF and longstanding PeAF ablation.[75] Recently, we reported that linear ablation from SVC to RA septum produced autonomic denervation effects on post-procedural heart rate variability and better clinical outcome in patients with paroxysmal AF.[76] Therefore, RA ablation may have autonomic modulation effects. As ganglionate plexi play a key role in the maintenance and initiation of AF,[77-80] its ablation in addition to CPVI improved clinical outcome of AF catheter ablation.[81, 82] However, mapping and ablation of the exact location of the galglionate plexi by endocardial approach remains difficult.[32, 83-85]

Narayan et al.[86] recorded AF activation with 64-pole basket catheters in both atria, and demonstrated the presence of electrical rotors and repetitive focal beats during AF. Although their definition of rotor is not the same to that of classical basic electrophysiology (unexcited but eminently excitable spiral wave core)[87, 88] and clinical data so far are limited, focal impulse and rotor modulation (FIRM) is promising as it terminated AF and improved clinical outcome.[86,89]

Surgical Maze Procedures

The recent European Society of Cardiology guidelines on AF managements[90] recommend surgical ablation for the following patients;

1) symptomatic AF patients undergoing cardiac surgery (IIA-A);

2) asymptomatic AF patients undergoing cardiac surgery in whom the ablation can be performed with minimal risk (IIB-C); and

3) patients with stand-alone AF who have failed catheter ablation and in whom minimally invasive surgical ablation is feasible (IIB-C).

Surgical maze procedure has some benefits compared with catheter ablation, such as the excision of left atrial appendage, ganglionated plexi ablation, and relatively feasible epicardial approach. Recently, a number of institutions reported that a minimally invasive maze procedure using thoracoscopic surgical ablation combined with ganglionated plexi ablation was able to provide AF free survival in over 80% of patients during the follow- up duration of 12 months.[32,84,91,92] Boersma et al. reported superior clinical outcome of surgical ablation than catheter ablation,[93] but a procedure related adverse events rate was significantly higher in surgical ablation (34.4%) than catheter ablation (15.9%). Therefore, highly selected patients with less amendable factors related to AF may be good candidates of maze procedure.[94]

Balanced Substrate Modification with Limited Tissue Damage

Although CPVI alone is not enough and there have been reports about more extensivesubstrate ablation resulting in better clinical outcome in patients with PeAF, more touches may generate more scar[95] and increase the risk of complication. Gibson et al. reported that pulmonary hypertension after catheter ablation is detected in 1.4% of patients without pulmonary vein (PV) stenosis,[96] in association with severe LA scarring, small LA dimension (≤45mm), high LA pressure, diabetes and obstructive sleep apnea.[96] The DECAAF (Delayed Enhancement - MRI determinant of successful Catheter Ablation of Atrial Fibrillation) study showed poor clinical outcome after AF ablation in patients with extensive atrial scar.[97]

Recently, we reported that long duration of RF ablation is an independent predictor of AF recurrence in patients with PeAF,[98] and that high LA pressure is associated with advanced LA remodeling related to low LA compliance and more frequent clinical recurrence of AF after catheter ablation.[99] Therefore, balanced substrate modification with limited tissue damage is mandatory to achieve better long-term clinical outcome, minimizing procedure related complication rate.

Future Directions for Persistent AF Ablation

In the last decade, there was an enormous progress in AF ablation skill, technique, mapping system, and catheter design. Although there is no argument that appropriate AF catheter ablation reduces AF burden significantly, a recurrence rate of AF is still substantial, especially in patients with PeAF. Therefore, it is now essential to also consider patient factors before procedure, including clinical characteristics, biomarkers or genetic factors.[100,101] As medical technology continues to progress, virtual ablation utilizing patient-specific computer simulation modeling may enable operators to choose the best ablation design for each patient.[102,103] Better understanding about AF pathophysiology and early precise intervention may improve clinical outcome of AF management.

Conclusion

Elimination of triggers without an additional substrate modification is not sufficient in patients with PeAF. However, current ablation techniques regarding substrate modification still have limitations, and recurrence and atrial tissue damage are inevitable. Keeping in mind "more touch, more scar," operators should generate most efficient substrate modification to achieve better long-term clinical outcome.

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