Published in final edited form as:
Circ Arrhythm Electrophysiol. 2011 August 1; 4(4): 426–428. doi:10.1161/CIRCEP.111.964841.

Complex Fractionated Atrial Electrograms: Is this the Beast to Tame in AF?

Omer Berenfeld, Ph.D. and **José Jalife, M.D.**
Center for Arrhythmia Research, University of Michigan, Ann Arbor, MI

Atrial fibrillation (AF), the most common sustained arrhythmia, represents a difficult scientific challenge and remains enigmatic even after more than one century of research. Already about a hundred years ago principles that could account for organization amidst much disorganized spatial and temporal patterns of activation were proposed to prevail in the form of reentrant activity.[1,2] During the last decades experimental and clinical studies have demonstrated that despite the spatiotemporal complexity of wave propagation during AF, maintenance of the arrhythmia in many cases depends on measurable deterministic properties of fast rotors and hierarchical distribution of activation rates.[3–7] However, any suggestion of organization underlying AF is met with skepticism as the proclaimed organization is quite elusive, particularly since the analysis and treatment of the arrhythmia in humans depends, for the most part, on catheter-based, relatively low resolution electroanatomical mapping.[8] As such, when the isolation of pulmonary veins (PVs) by radiofrequency ablation is insufficient to eliminate AF, most clinical electrophysiologists today move on to target areas of complex electrograms, whose ever changing morphologies, inter-beat intervals and amplitudes have somehow led to the notion that such areas may harbor the sources that maintain AF. In this context, Nademanee et al,[9] identified a particular class of electrograms, which he termed “complex fractionated atrial electrograms” (CFAEs), at sites outside the four PV ostia, on the posterior and anterior left atrial (LA) walls. Nademanee’s work stirred much interest among those studying AF, and since then many attempts have been made to automatically quantify CFAEs and extract from them a better understanding of AF mechanisms.[10–13] The ultimate common goal is to guide ablation procedures and increase their efficacy in patients with either paroxysmal or persistent AF.[9,14]

In this issue of CIRCAE, Ciaccio et al have extended the analysis of CFAEs by focusing on the spatial and temporal repeatability of CFAE patterns.[15] They propose a novel way to combine two methods to quantify repetitiveness in CFAE: linear prediction and Fourier reconstruction. The linear analysis method of the CFAEs signals captures the amount of similar morphological deflection patterns, regardless of whether such deflections appear in fixed or varying time intervals within predetermined epoch durations. Their Fourier-based analysis selects all those frequency components of the CFAE signals with power above a determined cutoff, allowing appreciation of the combined short and long term periodicities embedded in either the morphology of a single deflection (i.e., short term) or its reproducibility (i.e., long term) on the CFAEs. Lower prediction and reconstruction errors are considered indicative of increasing repetitiveness and decreasing randomness. The analysis shows that in paroxysmal AF patients, CFAE pattern repetitiveness is significantly lower (randomness higher) at antral sites outside PV ostia compared with LA free wall sites.

Correspondence: José Jalife, M.D. Center for Arrhythmia Research, University of Michigan, 5025 Venture Drive, Ann Arbor, MI 48108, Phone: 1-734-998-7500, Fax: 1-734-998-7511, jjalife@umich.edu.

Conflict of Interest Disclosures: None.

In longstanding AF, repetitiveness increases outside the PV ostia, especially outside the left superior PV ostium, and diminishes at the LA free wall sites. The analysis further shows that in persistent AF, there are no significant site-specific differences in CFAE repetitiveness at the selected LA locations used in this study. Concomitantly with the changes in CFAEs repeatability, and consistent with other clinical studies,[16–18] Ciaccio et al also found that the average DF magnitude was 5.32±0.29 Hz in paroxysmal AF and higher and more uniform in longstanding AF at 6.27±0.13 Hz. The authors conclude that in paroxysmal AF patients, CFAE repetitiveness is low and randomness high outside the PVs, particularly outside the left superior PV. As the substrate evolves toward longstanding persistent AF, CFAE repetitiveness becomes more uniformly distributed at disparate sites.

The interesting results of Ciaccio et al may be seen as an attempt to support the notion that as AF becomes persistent, it increasingly depends on drivers localized within atrial regions outside the PVs. However, the support is inconclusive due to both scarcity of spatial data and a lack of information on impulse propagation. Therefore, based on the data presented there is no way to infer the location of presumed discrete drivers in the paroxysmal or persistent AF patients studied by these authors. Justifiably, Ciaccio et al sought to categorize the repeatability of CFAEs. Yet, at the outset, their approach is poised to generate ambiguity in data interpretation, because repeatability implies temporal organization, and according to Nademanee's definition, CFAEs are not supposed to be temporally organized. In addition, the definition of CFAE used here lacks a solid mechanistic rationale, which begs the question of how one should rigorously establish the boundary between organized and non-organized elements of the CFAEs? Additional questions include: How should one interpret the finding that relatively more "organized" (repeating) CFAEs were found on the anterior left atrium in paroxysmal AF patients, but not in persistent AF patients? Is the higher organization in paroxysmal AF related to the fact that DF is lower in those patients compared with persistent AF patients? But, if that is the case, then how should one explain the increased CFAE organization in the PVs of persistent AF, where the DFs were higher than in paroxysmal AF at any location? Could that be related to a reduced refractory period across the remodeled atria of persistent AF?

Many studies, by us and others, have attempted to shed light on the origins of complex electrograms and to reconcile the co-existence of organized and complex activity in AF. Most such studies have not used Nademanee's definition of CFAEs.[9] For example, Kalifa et al used optical mapping of the posterior LA wall in a sheep heart model of acute AF to investigate the relationship between the spatial distribution of sites with high activation rate, variability in propagation velocity and direction, and the resulting irregularity in the local voltage.[6] By quantifying both the relative power at the DF (regularity index, RI) and counting the number of deflections, as well as assessing the variability in the voltage amplitude, they demonstrated that at the periphery of high-frequency AF drivers there is an area at which most fractionation occurs. Importantly, it was found that beyond that area, at longer distances from the high-frequency source, the activation rate was already reduced, and the organization of incoming waves was regained, which yielded a biphasic relationship between the DF of waves emanating from a localized source and their RIs. As such, we suspect that the relative increase in the organization of the CFAEs reported by Ciaccio et al on the anterior LA in paroxysmal AF patients, was in fact the result of a spatial transformation of DF in space between the AF driver and the recording site. In a more recent mechanistic study, Zlochiver et al demonstrated that rotor meandering might also underlie, at least in part, the electrogram fractionation that occurs close to the driver.[5] Based on the above results, it is reasonable to expect that, since the refractory period is shorter in persistent AF than paroxysmal AF,[19] reentry could become more stable in the former than in the latter.[20] This, in turn, may explain why, despite a general increase in DFs in the persistent AF patients analyzed by Ciaccio et al, the repeatability of the CFAEs in those

patients was greater, i.e., their CFAEs were more “regular” (except in the antral LA), than in paroxysmal AF patients.

Studies have demonstrated that the atria respond to activation rate increments with progressive deterioration of stable directionality and electrogram fractionation[4,21] and suggest that CFAEs may be unrelated to the primary arrhythmia mechanism, and simply represent transient pivoting, wavefront collision or sink-to-source mismatch at increasingly higher activation rates.[3,4,21–24] Moreover, experimental and clinical studies strongly suggest that, in paroxysmal AF, electrogram fractionation at the posterior LA wall is a reflection of fibrillatory conduction and a consequence of the dynamic interaction between high frequency re-entrant sources and the atrial anatomy. Further, high-density mapping has identified clusters of high DF sites with fractionation most likely observed adjacent to those sites.[6] Therefore, the transition to fractionation is not random, but reflects functional intermittence of atrial conduction in response to periodic input of exceedingly high frequency.

Atienza et al recently studied specifically the intermittent nature of irregular activity from a different perspective.[25] The original definition of CFAEs includes 2 different features: electrogram fractionation and short electrogram cycle length.[9] Accordingly, Atienza et al analyzed such features as separate variables to derive mechanistic insight of their possible interaction.[25] Their findings were as follows: i) in induced, paroxysmal AF, electrogram fractionation at the posterior LA wall was rate-dependent; ii) organized AF phases showed a highly stable and recurrent pattern of incoming waves of activation emanating from high-frequency sites at the PV-LA junctions area; iii) transitions from organized to fractionated electrograms were always preceded by progressive cycle length shortening leading to beat-to-beat changes in wavefront directionality, intermittent wavebreak and reentry around a line of functional block, most likely at the septo-pulmonary bundle; finally, iv) wavefront acceleration ahead of drifting rotors on the posterior LA wall and/or rotor meandering gives rise to intermittent local fractionation.

Taken together, the above results strongly support the conclusion that, since the instantaneous atrial activation frequency (i.e., 1/cycle length) invariably increases prior to fragmentation and decreases upon organization, the local frequency of activation is a major determinant of electrogram fragmentation. In other words, fragmentation in Nademanee’s original definition[9] of CFAEs is not an independent variable. Its dependence on atrial refractoriness and activation frequency is clear; for any given level of refractoriness, fractionation may or may not appear in the presence of low activation rates, but it is very likely to appear at a breakpoint as activation rate is increased.[4] The implication of that rule is simple: unless rigorously demonstrated otherwise, local fractionation is a poor criterion to select as an ablation target. The article by Ciaccio et al does not invalidate such a conclusion or provide clear answers to many questions still lingering around the nature of the CFAEs. Yet if combined with more mechanistic analyses, the novel approach outlined by Ciaccio et al might potentially help in the full characterization of the electrophysiological bases of AF. More importantly, it might help delineate what constitutes a CFAE and whether or not it is critical for AF maintenance.

Acknowledgments

Supported by NHLBI grants P01-HL039707, and P01-HL087226 and the Leducq Foundation.

Reference List

1. Mines GR. On circulating excitation on heart muscles and their possible relation to tachycardia and fibrillation. Trans R Soc Can. 1914; 4:43–53.

2. Lewis, T. The mechanism and graphic registration of the heart beat. 3. London: Shaw & Sons; 1925.
3. Wells JL Jr, Karp RB, Kouchoukos NT, MacLean WAH, James TN, Waldo AL. Characterization of atrial fibrillation in man: Studies following open heart surgery. PACE Pacing Clin Electrophysiol. 1978; 1:426–38. [PubMed: 95635]
4. Berenfeld O, Zaitsev AV, Mironov SF, Pertsov AM, Jalife J. Frequency-dependent breakdown of wave propagation into fibrillatory conduction across the pectinate muscle network in the isolated sheep right atrium. Circ Res. 2002; 90:1173–1180. [PubMed: 12065320]
5. Zlochiver S, Yamazaki M, Kalifa J, Berenfeld O. Rotor meandering contributes to irregularity in electrograms during atrial fibrillation. Heart Rhythm. 2008; 5:846–854. [PubMed: 18534369]
6. Kalifa J, Tanaka K, Zaitsev AV, Warren M, Vaidyanathan R, Auerbach D, Pandit S, Vikstrom KL, Ploutz-Snyder R, Talkachou A, Atienza F, Guiraudon G, Jalife J, Berenfeld O. 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; 113:626–633. [PubMed: 16461834]
7. Klos M, Calvo D, Yamazaki M, Zlochiver S, Mironov S, Cabrera JA, Sanchez-Quintana D, Jalife J, Berenfeld O, Kalifa J. Atrial septopulmonary bundle of the posterior left atrium provides a substrate for atrial fibrillation initiation in a model of vagally mediated pulmonary vein tachycardia of the structurally normal heart. Circ Arrhythm Electrophysiol. 2008; 1:175–183. [PubMed: 19609369]
8. Reddy VY, Morales G, Ahmed H, Neuzil P, Dukkipati S, Kim S, Clemens J, D'Avila A. Catheter ablation of atrial fibrillation without the use of fluoroscopy. Heart Rhythm. 2010; 7:1644–1653. [PubMed: 20637313]
9. 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. Journal of the American College of Cardiology. 2004; 43:2044–2053. [PubMed: 15172410]
10. Lin YJ, Tai CT, Kao T, Chang SL, Wongcharoen W, Lo LW, Tuan TC, Udyavar AR, Chen YJ, Higa S, Ueng KC, Chen SA. Consistency of complex fractionated atrial electrograms during atrial fibrillation. Heart Rhythm. 2008; 5:406–412. [PubMed: 18313599]
11. Ciaccio EJ. Localization of the slow conduction zone during reentrant ventricular tachycardia. Circulation. 2000; 102:464–469. [PubMed: 10908221]
12. Ciaccio EJ, Biviano AB, Whang W, Gambhir A, Garan H. Different characteristics of complex fractionated atrial electrograms in acute paroxysmal versus long-standing persistent atrial fibrillation. Heart Rhythm. 2010; 7:1207–1215. [PubMed: 20558323]
13. Ciaccio EJ, Biviano AB, Whang W, Wit AL, Coromilas J, Garan H. Optimized measurement of activation rate at left atrial sites with complex fractionated electrograms during atrial fibrillation. J Cardiovasc Electrophysiol. 2010; 21:133–143. [PubMed: 19793138]
14. Verma A, Novak P, Macle L, Whaley B, Beardsall M, Wulffhart Z, Khaykin Y. A prospective, multicenter evaluation of ablating complex fractionated electrograms (CFEs) during atrial fibrillation (AF) identified by an automated mapping algorithm: acute effects on AF and efficacy as an adjuvant strategy. Heart Rhythm. 2008; 5:198–205. [PubMed: 18242539]
15. Ciaccio EJ, Biviano AB, Whang W, Vest JA, Gambhir A, Einstein AJ, Garan H. Differences in Repeating Patterns of Complex Fractionated Left Atrial Electrograms in Longstanding Persistent as Compared with Paroxysmal Atrial Fibrillation. Circ Arrhythm Electrophysiol. 2011
16. Sanders P, Berenfeld O, Hocini M, Jais P, Vaidyanathan R, Hsu LF, Garrigue S, Takahashi Y, Rotter M, Sacher F, Scavee C, Ploutz-Snyder R, Jalife J, Haissaguerre M. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. Circulation. 2005; 112:789–797. [PubMed: 16061740]
17. Atienza F, Almendral J, Jalife J, Zlochiver S, Ploutz-Snyder R, Torrecilla EG, Arenal A, Kalifa J, Fernandez-Aviles F, Berenfeld O. Real-time dominant frequency mapping and ablation of dominant frequency sites in atrial fibrillation with left-to-right frequency gradients predicts long-term maintenance of sinus rhythm. Heart Rhythm. 2009; 6:33–40. [PubMed: 19121797]
18. Alcaraz R, Sandberg F, Sornmo L, Rieta JJ. Application of frequency and sample entropy to discriminate long-term recordings of paroxysmal and persistent atrial fibrillation. Conf Proc IEEE Eng Med Biol Soc. 2010; 2010:4558–4561. [PubMed: 21096222]

19. Van Wagoner, DR. Electrical Remodeling and Chronic Atrial Fibrillation. In: Zipes, DP.; Jalife, J., editors. Cardiac Electrophysiology: From Cell to Bedside. 4. Philadelphia: Sounders; 2004. p. 375-379.

20. Pandit SV, Berenfeld O, Anumonwo J, Zaritski RM, Kneller J, Nattel S, Jalife J. Ionic Determinants of Functional Reentry in a 2-D Model of Human Atrial Cells During Simulated Chronic Atrial Fibrillation. Biophys J. 2005; 88:3806–3821. [PubMed: 15792974]

21. Tai CT, Chen SA, Tzeng JW, Kuo BI, Ding YA, Chang MS, Shyu LY. Prolonged fractionation of paced right atrial electrograms in patients with atrial flutter and fibrillation. J Am Coll Cardiol. 2001; 37:1651–1657. [PubMed: 11345380]

22. Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA. High-density mapping of electrically induced atrial fibrillation in humans. Circulation. 1994; 89:1665–1680. [PubMed: 8149534]

23. Ortiz J, Niwano S, Abe H, Rudy Y, Johnson NJ, Waldo AL. Mapping the conversion of atrial flutter to atrial fibrillation and atrial fibrillation to atrial flutter. Insights into mechanisms Circ Res. 1994; 74:882–894.

24. Rostock T, Rotter M, Sanders P, Takahashi Y, Jais P, Hocini M, Hsu LF, Sacher F, Clementy J, Haissaguerre M. High-density activation mapping of fractionated electrograms in the atria of patients with paroxysmal atrial fibrillation. Heart Rhythm. 2006; 3:27–34. [PubMed: 16399048]

25. Atienza F, Calvo D, Zlochiver S, Grzeda KR, Martinez-Alzamora N, Gonzalez-Torrecilla E, Arenal A, Fernandez-Aviles F, Berenfeld O. Mechanisms of fractionated electrograms formation in the posterior left atrium during paroxysmal atrial fibrillation in humans. J Am Coll Cardiol. 2011; 57:1081–1092. [PubMed: 21349400]