Electrophysiologically Guided Substrate Modification During Sinus Rhythm
Personalized Approach to Nonparoxysmal Atrial Fibrillation

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Atrial fibrillation, the most common sustained cardiac arrhythmia, has a complex and multifaceted pathophysiology.1 The presence of a predisposing substrate, frequently encompassing atrial hypertrophy, fibrosis, and significant alterations of the extracellular matrix, is contributing to intra-atrial electric conduction delay as well as shortening and dispersion of atrial refractory periods. Triggers such as short-coupled supraventricular extrasystoles can initiate the arrhythmia acting on this pathological milieu with the potential contribution of modulating factors, such as the autonomic nervous system, ischemia, and hormones.

The initial clinical experiences of transcatheter ablation of atrial fibrillation (AF) were reported 20 years ago almost simultaneously by different groups.2,3 Mimicking atrial debulking and compartmentalization provided by surgical techniques such as the classical Maze procedure, these transcatheter approaches aimed at substantial atrial substrate modification. A few years later, the recognition by Haïssaguerre et al4 that most of the ectopic foci initiating AF were located in the pulmonary veins, shifted the attention of the electrophysiological community from substrate to triggers of the arrhythmia. The observation that ablation with local radiofrequency energy of the ectopic foci achieved 62% freedom from AF, paved the way for circumferential pulmonary vein isolation widespread use, which soon became the cornerstone of paroxysmal AF interventional treatment showing higher efficacy when compared with antiarrhythmic drugs.5 However, in patients presenting with persistent AF, pulmonary vein isolation proved to be insufficient if used as stand-alone ablation strategy showing only modest long-term success rates.6,7 These findings suggested the existence of a more complex electrophysiological substrate in patients with persistent AF with structures and mechanisms involved in facilitation and maintenance of the arrhythmia residing outside the pulmonary veins.8 As a consequence, efforts were redirected toward AF substrate modification with several non–pulmonary veins targets used as guidance for transcatheter ablation. Linear ablation between fixed anatomic structures (eg, left atrial roof and mitral isthmus) provided additional benefit to circumferential pulmonary vein isolation in patients with persistent AF.9,10 Subsequently, mapping and ablation of complex-fractionated atrial electrograms defined as either continuous reentry of the fibrillation waves into the same area or overlap of different wavelets entering the same area at different times, was proposed by Nademanee et al11 as a new ablative approach aiming at AF substrate modification. Other groups studied the role of autonomic nervous system in AF pathophysiology investigating the curative effects of partial vagal denervation secondary to atrial ganglia transcatheter ablation.12,13

In clinical practice, different combinations of these ablative approaches have been tested for the treatment of persistent AF. One of the most commonly used is the so-called stepwise approach encompassing pulmonary vein isolation followed by ablation of complex-fractionated electrograms and linear lines aiming at AF cycle length slowing and, possibly, arrhythmia termination by conversion directly to sinus rhythm or to an atrial tachycardia, which is then mapped conventionally and ablated.14 Although the stepwise approach confers acceptable long-term freedom from arrhythmia recurrence, success rates with a single procedure remain limited with the necessity of multiple procedures in most of the cases.15 Inevitably, this approach is associated with longer procedural times, patients exposure to higher radiation doses and, potentially, to an increased risk of complications. In addition, extensive ablation scheme determining substrate modification, can often result in significant impairment of left atrial function and occurrence of postprocedural atrial tachycardias.16,17

In the attempt to contribute to the challenging quest for the optimal ablation strategy in patients with persistent AF, Yang et al18 in this issue of Circulation: Arrhythmia and Electrophysiology, describe a voltage-based approach for atrial substrate modification in patients with persistent or long-standing persistent AF undergoing transcatheter ablation. After pulmonary vein isolation plus cavotricuspid isthmus ablation, patients cardiovertable to sinus rhythm, underwent high-density bipolar mapping of the left atrium to identify low-voltage zones (defined as bipolar voltage range between 0.1 and 0.4 mV) and sites with abnormal electrograms suggestive of local conduction delay in what the authors call transitional zones (defined as bipolar voltage range between 0.4 and 1.3 mV). Abnormal electrograms were defined as multiphasic signals with ≥3 positive or negative distinct peaks with duration of ≥50
ms. The subsequent substrate modification strategy consisted in ablation of low-voltage zones to achieve electric silence (bipolar electrogram <0.1 mV) and elimination of abnormal electrograms identified in the transitional zone. In addition, short linear lesions were performed between isolation lines or anatomic barriers and low-voltage zones to eliminate channels for potential reentrant activity. This ablation strategy was compared with a classic stepwise approach in an age- and sex-matched historical control group undergoing nonparoxysmal AF transcatheter ablation in the same center 2 years earlier. In the study group, among patients successfully cardioverted to sinus rhythm, 70% showed low-voltage zones or abnormal electrograms mainly in the anterior and posterior left atrial walls and in the atrial roof. During a median follow-up of 30 months, freedom from arrhythmic recurrences was 66% in the study group compared with 37% in the control group. Of note, AF recurrence was similar in the 2 groups (30% versus 32%), whereas atrial tachycardia incidence was significantly lower in the study group (3.5% versus 30%). These results were achieved with shorter procedural and fluoroscopy times and with lower complications rates in the study group when compared with the control group. The authors performed also a small mechanistic study presented in the same article: in 15 patients with persistent AF, after pulmonary vein isolation, complex-fractionated atrial electrograms mapping as well as sinus rhythm voltage mapping were performed demonstrating a colocalization of low voltage/transitional zones and slow conduction and rotational activation during atrial fibrillation/tachycardia.

The use of sinus rhythm voltage mapping as a tool to guide AF substrate modification was first described by the Leipzig group.19 Partially echoing this approach, the strategy proposed by Yang et al.,18 targeting potentially proarrhythmic regions of atrial fibrosis based on electrophysiological findings, proved to be feasible and effective in a similar population with nonparoxysmal AF (ie, persistent or long-standing persistent AF) with relatively short duration of the arrhythmia (median AF duration 15 months). The rationale for this approach was already investigated and reported by the same group in a previous study showing a parallel progression between atrial fibrosis and electrophysiological abnormalities in patients with AF.20 Such substrate-based ablation approach resembles what has been done during the past 10 years for ventricular tachycardia in which mapping during sinus rhythm has been successfully used to identify abnormal myocardial substrate amenable to ablation. The authors should be congratulated for their contribution that adds a small piece to the puzzle of the complex mechanisms and pathophysiology of persistent AF. However, a few limitations should be considered in interpreting the results of this study, namely the non–randomized design with all the inherent limitations and bias, the single-center setup with a significant time frame considered potentially favoring the innovative ablative strategy when compared with the historical stepwise approach. Also, it should be taken into account that patients successfully cardioverted to sinus rhythm after pulmonary vein isolation were probably a subset of subjects with less advanced left atrium structural and electric remodeling when compared with patients who needed a stepwise approach, potentially explaining the worst outcomes observed in the latter. To overcome these limitations, the same group of investigators has designed a multicenter randomized clinical trial (STABLE-SR, clinicaltrials.gov number NCT01761188), which hopefully will provide additional information about this topic.

This notwithstanding, several unanswered questions remain on persistent AF optimal ablation strategy. First, long-term durability of electrophysiological guided substrate modification has not been investigated to date. Second, the feasibility and usefulness of real-time integration between delayed-enhancement left atrium magnetic resonance imaging (effectively localizing and quantifying fibrosis) and high-density voltage mapping information will have to be tested in human. Third, it is still unclear whether pulmonary vein isolation per se is playing a role in atrial substrate modification and homogenization. In fact, large antral isolation areas may coincidentally eliminate fibrotic regions determining conduction block and intra-atrial reentry sustaining persistent AF. Fourth, besides the left atrium, other anatomic structures such as the coronary sinus, the left atrial appendage, and the right atrium (including superior vena cava) are involved in AF initiation and maintenance. Therefore, an electrophysiological guided substrate modification involving such structures should be implemented in the future. Finally, it will be interesting to test the impact of new available technologies, such as contact force-sensing and multipolar catheters on high-density mapping resolution and clinical outcome.

In conclusion, modification of nonparoxysmal AF substrate during sinus rhythm as proposed by Yang et al.18 is a new approach allowing personalization of the ablation scheme according to individual characteristics and providing good results with a low risk of iatrogenic atrial tachyarrhythmias. If these promising results will be replicated in the setting of properly designed prospective multicenter randomized clinical trials, a significant step forward in AF treatment will be made.

**Disclosures**

None.

**References**


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Supplemental Figure 1. Another example case of electrophysiologically substrate modification. Only local patches of LVZ were found and None of SR-AEs could be identified in TZ. So only LVZ homogenization was performed. Abbreviations are the same as in Figure 1.