Review Article

Adjunct ablation strategies for persistent atrial fibrillation—beyond pulmonary vein isolation

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Abstract: Atrial fibrillation (AF) is the most common sustained arrhythmia. Recent guidelines recommend pulmonary vein isolation (PVI) as the main procedural endpoint to control recurrent AF in symptomatic patients resistant to antiarrhythmic drugs. The efficacy of such procedure is higher in paroxysmal AF while is still unsatisfactory in persistent and long-standing persistent AF. This review will summarize the state-of-the-art of AF ablation techniques in patients with persistent AF, discussing the evidence underlying different approaches with a particular focus on adjunctive ablation strategies beyond PVI including linear ablation, ablation of complex fractionated atrial electrograms (CFAE), ablation of ganglionated plexi, dominant frequency, rotors and other anatomical sites frequently involved in AF triggers.

Keywords: Persistent atrial fibrillation; radiofrequency ablation; rotors; complex fractionated atrial electrograms (CFAE); ganglionated plexuses (GPs)

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Introduction

Atrial fibrillation (AF) is the most common atrial arrhythmias and his prevalence is continuously rising in Western countries (1). AF is a strong independent risk factor for stroke and heart failure, and is associated with a three-fold increase in mortality rates compared to patients with sinus rhythm (2). Catheter ablation is an established treatment to achieve and maintain sinus rhythm in patients with recurrent AF (3). In these patients, antiarrhythmic drug therapy typically has a suboptimal efficacy in controlling relapses. Multiple randomized clinical trials have demonstrated a superiority of catheter ablation to reduce AF, improve symptoms, quality of life and possibly reverse the AF-associated risk of thromboembolic complications (3-5). In order to develop effective ablation techniques, multiple studies have been performed to discover and validate electrophysiological and anatomic targets fundamental for triggering and maintaining the arrhythmia (6).

Pre-clinical and human studies have consistently shown that focal discharges from the pulmonary veins (PVs) are implicated in the initiation of AF in the majority of patients (7). Therefore, empirical PV isolation has been performed with high procedural success, particularly in patients with paroxysmal AF (8).

The most recent update of the guidelines has recommended catheter ablation in symptomatic paroxysmal AF refractory or intolerant to at least one Class 1 or three antiarrhythmic medications, and has also introduced new recommendations for catheter ablation in patients with persistent AF, significant left atrial dilatation and left ventricular dysfunction (9,10).

Disturbingly, the results with catheter ablation in patients with persistent and long-standing persistent AF have been shown worse compared to patients with paroxysmal AF, with a recurrence rate following pulmonary vein isolation (PVI) of up to 60% (11). Based on these findings, it has been suggested that patients with non-paroxysmal AF may require ablation of additional sites beyond the PVs to achieve success (12-15).

This review article will overview the state-of-the-art of AF ablation techniques in patients with persistent AF, with a particular focus on adjunctive ablation strategies beyond PVI.

Isolation of the left atrial posterior wall

The left atrial posterior wall should be considered as an extension of the PVs from an embryologic, anatomic and electrophysiological perspective (16). The surgical experience with AF ablation has confirmed a significant role of the posterior wall for triggering and maintaining the arrhythmia (17), with reports documenting AF localized only to the posterior wall (18,19). Oral *et al.* compared ablation of the posterior wall with circumferential PVs ablation in patients with chronic AF. In this randomized trial, 80 patients with chronic AF were assigned to circumferential PV ablation or to non-encircling linear ablation of the posterior wall. After a mean follow-up of 9 months, AF recurred in 28% of patients who underwent circumferential PVs ablation, compared to 25% of those who received posterior wall linear ablation (P=0.8 for comparison) (20).

Complex fractionated atrial electrograms (CFAE)

Persistent AF may be perpetuated even without continues ectopic discharge from PVs. One of the mechanisms supporting this may be the continuous propagation of multiple wavelets inside the atria as result of multiple functional re-entry circuits as described by Moe *et al.* (21,22). The anisotropic conduction of multiple wavelets, due to areas of slow conduction, and their clash, after turning around anatomical or functional pivots (i.e., sites of functional block), leads to the formation of (CFAE) (23). It has been postulated that reentrant circuits underlying AF substrate cannot be mapped because random but these observations demonstrate that AF substrates can be identified searching areas that have CFAEs (13). CFAE have been first systematically described by Nademanee *et al.* as low-amplitude potentials (0.06 to 0.25 mV) with consistent temporal and spatial stability and either fractionated atrial electrograms (composed by two or more deflections) or atrial electrograms with cycle length ≤120 ms. Applying a substrate-based approach targeting only areas with CFAE in patients with all forms of AF, Nademanee *et al.* reported very high success rates (91% at 1-year follow-up) (13).

After this initial report, other investigators have evaluated the adjunctive role of CFAE ablation (24). Haïssaguerre *et al.* incorporated CFAE ablation to their stepwise sequential ablation approach for patients with long-standing persistent AF. The stepwise approach included PVI, linear ablation across the roof of the left atrium between the left and right upper PVs and at the mitral isthmus, ablation at the inferior left atrium toward the coronary sinus and the base of the left atrial appendage, and left atrial ablation guided by CFAE mapping (18,19). Using this extensive ablation strategy with the procedural end-point of AF termination, the authors uniformly observed a prolongation of the AF cycle length followed by either organization in atrial tachycardia (87% of cases) or conversion to sinus rhythm (13% of cases). Atrial tachycardias were subsequently mapped and ablated (19).

In a subsequent study, Elayi *et al.* failed to find the same predictive value for periprocedural AF termination. In this study, after a mean follow-up of 25±6.9 months, 69% of patients who underwent PVI and CFAE ablation remained in sinus rhythm, without significant differences between those who had procedural termination/organization of AF and those who were converted to sinus rhythm at the end of the procedure with external cardioversion. Of note, periprocedural AF termination predicted the mode of recurrence, with a strong association with recurrent atrial tachycardia (P=0.022) (12).

Hunter *et al.* suggested a classification based on CFAE morphology (24). The authors defined different "grades" of CFAE, namely: Grade1—uninterrupted fractionated activity, that is, fractionated activity (defined as continuous deflections without pause at the isoelectric line for 70 ms) occupying 70% of the sample, and at least 1 uninterrupted episode of fractionated activity lasting 1 second; Grade 2—interrupted fractionated activity, that is, fractionated activity occupying 70% of the sample; Grade 3—intermittent fractionated activity, that is, fractionated activity occupying 30-70% of the sample; and Grade 4—complex electrograms, that is, discrete electrograms (70 ms) with complex morphology (5 direction changes), with fractionated activity occupying 30% of the sample (24). In this study, the authors hypothesized that continuous fractionated activity (i.e., Grades 1 and 2) may represent focal mechanisms, whereas less fractionated signals (Grade 4) are more likely to represent reentry. Intermittent fractionated activity (Grade 3) may be produced by passive wave front phenomena or superimposition of far-field and local electrograms, which are not critical for maintenance of AF (24). On the other hand, the available evidence does not support a clinical utility for such classification, and studies evaluating more limited CFAE mapping/ablation have provided mixed results (24-26). However, available evidence does suggest some additional benefit with CFAE ablation in patients with non-paroxysmal AF. In a meta-analysis of six randomized controlled trials including 360 patients with persistent and long-standing persistent AF, adjuvant CFAE ablation (mostly based on visual evaluation) in adjunct to PVI increased the rate of sinus rhythm maintenance over follow-up [risk ratio (RR) 1.35, 95% confidence interval (CI): 1.04-1.75; P=0.022] (27). Such benefit in terms of arrhythmia-free survival was counterbalanced by an increased relative risk of recurrent organized atrial tachycardias (RR 1.77; 95% CI: 1.02-3.07; P=0.04), longer procedural times (245.4±75.7 *vs.* 189.5±62.3 min, P<0.001), fluoroscopy times (72.1±25.6 *vs.* 59.5±19.3 min, P<0.001), and RF energy application times (75.3±38.6 *vs.* 53.2±27.5 min, P<0.001) (28).

Moving from the scenario of paroxysmal AF to persistent and long-standing AF, the atrial substrates perpetuating the arrhythmia become more and more important as well as their mapping and elimination by catheter ablation. In the original report by Nademanee *et al.* (13) the success rate of CFAEs ablation by itself was about 91% in the setting of both paroxysmal and persistent AF. The same group reported a success rate of 85% at 2 years among 674 patients (29). Unfortunately these encouraging data were not reproduced in randomized studies. Oral *et al.*, even with some limitations as the short ablation time, didn't found a better efficacy in patients who underwent CFAEs ablation after PV isolation *vs.* PV isolation alone (30).

Realistically CFAEs ablation may improve the outcome of patients with persistent AF only in addition to systematic PV isolation.

Ganglionated plexuses (GPs)

The cardiac autonomic nervous system reflects the general organization of the autonomic nervous system with his sympathetic part is organized in adrenergic fibers from the central nervous system (CNS) terminating in big ganglia near the axial CNS and post-synaptic adrenergic fibers terminating to the target organ and his parasympathetic part organized in adrenergic fibers from the CNS terminating in small ganglia within the target organ and short post-synaptic cholinergic fiber targeting organ cells. The cardiac autonomic ganglia known as GPs are located within epicardial fat (31-33) particularly within the antrum of PVs, the crux of the heart and the junction between right atrium and superior vena cava with a wide network connecting the GPs themselves and between GPs and atrial myocardium (34).

The central role of the autonomic nervous system in triggering and maintaining AF with several mechanisms (facilitation of spontaneous premature atrial depolarization, shortening of atrial and PV effective refractory period, increasing heterogeneity of refractoriness) has been highlighted in multiple studies (35,36). On this base several authors evaluated the role of GPs ablation as an adjunct to PVs isolation (31,37,38).

Usually GPs are localized on the endocardial surface of the atria by searching sites showing vagal response to high frequency stimulation (31,38), then radiofrequency energy is delivered at each site showing a positive response to stimulation. In a randomized trial, 67 patients with paroxysmal AF were assigned to either PVI or GP ablation followed by PVI (31). After a mean follow-up of 10 months, 45.5% of patients assigned to PVI only remained free from AF recurrence, compared to 73.5% in the GP ablation plus PV isolation group (38). Pachon *et al.* have developed a system for real-time spectral mapping using the Fast Fourier Transform in sinus rhythm (39). This method is able to identify myocardial areas where unfiltered atrial bipolar electrograms contains high frequencies (i.e., AF nests) (39). Arruda *et al.* evaluated the adjunctive role of AF nest ablation in a prospective randomized study (40). A total of 157 patients underwent randomization; AF nest ablation was shown to reduce AF recurrence rate, although the absolute benefit was marginal (9% absolute risk reduction in paroxysmal AF and of 10% in persistent AF patients) (40). Of interest, the distribution of autonomic nervous targets for AF ablation seems correlated with the distribution of CFAE at the level of PV antra. Therefore, the autonomic ganglia can be targeted as bystanders during conventional PVI or CFAE ablation (41,42). To further support this concept, other studies have shown a close interaction between CFAE and GP (42,43).

Dominant frequency

Mapping studies of AF indicate repetitive periodic elements, with peculiar frequency gradients from area with high dominant frequencies (DF) to regions with low DFs. Atrial regions with high DF may serve as AF drivers and may be associated with AF maintenance, thus representing potential targets for ablation (44). Sanders *et al.* performed a real-time spectral and frequency mapping of the left atrium in AF patients. In this study, ablation at sites of high DF resulted in significant prolongation of the AF cycle length (180±30 to 198±40 ms; P<0.0001; kappa =0.77) and AF termination during ablation in 17 of 19 patients with paroxysmal AF (45). On the other hand, none of the patients with persistent AF was terminated after targeting sites with high DF. The lack of significant benefit of high DF ablation in patients with non-paroxysmal AF has been confirmed in other studies (46,47). For instance, Verma *et al.* reported no improvement in 1-year arrhythmia-free survival with DF ablation in adjunct to PVI compared to PVI alone (46).

Rotors

Recent studies have reported the presence of stable rapid reentrant circuits within the atria of patients with AF, so called "rotors", that might provide an additional target during AF ablation (48-50).

In the pivotal work by the University of California San Diego a 64 pole basket catheter was used for panoramic right and left atrial mapping during AF. AF electrograms were analyzed using a novel system to identify sustained rotors (spiral waves), or focal beats (centrifugal activation to surrounding atrium) (51). Electrical rotors are defined as sequential clockwise or counterclockwise activation contours around a central elbow of rotation that is responsible for AF maintenance (51). Rotors and focal impulses were considered AF sources only if consistent in multiple recordings over >10 minutes, equating to thousands of cycles (51). The Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation (CONFIRM) trial provide the first demonstration that AF may be maintained by localized sources in the form of electrical rotors and focal impulses that are stable in location and can therefore be targeted for limited ablation (51). A total of 92 patients were divided in two arms and treated with ablation of focal sources [focal impulse and rotor modulation (FIRM)-Guided] followed by PVI (n=36), or PVI alone (n=71; FIRM-Blinded). Localized rotors or focal impulses were detected in 97% of patients: in particular, 80% of rotors were in the left atrium and 20% in the right atrium (51). FIRM ablation was associated with an acute termination or slowing of AF in 86% of patients, rendering AF non-inducible prior to PV isolation. Importantly, FIRM-guided ablation was associated with improved outcome over follow-up using implanted continuous electrocardiogram (ECG) monitors, with an overall freedom from AF of 82.4% versus 44.9% in the PVI-only group (P<0.001 for comparison) (51). Enlarged atria may limit the reliability of this approach, especially if the atrial volume exceeds the size of available basket catheters, as illustrated by Miller (52). Further studies are warranted to determine whether such benefits are consistent across the whole spectrum of patients with AF (52,53).

Non-PV triggers sites

The importance of non-PV trigger sites in recurrent AF following PVI has been increasingly recognized, especially in patients with non-paroxysmal AF. The coronary sinus, the ligament of Marshall (54-56), and the left atrial appendage (56) have all been implicated in recurrent AF following PVI. The ligament of Marshall usually can be ablated from the endocardial aspect of the left atrium inferior to the ostium of the left inferior PV, otherwise ethanol infusion in the vein of Marshall through an angioplasty wire and balloon has been demonstrated effective achieving electrical isolation of the ligament of Marshall in a substantial proportion of patients (57,58). Di Biase *et al.* have demonstrated a crucial role for the left atrial appendage in triggering recurrent AF in one third of cases undergoing repeat procedures. When a trigger from the left atrial appendage has been demonstrated, complete electrical isolation of the left atrial appendage should be performed in order to achieve success (59).

Final remarks

PVI is the cornerstone of current catheter ablative therapies for AF, with the highest efficacy in patients with paroxysmal AF. In patients with persistent and long-standing persistent AF, PVI alone has been associated with lower success rates. Over the last years, intense research has been directed towards the validation of adjunctive ablation strategies beyond PVI. Studies have suggested a marginal but concrete incremental benefit of extensive linear ablation strategies and atrial debulking with CFAE ablation, at the expense of increased risk of organized atrial arrhythmias, such as atrial tachycardia or flutter. Recent studies have highlighted the importance of targeting AF focal sources, such as rotors or additional non-PV trigger sites (e.g., ligament of Marshall, left atrial appendage). Further large randomized studies are warranted to better evaluate the benefits (and risks) of such adjunctive ablation strategies.

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