

EDITORIAL COMMENT

# Ablation of Persistent AF

## Have We Come Full Circle, or Are We Chasing Our Tails?\*



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*Nothing is impossible to a willing heart*  
The Proverbs and Epigrams of John Heywood  
(A.D. 1562) (1)

The long-term maintenance of sinus rhythm in patients in persistent atrial fibrillation (AF) remains a demanding task whatever therapeutic option is taken, but it is a challenge electro-physiologists and surgeons have enthusiastically pursued for several decades. Buoyed by the clinical success of catheter ablation of accessory pathways at the turn of the millennium, it appeared only a matter of time until AF, be it paroxysmal or persistent, would become a curable arrhythmia. Yet, despite intensive investigation, that has not yet come to pass.

The critical role of the pulmonary veins (PVs) in initiating AF is well established (2), and at least for paroxysmal AF, PV ablation appears to be sufficient to treat most patients. With single procedure success rates (defined by no recurrence of documented arrhythmia) of approximately 70% at 1 year (3) and long-term outcomes (3 to 5 years) of 80% for PV isolation (PVI) with multiple procedures (4,5), this assumption appears correct for paroxysmal AF. For patients with persistent AF (sustained arrhythmia lasting >7 days), the clinical results for PVI as a sole ablation strategy have been relatively disappointing, if not at 1 year (6), then certainly at 3- and 5-year follow-up (7,8). This has led to additional strategies to modify the atrial substrate. Due to the pioneering nature of this work, most studies driving clinical practice over the last decade have been single-center

retrospective studies. Although not all agree with it, the trend continues to be more and more ablation. As the techniques have become established and positions entrenched, it is only relatively recently that systematic meta-analysis (9) and multicenter prospective randomized studies have critically examined these strategies (10).

### ABLATION OF COMPLEX FRACTIONATED ELECTROGRAMS

One such prospective randomized single-center study by Vogler et al. (11) is presented in this issue of the *Journal*. Using a modified stepwise ablation strategy, they randomized patients with persistent AF to either PVI alone or to additional substrate ablation. The results suggest that additional substrate ablation offers little if anything to PVI alone, with 12-month, single-procedure success rates of 75% and 73.8%, respectively. However, before abandoning this substrate modification for patients with persistent AF, careful interpretation of these data are required.

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Temporal classification of patients with AF is fraught with difficulty. For example, the TRENDS data demonstrated that intermittent monitoring and patient factors influence clinicians to a greater extent than expected, leading to misdiagnosis of either paroxysmal or persistent AF (12,13). As such, although the intended population was patients with persistent AF, the duration of continuous AF might have been <1 week if the patient received early cardioversion. Although inappropriate diagnosis of paroxysmal or persistent AF is likely to influence all studies of patients with persistent AF, objective measures, such as left atrial (LA) diameter and area, AF cycle length, and CHA<sub>2</sub>DS<sub>2</sub>-VASc score, suggest that the population studied was perhaps more favorable compared with those in historical retrospective

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studies (14-16). For instance, in work by the Bordeaux group, mean LA diameter and AF cycle length were approximately 47 mm and 150 ms, respectively (15); in the current study, these were 44 mm and 170 ms, respectively. Across numerous studies and groups, LA diameter and AF cycle length have consistently been independent markers of freedom from AF following ablation (5,8,17-19).

Although PVI has become standardized, comparing ablation techniques is difficult, with the devil being in the details. The move toward a more antral ablation approach has undoubtedly improved success rates (20,21), although whether this is due to additional substrate ablation, ablation of ganglionic plexi (22), or inadvertent rotor ablation (23) remains controversial. Even defining the PV antrum is difficult, let alone standardizing the complex fractionated atrial electrogram (CFAE). The technique used in the study by Vogler et al. (11) is described as a stepwise ablation technique. The original description by the Bordeaux group of stepwise ablation included PVI, which was followed by (if necessary) biatrial ablation of CFAEs, and again (if necessary), linear lesions, followed by cardioversion, with completion of linear lesions if the bidirectional block had not already been achieved. Procedural termination of AF was the endpoint. The technique used by Vogler et al. (11) was more simply PVI and then randomization to either cardioversion or CFAE ablation (24). Linear lesions were only used if a patient transitioned to a macro-re-entrant tachycardia, which occurred in approximately one-third of all cases. The Bordeaux stepwise procedure is certainly an exacting procedure, and Vogler et al. are right to comment that the modified technique used in their study may accurately represent “real-world” practice.

The data appear to support the STAR-AF II (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II) trial, in which patients were randomized in a 1:4:4 manner to either PVI alone, additive CFAE ablation, or additive linear ablation, with no benefit shown with additional ablation compared with PVI alone (10). This was similar to an earlier randomized study in which the addition of CFAE ablation to PVI had no discernible effect regarding rhythm outcome (25). Together, these data suggest that CFAE ablation added to PVI does not confer an advantage to the patient in terms of AF-free survival, but it does increase procedural duration and bystander atrial ablation. This is substantially different from suggesting that stepwise ablation, as defined by the Bordeaux group, does not confer an advantage, especially because patients who had termination of AF by PVI alone were excluded from

the analysis in the study by Vogler et al. (11), equaling approximately 25% of patients before randomization. These patients were included in the original description of the technique, in which termination of AF by PVI alone was only achieved in 14%, again suggesting a more advanced AF phenotype in the original stepwise population compared with the current study.

That additional CFAE ablation does not confer a specific additional benefit should not be surprising; the underlying mechanisms of CFAEs are incompletely understood (26), and several different phenomena apparently can give rise to fractionated electrograms (27). Furthermore, the positive and negative predictive values of different qualities of CFAEs are little better than a coin toss (28).

## FACTORS CRITICAL TO SUCCESS

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The impressive overall AF termination rate in the study by Vogler et al., using PVI alone, highlights several important issues. Patient selection is clearly critical for achieving long-term technical and clinical success. Unfortunately, the noninvasive tools we use are fraught with their own limitations. Conversely, defining patients based on history and duration of AF appears simple, but in clinical practice is decidedly less so (13). Still, a noninvasive inverse potential mapping system, with limited availability at present, suggests that an important change occurs in the AF substrate in patients with persistent AF for 9 to 12 months, which affects the amount of ablation necessary to obtain a favorable rhythm outcome (29). Although cardiac magnetic resonance imaging (CMR) may categorize patients with a favorable versus a more unfavorable substrate (30), so far this has not seen widespread adoption. Various technical reasons may explain why (31), ranging from technical facets of the CMR process to the exact histological characteristics of fibrosis being assessed (32).

Procedural termination of AF is also somewhat controversial (5,8,15,16,18,19). Most studies suggest that procedural termination favors an improved long-term outcome from AF ablation and independently predicts success, although the magnitude can vary from a hazard ratio of 1.28 (19) to 3.8 (16) at 5 years. Procedural termination of an arrhythmia has been considered the gold standard from the early days of radiofrequency ablation, when the mechanism of arrhythmias seemed well understood. The problem with AF is that currently the underlying mechanisms are incompletely understood; therefore, although termination may be the gold standard endpoint,

unless this results from a specific lesion and a specific target (33), AF termination cannot be the ideal endpoint all of the time.

Although it may appear to a casual observer that the last decade of extensive LA ablation has come full circle back to PVI alone as an ablation strategy, encouragement remains for those of us who undertake ablation in these complex patients. Data, such as that presented in this issue of the *Journal*, should spur us to critically re-examine for whom and how persistent AF ablation is undertaken. Improved patient selection, “the willing heart,” with mechanistically derived ablation strategies tailored to the individual patient, may result in more acceptable long-term success rates.

In many ways, this was the ethos of the original stepwise procedure, with each step only undertaken if AF had not been terminated. However, to become widespread clinical practice, the same rigorous independent examination of novel techniques needs to be undertaken by the wider community of electrophysiologists, as has been done with CFAE ablation in the current study by Vogler et al. (11).

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## REFERENCES

1. Brainyquote. John Heywood quotes. Available at: <http://www.brainyquote.com/quotes/quotes/j/johnheywoo377091.html>. Accessed October 16, 2015.
2. 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.
3. Di Biase L, Elayi CS, Fahmy TS, et al. Atrial fibrillation ablation strategies for paroxysmal patients: randomized comparison between different techniques. *Circ Arrhythm Electrophysiol* 2009;2:113-9.
4. Ouyang F, Tiltz 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.
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. Ciconte G, Baltogiannis G, de Asmundis C, et al. Circumferential pulmonary vein isolation as index procedure for persistent atrial fibrillation: a comparison between radiofrequency catheter ablation and second-generation cryoballoon ablation. *Europace* 2015;17:559-65.
7. Tiltz RR, Rillig A, Thum AM, et al. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. *J Am Coll Cardiol* 2012;60:1921-9.
8. Wynn GJ, Das M, Bonnett LJ, et al. Efficacy of catheter ablation for persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized and nonrandomized controlled trials. *Circ Arrhythm Electrophysiol* 2014;7:841-52.
9. Providencia R, Lambiase PD, Srinivasan N, et al. Is there still a role for CFAE ablation in addition to pulmonary vein isolation in patients with paroxysmal and persistent atrial fibrillation? A meta-analysis of 1,415 patients. *Circ Arrhythm Electrophysiol* 2015;8:1017-29.
10. Verma A, Jiang C, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;372:1812-22.
11. 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.
12. Charitos EI, Stierle U, Ziegler PD, et al. A comprehensive evaluation of rhythm monitoring strategies for the detection of atrial fibrillation recurrence: insights from 647 continuously monitored patients and implications for monitoring after therapeutic interventions. *Circulation* 2012;126:806-14.
13. Charitos EI, Purerfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. *J Am Coll Cardiol* 2014;63:2840-8.
14. O'Neill MD, Jais P, Takahashi Y, et al. The stepwise ablation approach for chronic atrial fibrillation—evidence for a cumulative effect. *J Interv Card Electrophysiol* 2006;16:153-67.
15. O'Neill MD, Wright M, Knecht S, et al. Long-term follow-up of persistent atrial fibrillation ablation using termination as a procedural endpoint. *Eur Heart J* 2009;30:1105-12.
16. 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.
17. McCready JW, Smedley T, Lambiase PD, et al. Predictors of recurrence following radiofrequency ablation for persistent atrial fibrillation. *Europace* 2011;13:355-61.
18. Rostock T, Salukhe TV, Hoffmann BA, et al. Prognostic role of subsequent atrial tachycardias occurring during ablation of persistent atrial fibrillation: a prospective randomized trial. *Circ Arrhythm Electrophysiol* 2013;6:1059-65.
19. Schreiber D, Rostock T, Frohlich M, et al. Five-year follow up after catheter ablation of persistent atrial fibrillation using the “stepwise approach” and prognostic factors for success. *Circ Arrhythm Electrophysiol* 2015;8:308-17.
20. Arentz T, Weber R, Burkle G, et al. Small or large isolation areas around the pulmonary veins for the treatment of atrial fibrillation? Results from a prospective randomized study. *Circulation* 2007;115:3057-63.
21. Medi C, Sparks PB, Morton JB, et al. Pulmonary vein antral isolation for paroxysmal atrial fibrillation: results from long-term follow-up. *J Cardiovasc Electrophysiol* 2011;22:137-41.
22. Katritsis DG, Pokushalov E, Romanov A, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. *J Am Coll Cardiol* 2013;62:2318-25.
23. Narayan SM, Krummen DE, Clopton P, et al. Direct or coincidental elimination of stable rotors or focal sources may explain successful atrial fibrillation ablation: on-treatment analysis of the CONFIRM trial (Conventional ablation for AF with or without focal impulse and rotor modulation). *J Am Coll Cardiol* 2013;62:138-47.
24. Rostock T, Steven D, Hoffmann B, et al. Chronic atrial fibrillation is a biatrial arrhythmia: data from catheter ablation of chronic atrial fibrillation aiming arrhythmia termination using a sequential ablation approach. *Circ Arrhythm Electrophysiol* 2008;1:344-53.
25. Oral H, Chugh A, Yoshida K, et al. A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. *J Am Coll Cardiol* 2009;53:782-9.
26. Haissaguerre M, Wright M, Hocini M, Jais P. The substrate maintaining persistent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2008;1:2-5.
27. Narayan SM, Wright M, Derval N, et al. Classifying fractionated electrograms in human atrial

fibrillation using monophasic action potentials and activation mapping: evidence for localized drivers, rate acceleration and non-local signal etiologies. *Heart Rhythm* 2011;8:244-53.

**28.** Takahashi Y, O'Neill MD, Hocini M, et al. Characterization of electrograms associated with termination of chronic atrial fibrillation by catheter ablation. *J Am Coll Cardiol* 2008;51:1003-10.

**29.** Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. *Circulation* 2014;130:530-8.

**30.** Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA* 2014;311:498-506.

**31.** Karim R, Housden RJ, Balasubramaniam M, et al. Evaluation of current algorithms for segmentation of scar tissue from late gadolinium enhancement cardiovascular magnetic resonance of the left atrium: an open-access grand challenge. *J Cardiovasc Magn Reson* 2013;15:105.

**32.** de Jong S, van Veen TA, van Rijen HV, de Bakker JM. Fibrosis and cardiac arrhythmias. *J Cardiovasc Pharmacol* 2011;57:630-8.

**33.** Hansen BJ, Zhao J, Csepe TA, et al. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. *Eur Heart J* 2015;36:2390-401.

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come full circle " completely opposite from one s starting point They have come full circle since the new president started at the university " Idioms and examples. come full circle " come/go/turn full circle if something or someone has come full circle after changing a lot, they are now the same as they were at the beginning. My career has come full circle and I am back at the school where I started out as a teacher thirty" " New idioms dictionary. have come a full circle " complete a cycle, complete an endeavor or undertaking " English contemporary dictionary. go full circle " come/go/turn f...