Pitfalls in the definition of complex fractionated atrial electrograms for atrial fibrillation studies

Journal:	*Journal of Cardiovascular Electrophysiology*
Manuscript ID	JCE-19-0998
Wiley - Manuscript type:	Letter to the Editor
Date Submitted by the Author:	01-Nov-2019
Complete List of Authors:	Paggi Almeida, Tiago; Instituto Tecnológico de Aeronáutica, Division of Electronic Engineering; University of Leicester, Department of Cardiovascular Science; University of Leicester, School of Engineering Li, Xin; University of Leicester, Department of Cardiovascular Science; University of Leicester, School of Engineering Soriano, Diogo; Federal University of the ABC, Engineering, Modelling and Applied Social Sciences Centre Schlindwein, Fernando; University of Leicester, School of Engineering Ng, G. André; University of Leicester, Department of Cardiovascular Science

Letter to the Editor

Pitfalls in the definition of complex fractionated atrial electrograms for atrial fibrillation studies

Tiago P. Almeida, PhD[a,b,c]; Xin Li, PhD[b,c]; Diogo C. Soriano, PhD[d]; Fernando S. Schlindwein, PhD, DSc[c]; G. André Ng, MBChB, PhD, FRCP(Glasg), FRCP, FESC[b]

[a]Division of Electronic Engineering, Aeronautics Institute of Technology, Brazil; [b]Department of Cardiovascular Science, University of Leicester, UK; [c]School of Engineering, University of Leicester, UK; [d]Engineering, Modelling and Applied Social Sciences Centre, Federal ABC University, Brazil

Conflict of interests

Professor Ng has received research fellowship from St. Jude Medical and speaker fees and honoraria from Biosense Webster. TPA received research grants from São Paulo Research Foundation (FAPESP, Brazil, N. 2017/00319-8 and N. 2018/02251-4). DCS received support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil, N. 449467/2014-7 and N. 305616/2016-1). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Address for correspondence:

Dr. Tiago Paggi de Almeida,
Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital
Leicester LE3 9QP
Email: tiagopaggi@gmail.com
Tel: +44 (0)116 250 2438 / Fax: +44 (0)116 287 5792

Total number of words of the letter: 445 (excluding references)

To the Editor,

We read with great interest the study by Baher and colleagues.[1] Their work helps to consolidate the use of recurrence quantification analysis (RQA) in the investigation of cardiac dynamics during atrial fibrillation (AF). It also motivates further discussion on creative methods and biomarkers for studying such complex cardiac disorder.

As clearly pointed out by the editorial-invited perspective from Roney and Bishop[2], the multiple definitions of complex fractionated atrial electrograms (CFAEs) represent an important hurdle for the identification of atrial substrate. We have recently shown that CFAE target identification to guide radiofrequency ablation is dependent on the system used and settings applied.[3] Each system measures different aspects of the atrial electrograms (AEGs) to characterize the atrial substrate during AF. These factors induce inconsistencies and make the reproducibility of the AEG classification difficult. Using revised settings that minimize the differences in CFAE classification performed by individual system can decrease methodological heterogeneities and facilitate comparisons of CFAE mapping among different studies.

The authors should also be commended for integrating *in-silico* and *in-vivo* models in their study, which certainly provides further details on the underlying AF electrophysiology.[1] In the clinical arm of the investigation, a smaller portion of the patients (41%) was identified with persistent AF. Additionally, pulmonary vein isolation (PVI) terminated AF in all cases, which, despite intense debate, is challenging in persistent AF patients.[4] Finally, the underlying electrophysiology of CFAEs is remarkably different between paroxysmal and persistent AF, which might hinder a proper definition of active and passive CFAEs, even following AF termination.[5] These differences should be addressed using the method proposed by the authors. We have recently used RQA to investigate the effect of PVI on the underlying dynamics of persistent AF in 18 patients.[6] Although ablation with PVI did not terminate AF, our results show that the RQA variables were significantly affected by PVI, and that the variables were effective in discriminating CFAE *vs.* normal AEGs. On other work, we investigated changes in CFAE distribution induced by PVI in the same cohort.[7] Our results suggest that some atrial regions are

impervious to PVI, while others are affected by it. Nearly half of the atrial regions classified as CFAE at baseline continued as CFAE after PVI. These could represent atrial regions important in AF perpetuation, as they appear to be anchored in the atria and persisted after PVI.

Baher and colleagues should be praised for their work.[1] RQA is a versatile and compelling method that will certainly help improving our comprehension on the underlying dynamics of AF. Their method should be further explored in other cohorts – both *in-silico* and *in-vivo* – to study different underlying dynamics and electrophysiological mechanisms that participate in AF perpetuation.

References

1. Baher A, Buck B, Fanarjian M, et al. Recurrence quantification analysis of complex-fractionated electrograms differentiates active and passive sites during atrial fibrillation. *J Cardiovasc Electrophysiol.* 2019.

2. Roney CH, Bishop MJ. Preventing recurrence through analysing recurrence. *J Cardiovasc Electrophysiol.* 2019:1-3.

3. Almeida TP, Chu GS, Salinet JL, et al. Minimizing discordances in automated classification of fractionated electrograms in human persistent atrial fibrillation. *Med Biol Eng Comput.* 2016;54(11):1695-1706.

4. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med.* 2015;372(19):1812-1822.

5. Parkash R, Tang AS, Sapp JL, Wells G. Approach to the catheter ablation technique of paroxysmal and persistent atrial fibrillation: a meta-analysis of the randomized controlled trials. *J Cardiovasc Electrophysiol.* 2011;22(7):729-738.

6. Almeida TP, Schlindwein FS, Salinet JL, et al. Characterization of human persistent atrial fibrillation electrograms using recurrence quantification analysis. *Chaos.* 2018;28(8):085710-085711-085710-085712.

7. Almeida TP, Chu GS, Li X, et al. Atrial Electrogram Fractionation Distribution before and after Pulmonary Vein Isolation in Human Persistent Atrial Fibrillation—A Retrospective Multivariate Statistical Analysis. *Frontiers in physiology.* 2017;8(589).