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Running Title: **Electrophysiologically Guided Substrate Modification During Sinus Rhythm in Non-Paroxysmal 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 electrical conduction delay as well as shortening and dispersion of atrial refractory periods. Triggers like 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 were reported twenty 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 Haissaguerre and colleagues that most of the ectopic foci initiating atrial fibrillation were located in the pulmonary veins[4], 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 atrial fibrillation, paved the way for circumferential pulmonary vein isolation widespread use which soon became the cornerstone of paroxysmal atrial fibrillation interventional treatment showing higher efficacy as compared with antiarrhythmic drugs[5]. However, in patients presenting with persistent atrial fibrillation, 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 atrial fibrillation

with structures and mechanisms involved in facilitation and maintenance of the arrhythmia residing outside the pulmonary veins[8]. As a consequence, efforts were redirected towards atrial fibrillation substrate modification with several non-pulmonary veins targets used as guidance for transcatheter ablation. Linear ablation between fixed anatomical structures (e.g. left atrial roof and/or mitral isthmus) provided additional benefit to circumferential pulmonary vein isolation in patients with persistent atrial fibrillation[9,10]. Subsequently, mapping and ablation of complex fractionated atrial electrograms defined as either continuous re-entry of the fibrillation waves into the same area or overlap of different wavelets entering the same area at different times, was proposed by Nademanee and colleagues as a new ablative approach aiming at atrial fibrillation substrate modification[11]. Other groups studied the role of autonomic nervous system in atrial fibrillation 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 atrial fibrillation. 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 atrial fibrillation cycle length slowing and, possibly, arrhythmia termination by conversion either 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 post-procedural atrial tachycardias[16,17].

In the attempt to contribute to the challenging quest for the optimal ablation strategy in patients with persistent atrial fibrillation, Yang and colleagues 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 atrial fibrillation undergoing transcatheter ablation[18]. Following 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 to 1.3 mV). Abnormal electrograms were defined as multiphasic signals with ≥3 positive or negative distinct peaks with duration ≥50 ms. The subsequent substrate modification strategy consisted in ablation of low voltage zones to achieve "electrical 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 anatomical barriers and low voltage zones to eliminate channels for potential re-entrant activity. This ablation strategy was compared with a classic stepwise approach in an age- and sex-matched historical control group undergoing non paroxysmal atrial fibrillation transcatheter ablation in the same center two years earlier. In the study group, amongst 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. Over 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, atrial fibrillation

recurrence was similar in the two groups (30% vs. 32%) whereas atrial tachycardia incidence was significantly lower in the study group (3.5% vs. 30%). These results were achieved with shorter procedural and fluoroscopy times and with lower complications rates in the study group as compared with the control group. The authors performed also a small mechanistic study presented in the same manuscript: in 15 patients with persistent atrial fibrillation, following pulmonary vein isolation, complex fractionated atrial electrograms mapping as well as sinus rhythm voltage mapping were performed demonstrating a co-localization of low voltage/transitional zones and slow conduction and/or rotational activation during atrial fibrillation/tachycardia.

The use of sinus rhythm voltage mapping as a tool to guide atrial fibrillation substrate modification was first described by the Leipzig group[19]. Partially echoing this approach, the strategy proposed by Yang and colleagues, targeting potentially proarrhythmic regions of atrial fibrosis based on electrophysiological findings, proved to be feasible and effective in a similar population with non-paroxysmal atrial fibrillation (i.e. persistent or long-standing persistent atrial fibrillation) with relatively short duration of the arrhythmia (median atrial fibrillation 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 atrial fibrillation[20]. Such "substrate based" ablation approach resembles what has been done during the last ten 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 which adds a small piece to the puzzle of the complex mechanisms and pathophysiology of persistent atrial fibrillation. 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 as 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 electrical remodeling as compared with patients who needed a stepwise approach, potentially explaining the worst outcomes observed in the latter. In order 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 regarding this topic.

This notwithstanding, several unanswered questions remains regarding persistent atrial fibrillation optimal ablation strategy. First, long-term durability of electrophysiologically guided substrate modification has not been investigated so far. 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 atrial fibrillation. Fourth, besides the left atrium, other anatomical structures like the coronary sinus, the left atrial appendage and the right atrium (including superior vena cava) are involved in atrial fibrillation initiation and maintenance. Therefore, an electrophysiologically 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 non-paroxysmal atrial fibrillation substrate during sinus rhythm as proposed by Yang and colleagues 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 atrial fibrillation treatment will be made.

References

[1] Nishida K, Nattel S. Atrial fibrillation compendium: historical context and detailed translational perspective on an important clinical problem. Circ Res. 2014 Apr 25;114(9):1447-52.

[2] Swartz J.F., Pellersels G., Silvers J., Pattern L., Cervantez D. A catheter based curative approach to atrial fibrillation in humans. Circulation 1994; 90(Suppl I):I – 335 (abstract).

[3] Haïssaguerre M, Gencel L, Fischer B, Le Métayer P, Poquet F, Marcus FI, Clémenty J. Successful catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 1994; 5: 1045-1052.

[4] Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998; 339: 659-666.

[5] Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G,Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA; ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: A randomized controlled trial. JAMA 2010; 303:333-340.

[6] Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F Jr, Strickberger SA, Morady F. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation 2002; 105: 1077-1081.

[7] Gaita F, Riccardi R, Caponi D, Shah D, Garberoglio L, Vivalda L, Dulio A, Chiecchio A, Manasse E, Gallotti R. Linear cryoablation of the left atrium versus pulmonary vein cryoisolation in patients with permanent atrial fibrillation and valvular heart disease: correlation of electroanatomic mapping and long-term clinical results. Circulation. 2005 Jan 18;111(2):136-42.

[8] Gaita F, Calò L, Riccardi R, Garberoglio L, Scaglione M, Licciardello G, Coda L, Di Donna P, Bocchiardo M, Caponi D, Antolini R, Orzan F, Trevi GP. Different pattern of atrial activation in idiopathic atrial fibrillation: simultaneous multisite atrial mapping in patients with paroxysmal and chronic atrial fibrillation. J Am Coll Cardiol 2001; 37: 354-541.

[9] Ernst S, Ouyang F, Löber F, Antz M, Kuck KH. Catheter-induced linear lesions in the left atrium in patients with atrial fibrillation. An electroanatomic study. J Am Coll Cardiol 2003; 42:1271-82.

[10] Gaita F, Caponi D, Scaglione M, Montefusco A, Corleto A, Di Monte F, Coin D, Di Donna P, Giustetto C. Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. Circ Arrhythm Electrophysiol. 2008;1:269-75

[11] Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol 2004; 43:2044-2053.

[12] Gaita F, Riccardi R, Calò L, Scaglione M, Garberoglio L, Antolini R, Kirchner M, Lamberti F, Richiardi E. Atrial mapping and radiofrequency catheter ablation in patients with idiopathic atrial fibrillation. Electrophysiological findings and ablation results. Circulation. 1998 Jun 2;97(21):2136-45.

[13] Scherlag BJ, Nakagawa H, Jackman WM, Yamanashi WS, Patterson E, Po S, Lazzara R. Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation. J Interv Card Electrophysiol. 2005 Aug;13 Suppl 1:37-42.

[14] Haïssaguerre M, Hocini M, Sanders P, Sacher F, Rotter M, Takahashi Y, Rostock T, Hsu LF, Bordachar P, Reuter S, Roudaut R, Clémenty J, Jaïs P. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. J Cardiovasc Electrophysiol 2005; 16:1138-47.

[15] Scherr D, Khairy P, Miyazaki S, Aurillac-Lavignolle V, Pascale P, Wilton SB, Ramoul K, Komatsu Y, Roten L, Jadidi A, Linton N, Pedersen M, Daly M, O'Neill M, Knecht S, Weerasooriya R, Rostock T, Manninger M, Cochet H, Shah AJ, Yeim S, Denis A, Derval N, Hocini M, Sacher F, Haissaguerre M, Jais P. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. Circ Arrhythm Electrophysiol 2015;8:18-24.

[16] Cochet H, Scherr D, Zellerhoff S, Sacher F, Derval N, Denis A, Knecht S, Komatsu Y, Montaudon M, Laurent F, Pieske BM, Hocini M, Haïssaguerre M, Jaïs P. Atrial structure and function 5 years after successful ablation for persistent atrial fibrillation: an MRI study. J Cardiovasc Electrophysiol 2014; 25:671-9.

[17] Rostock T, Salukhe TV, Hoffmann BA, Steven D, Berner I, Müllerleile K, Theis C, Bock K, Servatius H, Sultan A, Willems S. Prognostic role of subsequent atrial tachycardias occurring during ablation of persistent atrial fibrillation: a prospective randomized trial. Circ Arrhythm Electrophysiol 2013; 6:1059-65.

[18] Yang G, Yang B, Wei Y, Zhang F, Ju W, Chen H, Li M, Gu K, Lin Y, Wang , Cao K, Kojodjojo P, Chen M. Catheter ablation of non-paroxysmal atrial fibrillation using electrophysiologically guided substrate modification during sinus rhythm after pulmonary vein isolation. Circ Arrhythm Electrophysiol (in press).

[19] Rolf S, Kircher S, Arya A, Eitel C, Sommer P, Richter S, Gaspar T, Bollmann A, Altmann D, Piedra C, Hindricks G,Piorkowski C. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol 2014; 7:825-833.

[20] Lin Y, Yang B, Garcia FC, Ju W, Zhang F, Chen H, Yu J, Li M, Gu K, Cao K, Callans DJ, Marchlinski FE, Chen M. Comparison of left atrial electrophysiologic abnormalities during

sinus rhythm in patients with different type of atrial fibrillation. J Interv Card Electrophysiol 2014; 39:57-67.