Journal of the American College of Cardiology Vol. 60, No. 7, 2012

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.06.009

EDITORIAL COMMENT

A FIRM Grip on Atrial Fibrillation*

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Since the seminal paper by Haissaguerre et al. (1) describing the importance of pulmonary vein (PV) triggers in the initiation of paroxysmal atrial fibrillation (AF), PV isolation has become the cornerstone of catheter ablation for AF, demonstrating acceptable results (2,3). By contrast, reported long-term success rates after catheter ablation for persistent or long-standing persistent AF are suboptimal at best, not uncommonly requiring repeat ablation attempts to establish sinus rhythm (4). The ablative strategy in nonparoxysmal AF typically involves targeting areas of complex fractioned electrograms and/or a stepwise approach that entails deployment of linear lesion sets within the left atrium (LA) (5,6). In these patients, triggers from the PVs are less dominant, and the arrhythmogenic substrate shifts to a larger portion of the LA. Since the underlying pathophysiologic mechanism of persistent AF remains ill defined, extensive substrate-based ablation may result in excessive destruction of LA tissue.

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Two experimental theories dominate our current thinking of how AF perpetuates. Moe et al. (7) described the multiple wavelet hypothesis stating that AF is initiated and sustained by reentrant self-perpetuating activation wavelets propagating in a random fashion through heterogeneous atrial tissue. In this anarchical model of AF, arrhythmia is sustained as long as adequate numbers of wavelets propagate simultaneously. Support for this hypothesis later came from studies by Allessie et al. (8) using a canine atrial model. Sustained AF could be induced by high rate atrial pacing and would persist after termination of pacing as long as acetylcholine infusion was continued. Electrogram analysis demonstrated simultaneous randomly circulating atrial reentrant waves. Recently, it was reported that in patients with long-standing persistent AF, dissociation between the LA endocardial and epicardial layers was present, with sites of breakthrough within the epicardial layer facilitating multiple wavelet reentry (9). One can infer from these observations that in an anarchical model of AF, propagation may be restricted but AF will not terminate during catheter ablation due to lack of a localized source.

The second theory describes the importance of localized drivers, reentrant or focal in nature, in the initiation of AF, generating a rhythm with extremely short cycle length that cannot conduct to remote myocardium in a 1:1 fashion, resulting in fibrillatory conduction (10). This type of AF follows a hierarchical mechanism. Targeting the local source, for example, a PV trigger, with drugs or catheter ablation will terminate AF (11). However, owing to the complex temporal interplay between AF driver and atrial substrate, electrical and structural remodeling may allow AF to persist even after the driver is removed.

In 2006, Kalifa et al. (12) provided new insight into the mechanistic basis of fractionated electrograms recorded during AF. In a healthy sheep model, AF was induced by pacing and maintained by acetylcholine infusion. Optical and electrical mapping during AF demonstrated the presence of stable rotors arising from the posterior LA wall. From the outer perimeter of these rotors, waves of varying direction and propagation velocity would emanate, resulting in electrogram fractionation. Support for the presence of rotors came from an earlier study by Waldo's group (13). Despite these reports, the concept of rotors in human AF remains uncertain.

In this context, the prospective comparative study by Narayan et al. (14) published in this issue of *JACC* sheds new light on the role of localized sources or rotors in the initiation and maintenance of AF. The authors report on the outcome of catheter ablation of AF targeting focal impulses and performing rotor modulation (FIRM) within the right and left atrium. Group 1 (81% of patients with persistent AF) underwent FIRM ablation followed by PV isolation, whereas group 2 (66% of patients with persistent AF) was treated by PV isolation alone. The study demonstrates that acute AF termination and AF slowing ≥10% was achieved in 56% and 31% of patients in group 1, respectively, but merely in 9% and 11% of patients in group 2, respectively. Importantly, during a median follow-up of 273 days, the single procedure success rate, defined as freedom from AF (<1% burden of AF utilizing implanted electrocardiography monitors or AF <30 s detected on intermittent monitors) was significantly higher in the FIRM ablation group (82.4% vs. 44.9%), whereas the time utilized to perform FIRM ablation had no significant impact on total ablation time.

This study provides several important messages that need to be fully appreciated. First, Narayan et al. (14) could demonstrate for the first time using a systematic approach the presence of localized sources, either rotors (70%) or focal impulses (30%), in nearly all patients. That was achieved by use of propriety computational software post-processing electrogram recordings from a 64-pole basket catheter placed within the left and right atrium. Second, the inves-

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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JACC Vol. 60, No. 7, 2012
August 14, 2012:637–8

tigators were able to terminate AF in 56% of patients using only 4.3 ± 6.3 min ablation time. Of note, this was before PV isolation was performed. Third, after a single procedure, 70.6% of patients were free of any atrial tachyarrhythmia. Importantly, in 86% of patients in the FIRM-guided group, very strict post-procedure surveillance was performed utilizing implanted loop recorders.

If confirmed, FIRM ablation has enormous potential to provide a novel treatment strategy for patients with persistent AF. For the first time, ablation could target the underlying pathophysiologic mechanism and not merely the AF trigger.

Certain limitations apply to the study by Narayan et al. (14). First, the computer software used to compute the AF maps for each patient is propriety software, and details on how these maps are rendered have yet to be published and reproduced by others. Second, FIRM mapping is performed using a commercially available basket catheter that provides limited recording capability along the LA septum, while the spline electrodes may not always be homogeneously distributed across the surface of the LA. Third, the CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) study enrolled a mixed patient cohort with paroxysmal and persistent AF. It is feasible to assume that outcome would be less favorable if only patients with persistent AF had been enrolled. The role of localized sources in patients with longstanding persistent AF is currently unknown, as FIRM ablation has yet to be tested in this patient population. It is anticipated that a significantly enlarged LA may prevent accurate mapping because of the relatively small size of the currently available basket catheter. Finally, while the authors should be praised for providing the electrophysiology community with a potentially groundbreaking new method for AF ablation, it remains the effort of a single working group, and as such, is a proof of concept that urgently needs to be reproduced and published by others.

In conclusion, the authors need to be congratulated on bringing to the electrophysiology community a truly novel approach to AF ablation. FIRM ablation bears enormous potential if other investigators can reproduce similar results. Electrophysiologists may at last be able to move from a "blind" substrate-based approach to a mechanistic ablation strategy targeting localized sources within the atria that perpetuate AF.

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REFERENCES

1. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–66.
2. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Heart Rhythm 2012;9:632–96.e621.
3. Ouyang F, Tilz R, Chun J, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation 2010;122:2368–77.
4. Weerasooriya R, Khairy P, Litalien J, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol 2011;57:160–6.
5. Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol 2004;43:2044–53.
6. Haissaguerre M, Sanders P, Hocini M, et al. Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. J Cardiovasc Electrophysiol 2005;16:1125–37.
7. Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. Am Heart J 1964;67:200–20.
8. Allessie MA, Lammers WJEP, Bonke FIM, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J, editors. Cardiac Arrhythmias. New York, NY: Grune & Stratton, 1985:265–76.
9. de Groot NM, Houben RP, Smeets JL, et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. Circulation 2010; 122:1674–82.
10. Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. Circulation 2000;101:194–9.
11. Jais P, Haissaguerre M, Shah DC, et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation 1997;95:572–6.
12. Kalifa J, Tanaka K, Zaitsev AV, et al. Mechanisms of wave fractionation at boundaries of high-frequency excitation in the posterior left atrium of the isolated sheep heart during atrial fibrillation. Circulation 2006;113:626–33.
13. Sahadevan J, Ryu K, Peltz L, et al. Epicardial mapping of chronic atrial fibrillation in patients: preliminary observations. Circulation 2004;110:3293–9.
14. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel W-J, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol 2012;60:628–36.

Key Words: ablation ■ atrial fibrillation ■ human ■ rotor ■ therapy.