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EDITORIAL

Catheter ablation of persistent atrial fibrillation: The importance of substrate modification

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Abstract

Accumulating data have shown that elimination of atrial fibrillation (AF) sources should be the goal in persistent AF ablation. Pulmonary vein isolation, linear lesions and complex fractionated atrial electrograms (CFAEs) ablation have shown limited efficacy in patients with persistent AF. A combined approach using voltage, CFAEs and dominant frequency (DF) mapping may be helpful for the identification of AF sources and subsequent focal substrate modification. The fibrillatory activity is maintained by intramural reentry centered on fibrotic patches. Voltage mapping may assist in the identification of fibrotic areas. Stable rotors display the higher DF and possibly drive AF. Furthermore, the single rotor is usually consistent with organized AF electrograms without fractionation. It is therefore quite possible that rotors are located at relatively "healthy islands" within the patchy fibrosis. This is supported by the fact that high DF sites have been negatively correlated to the amount of fibrosis. CFAEs are located in areas adjacent to high DF. In conclusion, patchy fibrotic areas displaying the maximum DF along with high organization index and the lower fractionation index are potential targets of ablation. Prospective studies are required to validate the efficacy of substrate modification in left atrial ablation outcomes.

Key words: Ablation; Atrial fibrillation; Persistent; Substrate; Dominant frequency

Core tip: A combined approach using voltage, complex fractionated atrial electrograms and dominant frequency mapping may be helpful for the identification of atrial fibrillation sources, and therefore for sufficient substrate modification in patients with persistent atrial fibrillation undergoing left atrial ablation.

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INTRODUCTION

Catheter ablation of atrial fibrillation (AF) is indicated in patients with symptomatic AF, refractory or intolerant to at least one class Ⅰ or Ⅲ antiarrhythmic medication[1-3]. Indications for catheter ablation of AF have expanded to include increasingly complex cases including patients with long-standing persistent AF and structural heart disease. Circumferential pulmonary vein antral isolation (PVAI) has become a standard therapy for paroxysmal AF[4]. On the contrary, PVAI displays a significantly lower success rate in patients with persistent or long-lasting persistent AF[1,2,5,6]. This difference suggests that the mechanisms underlying the maintenance of persistent AF are different in relation to paroxysmal AF. Recently, catheter ablation of stable rotors or focal sources in individuals with paroxysmal and persistent AF has given promising results[7-9]. Additional substrate modification is therefore required in the setting of persistent AF. However, the optimal ablation approach in these complex cases remains uncertain.

PATHOPHYSIOLOGY OF AF

AF represents the final common phenotype for multiple disease pathways and mechanisms that are incompletely understood. The multiple re-entrant wavelet hypothesis as a mechanism of AF was described by Moe and colleagues in 1959[10] with supportive experimental work by Alessie[11]. The "multiple re-entrant wavelet hypothesis" supports that fractionation of wavefronts propagating through the atria results in self-perpetuating "daughter wavelets". Multiple re-entrant wavelets are separated by lines of functional conduction block. The lines of the conduction block can occur around the anatomical structures within the atria with different inherent electrophysiological properties, such as scars, patchy fibrosis and myocardium, at different stages of recovery and excitability. However, this hypothesis can not easily explain why AF exhibits consistent spatial non-uniformities in rate and activation vector[12-14], how ablation may terminate AF relatively early in some cases before compartmentalization of meandering wavelets[1,6], or why extensive ablation often has little acute impact[1,15]. Alternatively, the "localised source hypothesis" is supported by elegant experiments in which localised spiral waves (rotors)[16,17] or focal sources[14] disorganise into AF. Stable microreentrant sources appears to be the most likely underlying mechanism of AF in experimental models[18,19]. Recent developments of patient-tailored and physiology-based computational mapping systems have identified localized electrical spiral waves, or rotors, and focal sources as mechanisms that may represent novel targets for therapy[7-9].

Studies have emphasised the importance of ion channel remodelling, changes in signalling pathways, oxidative stress, altered calcium handling, changes in atrial architecture, and altered connexin expression in the pathogenesis and maintenance of AF[20,21]. AF in turn causes AF-promoting abnormalities in each of these areas and enhances the vulnerability of the heart to AF induction and maintenance (AF begets AF)[21]. In particular, structural remodeling is characterized by atrial enlargement and tissue fibrosis. The presence of interstitial fibrosis leading to changes in cellular coupling results in spatial "non-uniform anisotropic" impulse propagation and is a potential cause of atrial activation abnormalities that may underlie the initiation and perpetuation of re-entrant arrhythmias including AF[22,23]. As AF progresses from paroxysmal to persistent, the atrial substrate becomes increasingly abnormal and displays a more prominent role in maintaining the arrhythmia[1,20,21]. In patients with persistent AF, a better understanding of arrhythmia mechanisms is therefore needed so that ablation approaches can be targeted to a clearly shown mechanism.

LEFT ATRIAL ABLATION

Pulmonary vein antral isolation

Despite the evolution of left atrial ablation strategies, PVAI remains the cornerstone of in both paroxysmal and persistent AF ablation procedures[1,2]. Isolation of wide circumferential areas around both ipsilateral pulmonary veins (PVs) with verification of conduction block is more effective than isolation of each individual PV using a segmental approach[4]. A lower success rate of PVAI as a stand-alone strategy has been reported in patients with persistent or long-lasting[1,2,5,6]. However, relatively new data on this topic have given contradictory results. The RASTA study have demonstrated that additional substrate modification beyond PVAI including ablation of non-PV triggers and ablation of complex fractionated electrogram sites does not improve single-procedure efficacy in patients with persistent AF[24]. The recently published STAR AF Ⅱ trial has clearly showed that additional substrate modification (fractionated atrial electrograms or linear lesions) following PVAI has no benefit in AF reduction[25]. A high incidence of PV reconnection is similarly observed in patients with and without recurrence of AF[26], suggesting that sustained PV isolation is not required for freedom from clinical recurrence of AF. This finding may be explained by the important substrate modification performed after the circumferential lines. In CONFIRM trial, AF sources were ablated coincidentally in 45% of cases after wide area circumferential ablation and left atrial roof line in persistent AF cases[8]. These data provide an alternative potential explanation for why PVAI treats AF in some patients and not others. Elimination of AF sources may explain why wide-area ablation is more

effective than ostial PV isolation, why AF may not recur in patients whose PVs have reconnected, why non-PV encircling lines or fractionated electrogram ablation may be effective and, potentially, why ablation success correlates with the extent of ablated tissue in persistent AF[8].

Linear lesions

Based on surgical MAZE procedures, linear lesions including roof and mitral isthmus lines have been also adapted in percutaneous left atrial ablation procedures providing additional substrate modification[27]. The additional benefit of linear lesions on top of ostial PV isolation has been prospectively demonstrated[28,29]. However, in these studies an ostial and not a wide circumferential PV isolation was performed. The intrapulmonary region has been also implicated as an important source of PV triggers[30]. In a randomized study, we investigated the efficacy of additional radiofrequency energy delivery in the interpulmonary isthmus following PVAI[31]. A continuous line in the interpulmonary isthmus connecting the anterior and the posterior part of the ipsilateral circumferential line creating a "theta" model (the Greek letter θ) was performed. Although patients with additional energy delivery in the interpulmonary isthmus displayed a better long-term outcome (free from arrhythmia recurrence), this was not statistically significant. Nevertheless, left atrial linear lesions remain technically challenging. Incomplete linear lesions may have a proarrhythmic effect[5,6]. Most atrial tachycardias result from gaps in the ablation lines.

DIRECT SUBSTRATE MODIFICATION STRATEGIES

Voltage mapping: Identification and modification of heterogeneous substrate and local barriers

As previously stated, interstitial fibrosis play a key-role in the pathophysiology of AF[22,23]. Delayed enhancement-cardiac magnetic resonance imaging (DE-CMRI) has demonstrated fibrosis and scarring in the left atrium of patients undergoing AF ablation[32,33]. Among patients with AF undergoing catheter ablation, atrial tissue fibrosis estimated by DE-CMRI has been independently associated with likelihood of recurrent arrhythmia[34,35]. Electroanatomic bipolar voltage mapping has been described to define the relationship between anatomic and electrophysiological abnormalities. Although, specific bipolar and unipolar voltage cut-off values have been reproducibly shown to accurately identify scar and/or fibrosis in the ventricles, data regarding voltage cut-off values in the atria are limited. In preliminary studies, the bipolar voltage cut-off value were set at < 0.05 mV for the identification of atrial scar, partly influenced by the background noise from early electroanatomic mapping systems, and < 0.5 mV for low-voltage regions[36,37]. In a recent study, the global mean left atrial bipolar and unipolar voltage amplitude in SR was 2.83 ± 2.25 and 4.12 ± 2.14 mV, respectively; 95% of all bipolar and unipolar electrograms recorded from the LA were > 0.50 and > 1.57 mV, respectively[38]. There was no difference in the segmental distribution of low-voltage areas between patients with AF and healthy controls. Jadidi *et al*[39] have demonstrated bipolar voltages of 0.63 ± 0.8 in dense DE-CMRI areas, compared with 0.86 ± 0.89 in non DE-MRI areas. These measurements were performed during AF. By using both electroanatomic mapping system and DE-MRI, Spragg *et al*[32] have demonstrated that the mean atrial voltage in areas identified as scar by DE-MRI was 0.39 ± 0.61 mV, while in areas identified as normal by DE-CMRI was 1.38 ± 1.23 mV. In a similar study, a bipolar voltage of < 0.38 ± 0.28 mV was associated with fully scarred atrial myocardium[40]. Kapa *et al*[41] using electroanatomic mapping along with DE-CMRI have shown that a bipolar voltage cut-off of 0.27 mV performed best for delineating scar (sensitivity: 90%, specificity: 83%).

Substrate mapping in patients with postinfarction cardiomyopathy and ventricular tachycardia may involve lowering the voltage cut-off that defines the scar in order to identify "channels" of relative higher voltage within the scar[42,43]. Conducting channels within the unexcitable scar areas (particularly those displaying late potentials) are considered as an appropriate ablation target[43]. In a similar way, scar homogenization may be also performed in left atrium. Rolf *et al*[44] have recently shown that catheter ablation at low voltage areas aiming to homogenize the diseased left atrium in addition to PVAI resulted in better long-term outcomes compared to PVAI alone. Catheter ablation of stable rotors in patients with paroxysmal and persistent AF has given promising results[7-9]. It is quite possible that these stable sources correlate with areas of atrial fibrosis where the site-specific micro-architecture of connective tissue fibres and the remaining myocardial fibres allows reentrant/rotor activation to occur and to sustain. The combination of localizing atrial fibrosis plus mapping of specific functional areas allowing re-entrant/rotor activation may hold promise for catheter based AF substrate modification in the future.

Mapping and ablation of complex fractionated atrial electrograms

Complex fractionated atrial electrograms (CFAEs) are seen in all forms of AF (paroxysmal and persistent). The underlying mechanisms of CFAEs remain controversial. Two leading hypothesis have been proposed for CFAEs formation. First, the "rotor hypothesis" where the rotor encounters heterogeneous substrate (*e.g.,* dispersion of refractoriness), and the CFAEs are the by-product of the reentrant rotor that breaks down at its boundary; the posterior left atrium is a histologically and

electrically complex region, in which firing from the PVs meets regions of functional block due to anisotropic conduction. The atrial signals in the area of this line of block are frequently fractionated[45]. As paroxysmal AF progresses to persistent AF, the progressive fibrotic and microarchitectural changes determine the propagation, collision, and fragmentation of the wave front as it emanates from focal triggers[46]. Second, the "autonomic hypothesis" where CFAEs indicate sites of ganglionated plexi[47,48]. Lin *et al*[48] showed in a canine model that CFAEs can be produced locally at the site where acetylcholine was topically applied. Moreover, CFAEs can be eliminated by ablating the GP at a distance, indicating that activating the "network" of the intrinsic cardiac autonomic nervous system may be a critical element in the formation of CFAEs.

The use of CFAEs has become an important tool in the clinical electrophysiology laboratory to guide catheter ablation of AF sources. However, their clinical significance is questionable. In Nademanee's original report, CFAEs were defined as (1) fractionated electrograms composed of >2 deflections and/or perturbation of the baseline with continuous deflection of a prolonged activation complex; and (2) atrial electrograms with very short cycle length (< 120 milliseconds)[49]. Nademanee *et al*[49] have demonstrated 92% freedom from AF one year after CFAEs ablation without PV isolation after two procedures. This level of success has not been reproduced by other groups. Ablation of CFAE as a stand-alone ablation strategy seems insufficient for the treatment of patients with persistent AF[50,51]. In addition, there are clear data that CFAEs ablation as an adjunct therapy to PVAI does not improve the success rate of left atrial ablation[52]. As previously reported, the recently published STAR AF II trial has clearly showed that additional substrate modification (fractionated atrial electrograms or linear lesions) following PVAI has no benefit in AF reduction[25].

Whether certain subtypes of CFAE, such as those exhibiting continuous fractionation or particular types of activation gradients, are more important than others is not known[53]. Using multipolar catheters and monophasic action potentials (MAPs) to define local activation and repolarization, Narayan *et al*[54] identified four types of CFAEs in human AF: (1) CFAEs with discrete rapid MAPs and pansystolic local activation (8%); (2) CFAEs with discrete MAPs after AF acceleration (8%); (3) CFAEs pattern with distinct MAPs and dissociated superimposed signals consistent with far-field electrograms (67%); and (4) CFAEs pattern without discrete MAPs (17%), consistent with spatial disorganization. CFAEs with discrete MAPs and pansystolic activation had shorter cycle length and lower voltage and trended to have higher dominant frequency than other CFAEs sites. The majority of CFAEs were the result of superimposed far-field atrial activations from overlying atrial structures. In contrast, only a small proportion of CFAEs exhibited rapid, discrete, organized MAP recording activity consistent with an AF driver. Jadidi *et al*[39] have elegantly shown that the distribution of fractionated electrograms is highly variable, depending on direction and rate of activation. Fractionation in sinus rhythm and pacing rhythms mostly resulted from wave collision. All sites with continuous fractionation in AF displayed normal voltage in sinus rhythm, suggesting absence of structural scar[39]. Thus, many fractionated electrograms are functional in nature, and their sites dynamic. The same group of investigators has demonstrated an inverse relationship between fractionated electrograms and atrial fibrosis in persistent atrial fibrillation[55]. Ninety percent of continuous CFAE sites occur at non-delayed-enhancement and patchy delayed-enhancement LA sites. Finally, there are many limitations arising from the definition of CFAEs. Lee *et al*[56] aimed to determine the prevalence and spatial correlation of CFAEs using two definitions: (1) multicomponent/continuous electrograms; and (2) AF cycle length < 120 ms. Multicomponent/continuous electrograms and sites of short CL activity (< 120 ms) identified different atrial regions.

Dominant frequency mapping

Dominant frequency (DF) mapping is aimed at identifying localized sites of high DF during AF[57]. Initial reports using optical mapping systems have identified the presence of localized regions of high-frequency activity demonstrating spatiotemporal periodicity which may act as drivers of AF[19]. Most importantly, the highest DF using spectral analysis of the biatrial electrogram correlates well with the rotor frequency observed during optical mapping[58], suggesting that this technique of signal decomposition and DF analysis may allow identification of reentrant circuits sustaining AF. Sites of high DF typically show rapid periodicity but lack significant fractionation[47]. In paroxysmal AF, the high DF sites are more prevalent within the PVs, whereas in persistent AF, the high DF sites commonly exist within the left atrium[57]. Retrospective analyses have shown that ablation at such high DF sites results in slowing and termination in a significant proportion of paroxysmal AF patients, indicating their role in AF maintenance[57,59,60]. The higher AF recurrence rate in patients with non-ablated high DF sites at the end of the procedure supports the important role of extrapulmonary sites in persistent AF maintenance[60].

Sites showing DFs that were at least 20% higher than their surrounding points were identified as primary and secondary high DF sites[57,59,60]. Two indices from fast Fourier transform (FFT) power spectrum analysis describe the degree of organization within AF: (1) the regularity index, defined as the ratio of the area under the dominant peak in the power spectrum to the total area[47]; and (2) the organization index, a ratio consisting of the sum of the areas under the dominant peak and its harmonics divided by the

total area[61].

High DF sites typically show rapid periodicity but lack significant fractionation[47]. Kumagai *et al*[62] have shown that high DF sites and continuous CFAEs sites overlap in only 14% of mapped areas after PVAI. Lee *et al*[56] have demonstrated a poor direct spatial correlation between sites of multicomponent/continuous electrograms and sites of high DF, with only 23.1% of multicomponent/continuous electrograms sites occurring at the same location as a site of high DF. Spatial analysis confirmed that the vast majority (84%) of the multicomponent/continuous electrograms sites occurred directly adjacent (< 2.5 mm) to a site of high DF[57]. If high DF identifies a focal source, then visual fractionation may represent wave front breakup at the periphery. Stiles *et al*[63] reported similar findings. Correlation between CFAEs and DF was poor. Exploration of their spatial relationship demonstrates CFAEs in areas adjacent to high DF (within 10 mm in 80% and 10-20 mm in 10%). Lin *et al*[64] demonstrated that the most consistent CFAEs activity is observed near maximum DF sites and that the core of the widely distributed continuous CFAEs is correlated with the sites of maximum DF. Maximal fractionated sites are observed in the center or the boundary region of maximum DF sites.

High DF sites have been negatively correlated to the amount of fibrosis, whereas fractionation index was positively correlated with fibrosis in the posterior left atrium[65]. Atrial fibrosis as defined by DE-CMRI have been associated with slower and more organized electrical activity but with lower voltage than healthy atrial areas[55]. As suggested by Koduri *et al*[65], the increased regularity of electrograms (indicated by increased organization index) in the presence of slower activation rates (indicated by lower DFs and higher fractionation index sites) in experimental heart failure models may indicate the presence of regions of underlying fibrosis.

Currently, there are several limitations of DF mapping as an ablation strategy. These factors include lack of high-resolution mapping to precisely locate DF sites, real-time analysis of DF, and spatiotemporal stability of DF sites[66].

HOW TO PERFORM SUBSTRATE MODIFICATION IN PERSISTENT AF ON TOP OF PVAI?

Summarizing the above data, it's clear that the additional substrate modification involving linear lesions and CFAEs sites in patients with persistent AF is debatable. Based on the recent findings by Narayan's group[7-9], elimination of AF sources (principally rotors) should be the goal in persistent AF ablation. How can we localize these AF sources with current diagnostic modalities? A combined approach using voltage, CFAEs and DF mapping may be helpful for this purpose. Voltage mapping may assist in the identification of fibrotic areas. Tanaka *et al*[67] have demonstrated that the largest fibrotic patches and the PV ostia are potential anchoring sites for "micro-anatomical" reentry. In their experiments, the fibrillatory activity is maintained by intramural reentry centered on fibrotic patches and that it appeared at the posterior left atrial wall as breakthroughs. The average area of fibrosis in the periphery is significantly larger than in the center. Differences in voltage amplitude may be important to identify relatively healthy areas within the patchy fibrotic tissue. For this purpose, upper and the lower voltage thresholds have to be decreased in decrements.

Stable rotors display the higher DF and possibly drive AF[18,19,57,58]. Furthermore, the single rotor is usually consistent with organized AF electrograms without fractionation[68]. It is therefore quite possible that rotors are located at relatively "healthy islands" within the patchy fibrosis. This is supported by the fact that high DF sites have been negatively correlated to the amount of fibrosis[65]. This assumption also explains why CFAEs are the by-product of the reentrant rotor that breaks down at its fibrotic boundaries[67]. As previously reported, correlation between CFAEs and high DF sites is poor. CFAEs are located in areas adjacent to high DF (within 10 mm)[62]. Regularity index showed that fractionation is low within the area with the maximum DF and high within a band of approximately 3 mm at boundaries with lower-frequency domains[47]. CFAEs mapping has to be therefore performed with great caution. Only CFAEs with a discrete MAP should be targeted for ablation[53]. Of note, these are low voltage and high DF sites[53]. In conclusion, areas with relatively higher voltage compared to the surrounding tissue displaying the maximum DF along with high organization index are potential targets of ablation. Prospective studies are required to validate the efficacy of substrate modification in left atrial ablation outcomes.

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