Strategy and Outcome of Catheter Ablation for Persistent Atrial Fibrillation

— Impact of Progress in the Mapping and Ablation Technologies —

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Pulmonary vein (PV) antrum isolation (PVAI) is effective in treating paroxysmal atrial fibrillation (AF) but is less so for persistent AF. A recent randomized study on the ablation strategies for persistent AF demonstrated that 2 common atrial substrate modifications, creation of linear lesions in the left atrium and ablation of complex fractionated electrogram sites, in addition to PVAI did not improve the outcome compared with stand-alone PVAI, suggesting the necessity of a more individualized, selective approach to persistent AF. There are emerging technologies, including high-resolution mapping with the use of multi-electrode catheter and auto mapping system and contact force (CF) guide ablation; the former allows rapid and accurate confirmation of the completeness of PVAI, and the latter enhances the achievement of durable ablation lesions more securely. Ablation for fibrotic area(s) has been proposed as a new approach for substrate modification, and high-resolution mapping is useful to define the area with low-voltage electrograms, a surrogate marker for atrial fibrosis. Ablation for non-PV triggers in addition to PVAI improves the outcome of persistent AF. Further, durable isolation of the left atrial posterior wall may reduce AF recurrence. These ablation strategies with concomitant use of the emerging technologies are strongly expected to enhance the effectiveness of catheter ablation for persistent AF.

Key Words: Catheter ablation; Catheter mapping technology; Contact force sensing; Persistent atrial fibrillation

Since the landmark study of Haïssaguerre et al demonstrating that the triggers initiating atrial fibrillation (AF) originate from the pulmonary veins (PVs), catheter ablation targeting PV has become an established strategy for paroxysmal AF.¹ The recognition that AF trigger sites were located within the PV antrum in the majority of cases led to extended, circumferential PV antrum isolation (PVAI) as an ablation procedure for AF. The recurrence of atrial tachyarrhythmias was reported to be significantly less in patients with large isolation areas around both ipsilateral PVs than in those with segmental PV isolation.² A recent study showed that, in patients with paroxysmal AF undergoing extended PVAI, the rate of late recurrence was lower than that previously reported with segmental or less extensive antral isolation.³ Today, PVAI is the cornerstone of catheter-based therapies for paroxysmal AF. However, the success rates of catheter ablation in cases of persistent AF are significantly lower than those for paroxysmal AF. Progressive atrial remodeling in persistent AF has been regarded as a reason for the low efficacy of the treatment in persistent AF. Therefore, additional ablation strategies for modifying and eliminating the AF-sustaining atrial substrate have been developed and challenged.

Recently, there has been technological progress in both 3D mapping systems and ablation catheters, which enable us to create precise high-resolution mapping and a durable

ablation lesion. These novel technologies will promisingly bring new strategies of ablation and enhanced effectiveness and safety. Here, we review the previous reports on catheter ablation for persistent AF, and then introduce possible strategies for persistent AF ablation under concomitant use of the new technologies.

Previous Reports on Ablation Strategies for Persistent AF

Prior common procedures for persistent AF ablation include creation of linear lesions in the left atrium (LA) and focal ablation targeting complex fractionated electrograms (CFAEs). The stepwise ablation approach consisting of PV isolation and CFAE and linear ablation aimed at AF termination was introduced by Haïssaguerre et al in 2005.^{4,5} Subsequent large registries, however, reported single-procedure success rates of only 35% and 48%, respectively, at 12 months.^{6,7} A single-center randomized trial, CHASE-AF (Randomized Catheter Ablation of Persistent Atrial Fibrillation Study), investigated the stepwise approach aimed at AF termination vs. PV isolation alone in persistent AF⁸ and found no difference in arrhythmia recurrence but a higher incidence of atrial tachycardia with the stepwise approach. Recently, the Alster-Lost-AF trial (Ablation at St. Georg Hospital for Long-Standing Persistent Atrial Fibrillation) failed to demonstrate an additional

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Figure 1. Kaplan-Meier estimates of freedom from atrial fibrillation after a single procedure. There were no significant differences between pulmonary vein isolation (PVI), PVI plus electrograms and PVI plus lines ($P=0.15$). (Adapted with permission from Verma A, et al.¹⁰)

benefit of the stepwise approach aimed at AF termination over PV isolation alone for patients with persistent and long-standing persistent AF.⁹ Those results suggested that substrate modification aimed at AF termination cannot reduce AF recurrence.

A multicenter randomized trial, STAR AF II (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II), of 589 patients with persistent AF compared initial stand-alone PVAI to PVAI with additional ablation of CFAEs or linear ablation and found that additional ablation did not reduce the recurrence of AF.¹⁰ At 18 months, AF recurrence occurred in 41% of patients with PVAI alone, 51% of patients with PVAI plus CFAE ablation and 54% of patients with PVAI plus linear ablation (Figure 1).¹⁰ Although AF recurrence rates were not significantly different among the 3 groups, it was rather higher in patients undergoing additional ablation. Extensive ablation strategies applied to healthy myocardium may have caused new areas of arrhythmogenesis. Thus arrhythmogenic substrates for persistent AF should be characterized in individual patients and a more selective ablation strategy is necessary in addition to PV isolation. It should be pointed out, however, that PVAI alone achieved successful outcomes in more than a half of the patients. That study¹⁰ had a great effect on recent ablation strategy for persistent AF. Despite its relatively low efficacy, stand-alone PV isolation is becoming the primary ablative strategy for persistent AF. New ablation strategies other than CFAEs and linear ablation are required to further improve the outcome after ablation for persistent AF.

Efficacy of PVAI for AF

PVAI is established as an effective strategy for paroxysmal AF. Miyazaki et al reported that approximately 70% of

patients with paroxysmal AF were in sinus rhythm without any antiarrhythmic drugs with a mean follow-up of 2.5 years after single PVAI procedure.¹¹ PV reconnection was reported to be a major cause of AF recurrence after PVAI.¹² It was shown, however, that 90% of paroxysmal AF patients without AF recurrence after PV isolation had PV reconnection and therefore sustained PV isolation might not be required for freedom from clinical recurrence,¹³ suggesting that reconnection of PV not having AF triggers does not cause AF recurrence. In other words, the triggers of paroxysmal AF are limited to local area(s) and ablation of this specific area could suppress the occurrence of AF. It was reported that, in patients with paroxysmal AF originating from the superior vena cava (SVC) only, SVC isolation not accompanying PV isolation could maintain sinus rhythm in approximately 70% of the patients for 5 years.¹⁴ Accurate identification of the site(s) of AF-initiating trigger, however, is often difficult, so empiric isolation of all 4 PVs and the antrum is an appropriate strategy for AF ablation. Thus, durable isolation of all 4 PVs and the antrum should be aimed for to minimize AF recurrence.

On the other hand, the efficacy of PVAI for persistent AF has been limited, and associated with less favorable outcomes.^{15,16} PV reconnection was reported to be a cause of AF recurrence even in patients with persistent AF.¹⁷ Elayi et al reported that only 40% of patients with persistent AF maintained sinus rhythm, with a mean follow-up of 16 months, after a single procedure but 83% of patients did so after a second procedure.¹⁸ In persistent AF, the sites of AF initiation and maintenance may be diffuse in the 4 PVs and their antrum, and conduction recurrence even in 1 PV may result in AF recurrence. In other words, permanent electrical isolation of all 4 PVs and antrum is required for ablation of persistent AF.

Figure 2. Left atrial and pulmonary vein (PV) voltage map with a CARTO3 CONFIDENSE™ module and multi-electrode catheter, PENTARAY®, after circumferential ablation of the PV antrum. The color gradient indicates the serial changes in the electrogram amplitude from purple >0.5 mV to red <0.1 mV. **(A)** Although the PV potential was not recorded after radiofrequency application for the PV antrum and carina, residual potentials were recorded in the left PV antrum (white arrow). **(B)** Residual potential in the PV antrum has disappeared after additional ablation. PV, pulmonary vein.

Contact Force and Mapping Technologies for Complete and Durable PV Isolation

An irrigated radiofrequency ablation catheter with a contact force (CF) sensor is now widely available for clinical use. Insufficient CF results in an ineffective lesion and conduction recurrence, whereas ablation with sufficient CF can create a sufficient and therefore durable lesion, although excessively high CF (≥ 40 g) may be associated with adverse effects such as thrombus formation and steam pop.¹⁹ CF during PV isolation was reported to correlate with clinical outcome.²⁰ Kimura et al demonstrated the effectiveness of CF monitoring during PV isolation in paroxysmal AF.²¹ A TOCCATA study reported that AF recurrence was universally noted when average CF was <10 g and maintenance of sinus rhythm was best achieved when average CF was >20 g.²⁰ We showed that PV isolation done with CF of 10–20 g significantly reduced AF recurrence in paroxysmal AF compared with the procedure without CF monitoring.²² A TOCCASTAR study compared the outcomes of CF- vs. non-CF-guided catheter ablation in a prospective, randomized study, and demonstrated that when optimal CF ($\geq 90\%$ ablations with CF ≥ 10 g) was obtained, CF-guided ablation was associated with improved effectiveness compared with non-CF-guided ablation.²³ Recently, Hussein et al showed that, in patients with persistent AF, CF-guided ablation significantly reduced the AF recurrence during 1-year follow-up compared with non-CF-guided ablation (27.6% vs. 46.4%).²⁴ All these studies suggest that low CF values, especially <10 g, are associated with PV reconnection and AF recurrence, whereas CF values >10 g are effective.

The force-time integral (FTI) is an index to assess the lesion formation. EFFICAS I study proposed a target CF of 20 g and minimum FTI of 400 g for each new lesion.²⁵ Chikata et al. reported that the optimal FTI value for achieving an effective lesion is dependent on the underlying atrial wall thickness.²⁶ They proposed FTI/wall thickness defined as FTI divided by wall thickness of the PV atrial segment and FTI/wall thickness 100 g/mm as a suitable

target for effective ablation. Das et al reported that FTI of 230 g was associated with no reconnection of the posterior/inferior segments at repeat electrophysiology study.²⁷ Although FTI was proposed as a marker to assess lesion formation and widely used for AF ablation, universal consensus has not been reached on the value required to create a durable lesion.

CF is one of the surrogate markers of ablative energy delivery, and radiofrequency power, impedance, temperature, and other factors remain in place. A novel marker of ablation lesion formation that incorporates power in addition to CF and time in a weighted formula was found to accurately estimate ablation lesion depth.²⁷ This formula, termed as the ablation index, was reported to reduce the incidence of acute PV reconnection and atrial tachyarrhythmia recurrence rates compared with CF-guided ablation.²⁸ Further studies are needed to confirm its efficacy.

Endpoint of PVI

Complete PVAI should be the endpoint of AF ablation. A lasso catheter placed in the PV is widely used for confirmation of PVAI: the disappearance of PV potentials is considered as an electrical disconnection between the PV and LA. However, this does not necessarily indicate isolation of the entire PV antrum. The PV carina and antrum are reported to be an important source of AF triggers. Takigawa et al reported that pacing from the PV carina captured the LA in 21% of patients, even after a successful encircling ipsilateral PV isolation, and non-isolated PV carina was a significant predictor of AF recurrence.²⁹

3D mapping systems are widely utilized to support the procedure of PV isolation, and can confirm the completeness of PVAI by creating a voltage map after PVAI. Recently, a novel mapping system and module, which annotates the points automatically and accurately, became available. By using multi-electrode catheters, a high-density voltage map can be created quickly and easily. Using a small basket array of 64 electrodes (IntellaMap Orion™, Boston Scientific, Cambridge, MA, USA) concomitantly,

Figure 3. (A–D) Regional ablation of low-voltage area. (Adapted with permission from Yamaguchi T, et al.³⁹)

Figure 4. (A–D) Box isolation of fibrotic area (BIFA). PV, pulmonary vein. (Adapted with permission from Kottkamp H, et al.³⁶)

a novel mapping system RHYTHMIA HDx™ (Boston Scientific) was reported to be able to confirm the completeness of PVAI with a high level of confidence.³⁰ Also, the high-density map created by a CARTO3 CONFIDENSE™ module (Biosense Webster, Diamond Bar, CA, USA) and a multi-electrode catheter PENTARAY® (Biosense Webster)

can be used to confirm complete PVAI. An example is shown in **Figure 2**. Even though potentials within the PV disappeared after circumferential PVAI, residual potentials were found in the left PV antrum (**Figure 2A**). By applying ablation to the gap site on the PVAI line, the residual potentials disappeared and complete PVAI was achieved

Figure 5. Diagram of the prevalence and distribution of sustained non-pulmonary vein (PV) triggers in patients with paroxysmal (PAF), persistent (PERS), and long-standing persistent (LS PERS) atrial fibrillation (AF) undergoing first-time ablation. (Adapted with permission from Santangeli P, et al.⁴⁴)

(Figure 2B). Routine confirmation of the completeness of PVAI is expected to improve the outcome of AF ablation. Further studies are needed to confirm the usefulness of these novel mapping systems.

Possible Strategies for Persistent AF Ablation

Ablation of Fibrotic Area

Atrial structural remodeling involving atrial fibrosis and scarring is a well-recognized factor in AF pathogenesis. LA scarring defined by a complete absence of electrical activity by a circular mapping catheter was reported to be an independent predictor of AF recurrence after PV isolation.³¹ LA fibrosis and scarring can be detected by delayed enhancement MRI (DE-MRI). Regions of enhancement on DE-MRI are well correlated with low-voltage regions on electroanatomical maps.³² Mahnkopf et al reported that the amount of atrial fibrosis detected by DE-MRI had a positive correlation with the rate of AF recurrence after PVAI and almost all patients with massive LA fibrosis (>35% of LA wall enhancement) had AF recurrence after PVAI.³³ Rolf et al reported that additional ablation for low-voltage areas defined as <0.5 mV recorded during sinus rhythm reduced AF recurrence after PV isolation.³⁴ Several studies reported similar findings, although the methods for detecting and ablating low-voltage areas differed.³⁵⁻⁴⁰

Anter et al compared the mapping resolution in scar-related atrial arrhythmias between 3.5-mm electrode tip catheters (THERMOCOOL®) and 1-mm multi-electrode-mapping catheters (PENTARAY®), and demonstrated that mapping with the latter electrode catheter reduced the

total area of bipolar voltage <0.5 mV compared with the former and was therefore more reliable.⁴¹ Catheters with smaller electrodes and closer interelectrode spacing may be suitable to determine the area of low voltage more accurately. Yamaguchi et al demonstrated the usefulness of regional ablation of low-voltage areas (Figure 3),³⁹ while Kottkamp et al proposed circumferential isolation of low-voltage areas, so-called box isolation of fibrotic areas (BIFA) (Figure 4).³⁶ BIFA would be suitable for patients with massive fibrosis in the LA, although its effect in such cases is reported to be limited.⁴⁰ Catheter ablation targeting a fibrotic area characterized by low voltage is considered as modification or elimination of the substrate for persistence of AF and may be a possible, effective strategy for treating persistent AF. Randomized studies are required to confirm the efficacy of this new approach.

Ablation of Non-PV Triggers

Patients with non-PV triggers have a worse outcome after AF ablation than those without non-PV triggers.⁴² Catheter ablation of these non-PV triggers added to PV isolation was shown to improve the outcome in paroxysmal AF.⁴³ Localization of non-PV AF triggers, however, is still challenging, particularly when multifocal non-PV triggers are targeted. Santangeli et al reported that non-PV triggers were elicited in 11% of AF patients and these triggers were typically clustered in discrete anatomic regions such as the inferior mitral annulus, posterior LA, interatrial septum, particularly at the fossa ovalis/limbus region, crista terminalis, Eustachian ridge, coronary sinus (CS), and the SVC (Figure 5).⁴⁴ Empiric ablation at these common non-PV

trigger sites, however, was shown to have no efficacy in persistent AF.⁴⁵ Empiric SVC isolation in addition to the PV isolation was shown to improve the outcome only in paroxysmal AF and not in persistent and long-standing persistent AF.^{46,47} On the other hand, limited ablation targeting PVs and documented non-PV triggers improved the maintenance of sinus rhythm in persistent and long-standing persistent AF.⁴⁸ These results suggest that localization and ablation of documented non-PV triggers is important to improve the outcome of ablation for persistent AF.

In patients without spontaneously firing non-PV triggers, some methods are used to provoke and localize them.⁴⁹ Isoproterenol is most commonly used, and a high-dose (i.e., infusion of 20–30 µg/min or bolus infusion of 10–20 µg) is often required to provoke non-PV triggers. Cardioversion of AF during low-dose isoproterenol infusion is sometimes useful. By assessing the P wave morphology and intra-atrial activation pattern using multipolar catheters placed in the right atrium, CS and SVC, non-PV triggers can be roughly localized in many cases. Further accurate localization can be accomplished by manipulating the multipolar mapping catheter or ablation catheter. The protocol for provoking and localizing the non-PV triggers, however, has not been standardized yet, and therefore ablation for non-PV triggers has not been performed as a routine procedure. A recent European survey reported that only a minority of operators routinely perform non-PV trigger provocation and ablation in the patients with persistent AF.⁵⁰ The optimum methods for provoking and mapping non-PV triggers remain to be established.

Posterior Wall Isolation

The LA posterior wall is targeted as a site of non-PV triggers or fibrotic areas,^{35,44} but the outcome of routine LA posterior wall ablation remains controversial. Some studies show efficacy of LA posterior wall isolation in addition to PV isolation,^{51,52} but others have not.⁵³ These previous studies did not use CF technology for ablation and therefore might have resulted in incomplete or non-durable isolation of the posterior wall. Bai et al showed that, in patients with persistent AF, LA posterior wall isolation, which was proven by repeat procedure, provided an additional improvement in outcome after PV isolation.⁵⁴ A recent study suggested the usefulness of routine adenosine challenge for dormant LA posterior wall conduction in improving the success rate of ablation of persistent AF.⁵⁵ Thus, durable isolation of the LA posterior wall could improve the outcome of ablation for persistent AF.

Ablation of Rotational Activity

Rotors have been thought to be responsible for perpetuation of AF,⁵⁶ and catheter ablation of rotors was proposed as a new ablation strategy for AF. Rotors can be identified through the proprietary focal impulse and rotor modulation (FIRM) computational mapping system. Early studies have reported that FIRM-guided ablation in addition to PV isolation results in high rates of acute AF termination and long-term freedom from recurrent atrial tachyarrhythmia.^{56,57} More recent studies, however, have failed to confirm these early findings.^{58,59} At the present time, FIRM-guided ablation has not been universally adopted. Multicenter, prospective, randomized studies are necessary to evaluate the efficacy and clinical utility of this strategy for ablating AF.

Conclusions

Durable lesion formation with optimal-level CF-guided ablation and usage of novel high-resolution mapping systems for confirmation of a complete ablation line are key to reducing AF recurrence after catheter ablation for not only paroxysmal but also persistent AF. Additional strategies to PV isolation, including ablation of low-voltage, fibrotic areas and of non-PV triggers, done using these novel technologies seem to beneficially effect the outcome of ablation procedure for persistent AF.

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