JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 3, NO. 11, 2017

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2017.07.001

EDITORIAL COMMENT

Focal Sources

Another Potentially Important Target for Persistent Atrial Fibrillation?*

Gregory F. Michaud, MD, Sharon Shen, MD

Atrial fibrillation (AF) remains one of the most prevalent cardiovascular diseases worldwide, affecting more than 33 million persons with associated rising health care costs totaling $26 billion in the United States alone (1,2). Although data favor catheter ablation over antiarrhythmic drug therapy in terms of quality of life and AF-free survival (3,4), the long-term single procedural success with catheter ablation in persistent AF is at best ~40% (5,6). Despite promising single-center experiences, randomized studies have shown that adjunctive ablation strategies such as targeting complex fractionated atrial electrograms (CFAEs) or segmentation of the left atrium with lines of block do not improve single or multiple procedure arrhythmia-free survival (7,8). Many other strategies are under investigation, but results of randomized controlled trials are not available.

SEE PAGE 1220

In that context, this well-written study by Kochhäuser et al. (9) in this issue of *JACC: Clinical Electrophysiology*, explores the idea of identifying and ablating focal sources of AF and characterizes their spatial relationship to areas of CFAE with and without continuous electrical activity (CEA) using a subset of patients from the SELECT AF (Selective complex fractionated atrial electrograms targeting for atrial fibrillation study) (10). The SELECT AF trial was a randomized comparison of patients with persistent and high-burden paroxysmal AF who, in addition to pulmonary vein isolation, underwent standard CFAE ablation versus CFAE ablation limited to areas with CEA. Briefly, the authors identified periodicity in bipolar left atrial electrograms using offline software and defined focal sources as periodic electrograms with a QS unipolar morphology. Using this methodology, the authors found a total of 77 focal sources in 51 patients (median of 1 per patient), which were more commonly on the border zone of CFAEs (49%) than CEAs (7.8%). Of note, most of the focal sources localized to the pulmonary vein ostium/antrum (48%). Because focal sources were more likely to be on the border zone of CFAEs than inside them, the authors conclude that CFAEs play a passive role in AF perpetuation and focal sources are often left unablated during ablation targeting CFAEs. The described spatial relationship between focal sources and CFAEs in this study, although thought-provoking, does not provide clear evidence for a mechanistic relationship.

To determine the relative importance of such focal sources in persistent AF, the authors assessed the association of coincidental focal source ablation and AF recurrence and found that the median number of focal sources was not significantly different between patients with and without AF recurrence; however, the median number of unablated focal sources was significantly higher among patients with AF recurrence. Patients most frequently had a single focal source, which clearly does not account for the entire mechanism in most patients with AF. In their univariate analysis, CEA ablation approach and number of unablated focal sources were associated with

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

From the Vanderbilt University Medical Center, Nashville, Tennessee. Dr. Michaud has received honoraria from Biotronik, Medtronic, Biosense Webster, Abbott, and Boston Scientific. Dr. Shen has reported that she has no relationships relevant to the contents of this paper to disclose.

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

higher AF recurrence; however, in multivariable analysis, CEA approach remained the only significant predictor. Because this was a nonrandomized study and the targeted sites for ablation were not specifically focal sources, we have learned from similar study designs that it is a mistake to draw any conclusions concerning cause and effect.

This study points out the potential importance of focal sources in the perpetuation of AF, but conclusions on the mechanistic importance are limited by how focal sources were identified. The presence of focal sources in persistent AF itself is controversial. Some sources dispute the presence of focal sources during ongoing AF (11), whereas others support focal sources (12). Although there is a rationale for the methodology used to identify focal sources (13), this has not been validated sufficiently to determine the sensitivity and specificity, let alone spatial accuracy. Additionally, the definition of QS used in this article (R/S <0.1 in 90% of activations) may be seen at an endocardial breakthrough of an epicardial source or where source-sink mismatches occur.

The potentially transient nature of focal sources is not addressed in this study. Because regions with focal sources may fire for a time and then become passively activated, a 2.5-s recording sample may not be sufficient to identify all sources. Similarly, mapping was performed with a bipolar ablation catheter electrode, which does not afford the same fidelity as recording from a multipolar catheter with a smaller electrode (3.5 vs. 1 mm).

As with other good studies that generate a hypothesis, focal source ablation will need to be assessed in future randomized controlled trials. Until we have a clear understanding of the mechanism(s) of persistent AF and how to identify the critical substrate, we will continue to squeeze the left atrial electrogram in the hope of finding a drop of understanding.

ADDRESS FOR CORRESPONDENCE: Dr. Sharon Shen, Vanderbilt University Medical Center, 1215 21st Avenue South, MCE 5th Floor, South Tower, Nashville, Tennessee 37232-8802. E-mail: sharon.shen@vanderbilt.edu.

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation 2017;135:e146–603.

2. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837–47.

3. Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. Circ Arrhythm Electrophysiol 2009;2:626–33.

4. Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). Eur Heart J 2014;35:501–7.

5. Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc 2013;2:e004549.

6. Scherr D, Khairy P, Miyazaki S, et al. 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.

7. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372:1812–22.

8. Vogler J, Willems S, Sultan A, et al. Pulmonary vein isolation versus defragmentation: the CHASE-AF Clinical Trial. J Am Coll Cardiol 2015;66:2743–52.

9. Kochhäuser S, Verma A, Dalvi R, et al. Spatial relationships of complex fractionated atrial electrograms and continuous electrical activity to focal electrical sources: implications for substrate ablation in human atrial fibrillation. J Am Coll Cardiol EP 2017;3:1220–8.

10. Verma A, Sanders P, Champagne J, et al. Selective complex fractionated atrial electrograms targeting for atrial fibrillation study (SELECT AF): a multicenter, randomized trial. Circ Arrhythm Electrophysiol 2014;7:55–62.

11. de Groot NMS, Houben RPM, Smeets JL, et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease. Epicardial Breakthrough 2010;122:1674–82.

12. Lee S, Sahadevan J, Khrestian CM, Cakulev I, Markowitz A, Waldo AL. Simultaneous biatrial high-density (510–512 electrodes) epicardial mapping of persistent and long-standing persistent atrial fibrillation in patients. New insights into the mechanism of its maintenance. Circulation 2015;132:2108–17.

13. Gizurarson S, Dalvi R, Das M, Ha ACT, Suszko A, Chauhan VS. Hierarchical schema for identifying focal electrical sources during human atrial fibrillation. J Am Coll Cardiol EP 2016;2:656–66.

KEY WORDS atrial fibrillation, catheter ablation, focal sources, mechanisms