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Review Article

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Catheter Ablation of Long-standing Persistent Atrial Fibrillation: a Reckless Challenge or a Way to Real Cure?

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ABSTRACT

Long-standing persistent atrial fibrillation (L-PeAF) is a category in which rhythm control is attempted while atrial fibrillation (AF) is maintained for more than 1 year. Because AF is a progressive disease and L-PeAF accompanies significant electrical and structural remodeling of atria, it is difficult to restore and maintain sinus rhythm in patients with L-PeAF. Nonetheless, the rhythm outcome is being increasingly improved by the development of sophisticated mapping devices, highly efficient catheters, and evidence-based ablation strategies, and the rational choice of patient selection criteria. This review discusses the evolution of the rhythm control outcome of L-PeAF and its future direction of development.

Keywords: Persistent atrial fibrillation; Catheter ablation; Pulmonary veins

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 (AADs)-resistant AF in current guidelines for AF management.[1] Recently, it was reported that AF catheter ablation reduced mortality in patients with heart failure by about 40%,[2] and incidence of ischemic stroke[3] and dementia[4] compared to medical therapy. Nevertheless, AF is a progressive disease and continues to have a constant rate of recurrence after ablation. The main target of AF catheter ablation is the pulmonary veins (PVs), and durable circumferential pulmonary vein isolation (CPVI) is the cornerstone of this procedure.[5] However, AF catheter ablation remains challenging in patients with persistent atrial fibrillation (PeAF) and long-standing persistent atrial fibrillation (L-PeAF).[6] As evidenced by a substantially high recurrence rate, CPVI alone has been considered insufficient in catheter ablation for PeAF.[7] 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%.[6] Moreover, Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR-AF) II trial documented no incremental benefit of additional extra-PV-left atrial (LA) ablation compared to CPVI alone in patients with PeAF.[8] In contrast, long-term AF control rate becomes 72–79% with or without AAD by performing 1.3–2.3 additional procedures for recurred AF patients.[9] 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.

PATHOPHYSIOLOGY OF PERSISTENT ATRIAL FIBRILLATION

AF is a progressive disease and the mechanism for generation of AF is not yet fully understood.[10][11] Coumel[12][13] 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.[14-16] Generally, PV isolation at the level of PV antrum is the mainstay of catheter ablation for AF,[17-19] but PV isolation may not be enough for PeAF with multiple non-PV triggers. Verma et al.[20] considered CFAE-guided ablation to be well-suited for non-PV substrate and trigger ablation, and Lemery et al.[21] 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,[22] histological change,[23] higher number of co-morbid factors,[24] and more frequent overall cardiovascular events.[25] Significant structural remodeling makes atria susceptible to a continuous wave break and the maintenance of fibrillation by increasing critical mass.[26] Anti-fibrillatory effects of critical mass reduction have been proved with radiofrequency (RF) energy delivery,[25][27] cut and sew operation,[28] pharmacologic effect,[26] and pacing effects[29] in ex-vivo and in vivo animal model as well as human heart models.[30][31] 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.

WHAT DID WE LEARN IN THE PAST 10 YEARS?

Over the past 10 years, we have learned that AF is a chronic progressive disease and not curable by catheter ablation. Although the development of efficient ablation catheters and sophisticated mapping systems has improved the outcome of AF ablation, the long-term recurrence rate is still close to 50%. Nonetheless, we were able to evaluate the results of our procedure because we performed consistent and steady rhythm monitoring based on the 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society expert consensus statement guidelines[32] in Yonsei AF ablation cohort (ClinicalTrials.gov Identifier: NCT02138695). Among the prognostic factors associated with the patient's characteristics, a young female,[33] high pericardial fat volume,[34] being overweight,[35] longer PR interval,[36] and high LA pressure[37] were factors associated with a higher clinical recurrence rate after AF ablation. In particular, the outcome of catheter ablation in patients with L-PeAF was affected by the pre-ablation external cardioversion energy[38] or specific genetic factors, such as the *ZFHX3* genetic trait.[39] Regarding the intra-procedural factors, appropriate parasympathetic modulation by AF ablation measured by the heart rate variability (HRV)[40] and the absence of post-ablation extra-PV triggers[41]

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were related to a good rhythm outcome after AF ablation. Among the patients with PeAF, recurrence was lower in those with a posterior wall isolation in the de novo ablation.[42] However, for the patients who improved from PeAF to paroxysmal AF after using antiarrhythmic drugs, additional linear ablation after the CPVI did not affect the outcome.[43] Among the patients with L-PeAF, additional CFAE ablation after the CPVI plus linear ablation did not improve the rhythm outcome.[44]

ROLE OF CIRCUMFERENTIAL PULMONARY VEIN ISOLATION IN PERSISTENT ATRIAL FIBRILLATION

In 1993, Schwartz initially described a catheter-based technique for linear ablation of PeAF (AHA abstract, *Circulation.*1993;90:335). In 1998, Haïssaguerre et al.[17] 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.[45] Verma et al.[8] proved equivalent efficacy of CPVI compared to additional linear ablation or CFAE-guided ablation in randomized clinical trial; STAR AF II. In spite of this clinical results, in patients with L-PeAF, it is associated with a high recurrence rate (60% in a year) due to extensive atrial substrate remodeling and atrial dilatation.[14][29] However, it still remains the most important step of ablation for PeAF for the following reasons: 1) AF triggers frequently arise from PVs[46]; 2) cardiac autonomic nerves reach the heart mainly along the PV antral area[14][47][48]; and 3) CPVI itself reduces about 15–17% of LA critical mass. In other words, CPVI is effective in elimination of PV triggers,[49][50] cardiac autonomic denervation,[51] and substrate modification in both paroxysmal AF and PeAF.

STEPWISE APPROACH FOR PERSISTENT ATRIAL FIBRILLATION ABLATION: LINEAR ABLATION

A stepwise approach of adding linear ablations to CPVI has been known to be an effective AF substrate modification. [52-54] This stepwise AF ablation was first introduced by Haïssaguerre et al.[52] 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,[9][53][55-57] and a meta-analysis (odds ratio, 0.22; 95% confidence interval, 0.1–0.49; p<0.001).[58] As increments of linear ablation lesions, 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[59-61] is not always accurate; and 4) excessive ablation to achieve bidirectional block may increase the risk of collateral damage. 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.[42]

Korean Circulation Journal

COMPLEX FRACTIONATED ATRIAL ELECTROGRAM GUIDED ABLATION

CFAE was initially introduced by Konings et al.[62] as an electrogram showing high frequency and irregularity that were recorded by high density mapping of AF at right atrium. Afterward, Nademanee et al.[63] reported that CFAE area recorded by a bipolar catheter represented an electrophysiologic substrate of AF and an ideal target for ablation to eliminate AF. Clinically, CFAE is known to play a role in maintaining AF,[64)65] co-localize with the autonomic ganglionate plexi,[21] and act as a target for AF catheter ablation.[63)65] However, CFAE-guided ablation has its limitations: it is somewhat subjective and is based on uncertain pathophysiology. The mechanism of CFAE is still controversial as CFAE can be generated by anatomical factors (such as complex anisotrophy),[52)63)66)67] histologic factors (focal myocardial fibrotic scar),[68] or functional reentries.[69-72] We previously reported that CFAE is primarily located in the area of low voltage and conduction velocity, surrounded by high voltage areas,[73] and that CFAE cycle length is longer in patients with remodeled atrium.[74] 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. Oral et al.[75] reported that an additional ablation of CFAE after CPVI did not improve clinical outcome of RFCA. 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.[58]

ABLATIONS FOR LEFT ATRIAL APPENDAGE, RIGHT ATRIAL ABLATION, GANGLIONATE PLEXI, OR ROTOR

Di Biase et al.[76] reported that LA appendage was an arrhythmogenic structure and that electrical isolation of LA appendage reduced AF recurrence after catheter ablation. LA appendage has highly bumpy surface vulnerable to wave break[77] and is co-localized with ligament of Marshall and ganglionate 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.[78)79] In fact, Kim[80] reported over 50% chance of AF termination by additional RA CFAE ablation when LA ablation alone was not successful in patients with L-PeAF. Although random study on routine RA CFAE ablation did not show incremental efficacy compared with LA ablation,[81] RA inter-caval linear ablation and superior vena cava (SVC) isolation improved clinical outcome of PeAF and L-PeAF ablation.[82] Kang et al.[40] reported that linear ablation from SVC to RA septum produced autonomic denervation effects on post-procedural HRV and better clinical outcome in patients with paroxysmal AF, but not in those with PeAF.

Narayan et al.[83] 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 was not the same to that of classical basic electrophysiology (unexcited but eminently excitable spiral wave core),[84)85] focal impulse and rotor modulation was reported to improved clinical outcome.[83)86] However, clinical data from other groups are controversial so far.[87]

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SURGICAL ATRIAL FIBRILLATION ABLATION

The recent European Society of Cardiology guidelines on AF managements[88] 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 LA appendage, ganglionated plexi ablation, and relatively feasible epicardial approach. Recently, a number of institutions reported that a minimally invasive AF surgery 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.[49][89-91] Boersma et al.[92] reported superior clinical outcome of surgical ablation than catheter ablation, 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 AF surgery.[93] However, recent randomized controlled trial failed to show superior efficacy of minimally invasive thoracoscopic PV isolation with LA appendage ligation compared to catheter ablation in spite of significantly higher complication rate.[94]

BALANCED SUBSTRATE MODIFICATION WITH LIMITED TISSUE DAMAGE

Although CPVI alone may not be enough in patients with PeAF, more extra-PV LA ablations may generate more scar[95] and increase the risk of complication. Gibson et al.[96] reported that pulmonary hypertension after catheter ablation was detected in 1.4% of patients without PV stenosis, in association with severe LA scarring, small LA dimension (≤45 mm), high LA pressure, diabetes and obstructive sleep apnea. The Delayed Enhancement-magnetic resonance imaging determinant of successful Catheter Ablation of Atrial Fibrillation (DECAAF) study showed poor clinical outcome after AF ablation in patients with extensive atrial scar.[97] Shim et al.[98] reported that long duration of RF ablation was an independent predictor of AF recurrence in patients with PeAF. Park et al.[37] demonstrated that high LA pressure was associated with advanced LA remodeling related to low LA compliance and more frequent clinical recurrence of AF after catheter ablation. 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 LONG-STANDING PERSISTENT ATRIAL FIBRILLATION 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 L-PeAF. Therefore, more focused mapping and ablation of non-PV triggers might be the solution for better rhythm outcome of PeAF ablation rather than an empirical extra-PV LA ablations. It is now essential to also consider patient factors before procedure, including clinical characteristics, biomarkers or genetic factors.[99][100] As medical technology

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continues to progress, computer simulation guided ablation utilizing patient-specific virtual AF modeling may enable operators to choose the best ablation design for each patient.[101)102)] RF energy titration depending on patient characteristics and atrial wall thickness is another important issue to overcome. 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 may not be sufficient in patients with PeAF. However, current ablation techniques regarding substrate modification still have many 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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