Different Definitions of Complex Fractionated Atrial Electrograms do not Concur with the Clinical Perspective

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Abstract

Complex fractionated atrial electrograms (CFAEs) have been suggested as potential targets for ablation for persistent atrial fibrillation (AF), but there is no consensus on their definition. This study aimed to quantify the impact of different CFAE definitions on automated CFAE detection based on NavX criteria, and compare them with visual assessment. Baseline and post pulmonary vein isolation continuously-recorded bipolar electrograms obtained using a decapolar catheter placed into the coronary sinus from six persistent AF patients were analysed using different time-windows. Automatic CFAE detection algorithm based on selected negative deflections was developed. Three different CFAE definitions, as described in the literature, were evaluated, and electrograms were labelled as fractionated or non-fractionated according to each definition. Fractionation interval and $CFAE_{mean}$ *were assessed based on each definition, followed by a blinded visual inspection of a clinician. The results show that the electrogram window size did not change overall* $CFAE_{mean}$*. However, different CFAE definitions impacted fractionation significantly on both pre-/post-ablation groups. If automated algorithms are to be used in clinical practice, differences in CFAE definitions might have significant impact on CFAEs quantification.*

1. Introduction

Ectopic activities in the vicinity of the pulmonary veins (PVs) have been proven to be important sites responsible for triggering atrial fibrillation (AF) in patients with paroxysmal AF [1], while atrial substrate remodelling is believed to be responsible for maintaining AF in patients with persistent AF [2]. Regions of the atria demonstrating complex fractionated activation have been suggested to represent remodelled atrial substrate, and hence to be important sites for ablation in patients with persistent AF [3]. Different definitions have been proposed to measure complex fractionated atrial electrograms (CFAEs) [4]. However, the lack of consensus among definitions and the subjectivity of the proposed techniques might affect the identification of CFAEs and the ablation strategies [4]. As a consequence, the reproducibility of the success rate during ablation guided by CFAEs in AF is low [3, 5].

CFAEs were initially described as being [3]: 1) Atrial electrograms (EGMs) that have fractionated activation composed of two deflections or more, and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-s recording period; 2) Atrial EGMs with a very short cycle length (120 ms) averaged over a 10-s recording period. Different CFAEs algorithms have been proposed to integrate 3-D electro-anatomical mapping systems to help ablation guided by CFAEs, one being the EnSite NavX (St. Jude Medical, St. Paul, MN, USA), based on selected negative deflections (-dV/dt) [6]. The selection of such deflections relies on parameters (e.g. refractory period, deflection duration, peak-to-peak voltage amplitude) that can be altered by the clinician. In the attempt to optimise CFAEs mapping, research centres have considered different settings for the current parameters (Table 1). Different definitions might affect CFAEs quantification, which would justify the low reproducibility of CFAEs guided ablation outcomes.

Table 1. Different CFAE definitions assessed.

Definitions	Parameters	
	Amplitude Peak-to-peak (mV)	Cycle Length (ms)
Definition 1[3]	≤ 0.15	≤ 120
Definition 2[7]	0.05 – 0.5	30 – 120
Definition 3[8]	0.06 – 0.25	50 – 120

In the present work, we investigated how different CFAE definitions within NavX criteria affect fractionation. Three different CFAE definitions [3, 7, 8] were evaluated in continuously-recorded EGMs. EGM segments were labelled as fractionated or non-fractionated according to each definition, followed by a blinded visual inspection performed by a clinician.

2. Methods

2.1. Clinical Procedure

Six persistent AF [9] patients undergoing catheter ablation were enrolled in this study. A decapolar catheter placed into the coronary sinus (CS) continuously recorded up to 50 s of atrial EGMs for offline analysis. Bipolar EGMs were collected for both pre- and post-PV isolation, band pass filtered in 30-250 Hz and notch filtered in 50 Hz. EGMs from leads CS1-2 and CS3-4 were removed from the analyses due to common far-field interference from ventricular activation. The EGMs were segmented and analysed over three different time-windows: 2.5 s, 5 s and 8s.

2.2. NavX Criteria

NavX algorithm is a time interval based algorithm developed by St. Jude Medical to quantify CFAEs in EGM. NavX provides online automated identification and electro-anatomical display of CFAE based on $CFAE_{mean}$. $CFAE_{mean}$ is defined as the average time between fractionation intervals (FIs). FIs are time intervals between consecutive discrete selected negative deflections (-dV/dt) inside a specific EGM time-window set by the user (from 1 s to 8 s) [6]. The negative deflections must meet three criteria, adjustable by the user, in order to be marked [10]: exceed a peak-to-peak threshold greater than the baseline noise; time duration smaller than a threshold to avoid detection of broad ventricular far-field events; exceed a refractory period after the previous marked deflection to minimise multiple detections of a single deflection.

A script based on NavX criteria was developed in MATLAB, as illustrated on Figure 1. Initially, the negative derivative (-dV/dt) of the EGM (Figure 1a) was calculated (Figure 1b). The beginning and the end of a negative deflection were marked, and the duration of the deflection was assessed and compared with a time threshold to avoid detection of broad ventricular far-field event (Figure 1b). Similarly, the peak-to-peak voltage value of the deflection was evaluated (Figure 1c). If the peak-to-peak value was smaller than a voltage threshold set by the user, the deflection was disregarded. If the deflection met these two criteria, the instant of maximum-negative slope within the deflection was marked (Figure 1c). The time between subsequent marked deflections was found and, if it was smaller than a refractory period set by the user, the second deflection was disregarded (Figure 1d). The remaining selected deflections were used to compute the FIs and, consequently, the $CFAE_{mean}$ within a time-window.

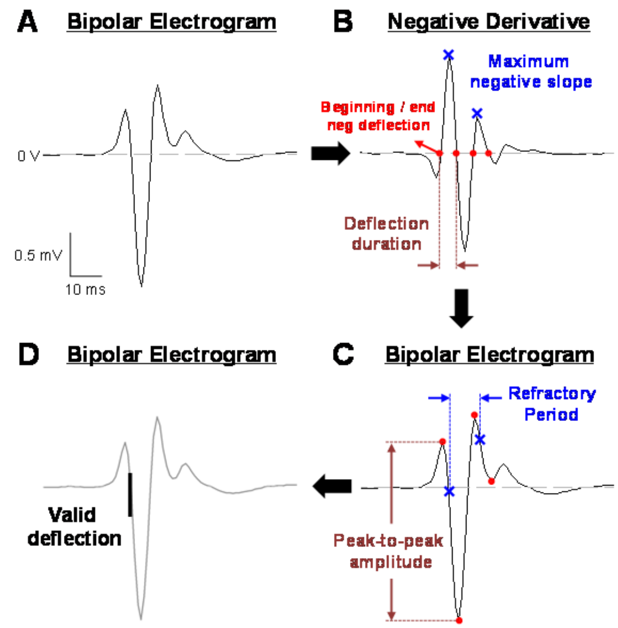

Figure 1. Illustration of script based on NavX criteria evaluated in MATLAB. a) Electrogram segment to be analysed; b) negative derivative (-dV/dt) of the electrogram. The beginning and end of negative deflections are annotated. The deflections durations and the time instant of maximum negative slope are marked; c) the beginning and end of negative deflections and time instant of maximum negative slope are projected back to the electrogram. The peak-to-peak of the deflection is measured and the refractory period is taken into account; d) if the maximum negative deflection meets three criteria adjustable by the user (refractory period, deflection duration, peak-to-peak voltage amplitude), the deflection is marked as a valid deflection.

2.3. CFAE Definitions

Once the valid deflections were marked, the time intervals between these deflections were identified, here referred as FI. Afterwards, the mean FI within an EGM time-window was computed and referred to as $CFAE_{mean}$. Three different CFAE definitions were evaluated (Table 1). Accordingly, an EGM time-window was considered fractionated if the $CFAE_{mean}$ for that time-window was within the following range:

- Definition 1: $CFAE_{mean} \leq 120$ ms;
- Definition 2: 30 ms $\leq CFAE_{mean} \leq 120$ ms;
- Definition 3: 50 ms $\leq CFAE_{mean} \leq 120$ ms.

2.4. Study Organization

Mean $CFAE_{mean}$ (±SD) was detected according to each distinct definition. $CFAE_{mean}$ was compared pre- and post-ablation, in a total of 36 EGMs divided in segments of 2.5 s, 5 s and 8 s, providing a total of 720, 360 and 216 time-windows, respectively. For each time-window, EGM segments were labelled as fractionated or non-fractionated according to the $CFAE_{mean}$ thresholds for each definition.

Additionally, the CFAEs automatic classifications were compared with the visual inspection performed by a clinician. An ‘error (%)’ was quantified based on the disagreement between the clinician inspection and the labels from each definition and time-windows.

Statistical differences between distributions from different definitions were assessed by Kruskal-Wallis test. The level of statistical significance was set at a $P<0.05$.

3. Results

Figure 2 (left) highlights the differences between CFAE detections from the marked deflections identified by the different definitions in 300 ms of an EGM segment, with each respective $CFAE_{mean}$ for this particular small time-window. Figure 2 (right) shows the FI distributions found by each CFAE definition for pre-ablation EGMs of one patient, segmented in time-windows of 2.5 s. FI distributions differed significantly between the three definitions ($P\leq0.0001$).

Figure 3 shows the mean (±SD) of the $CFAE_{mean}$ both pre-/post-ablation EGMs of the entire population using different time-windows (2.5 s, 5 s and 8 s).

There was no significant difference on $CFAE_{mean}$ between different time-windows within the same definition (P = NS). However $CFAE_{mean}$ differed significantly between different definitions ($P\leq0.0001$) and pre-/post-ablation ($P\leq0.0001$).

Figure 4 assesses the agreement between CFAE definitions and a clinical perspective of fractionation. Accordingly, definition 1 disagreed in 58.43 (± 6.554) % in average, 43.23 (± 5.625) % in definition 2 and 38.18 (± 8.689) % in definition 3.

4. Discussion and conclusions

The results indicated that PV isolation significantly increased $CFAE_{mean}$ for the three definitions (Figure 3), supporting the evidence that PVs play an important role in triggering or maintaining AF [1]. The results also suggested that different CFAE definitions annotated different negative deflections (Figure 2), affecting the FI distribution and, consequently, $CFAE_{mean}$ (Figure 3). Therefore, the results evidenced that $CFAE_{mean}$ is highly dependent on the chosen CFAE definition. Accordingly, different CFAE definitions will quantify CFAEs differently, which might have an impact in the outcome of CFAE guided ablation procedures. For instance, Nademanee and colleagues [3] reported that AF terminated in 91% of the cases after CFAE guided ablation, with CFAEs defined according definition 1; Verma *et al.* [7] reported that AF terminated in 54% of the cases after CFAEs guided ablation, with CFAEs defined according definition 2.

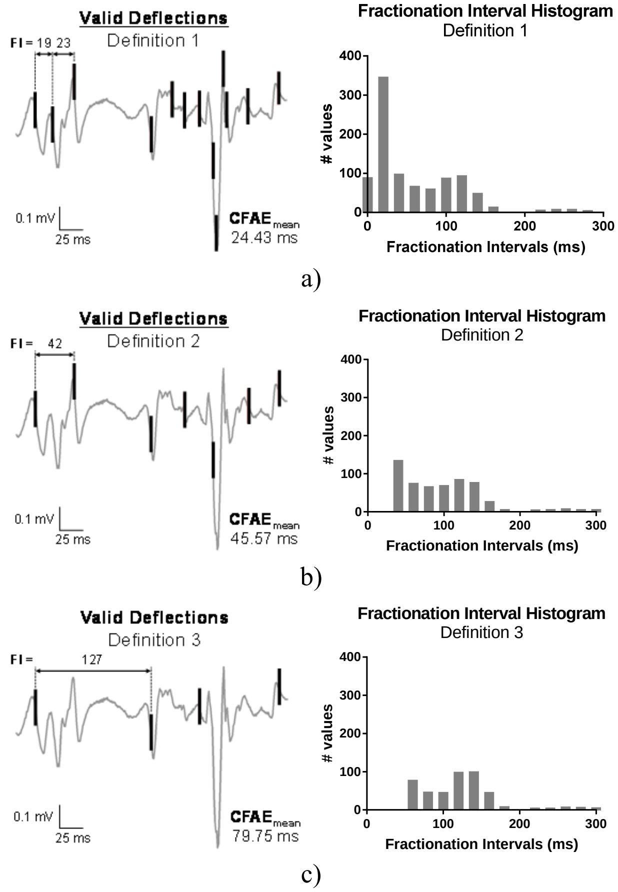

Figure 2. Valid deflections during 300 ms electrogram segment with the respective $CFAE_{mean}$ (left) and selected marked fractionation intervals (FI) in milliseconds (ms), and the FI distribution for one patient considering 2.5 s time-windows (right). a) Definition 1; b) Definition 2; c) Definition 3.

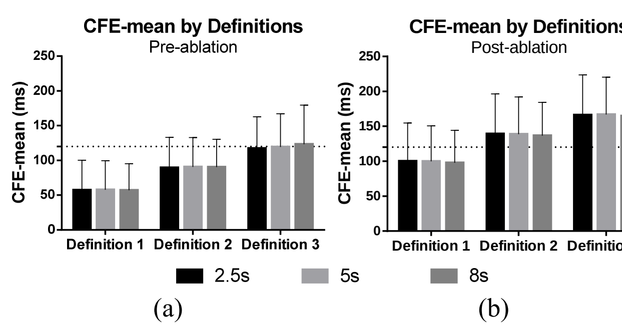

Figure 3. Mean (±SD) $CFAE_{mean}$ according each CFAE definition and different time-windows (a) pre- and (b) post-ablation.

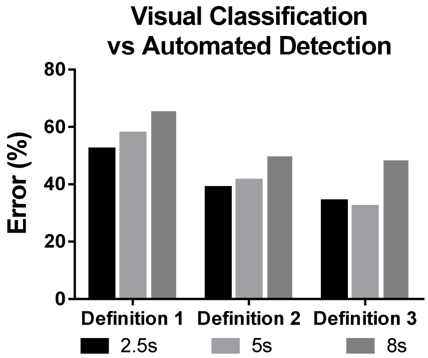

Figure 4. Percentage error calculated from the comparison between automated CFAE detection algorithm with different parameters and clinical perspective.

The size of the time-window (2.5 s, 5 s and 8 s) had little influence on $CFAE_{mean}$ either in baseline or after PV isolation (Figure 3), differently from what has been suggested in previous studies [6]. The fact that definition 1 [3] does not consider a refractory period had a profound impact on $CFAE_{mean}$ and should be avoided. However, one should keep in mind that the study performed by Nademanee *et al.* was pioneering in CFAEs [3].

Figure 4 shows an overall lack of agreement between the different CFAE definitions on the automated algorithm and the clinical perspective of CFAEs, suggesting that automated CFAE detection systems must be used with caution. However, automated software for CFAE detection is important in the clinical practice, providing significant information to support the expertise of the clinician.

In conclusion, different CFAE definitions used in automated CFAE algorithms might have profound impact on CFAE quantification. Additionally, CFAE quantification by automated software might not reproduce the clinical perspective of fractionation. Consequently, although automated CFAEs detection systems provide further details during ablation procedures, the clinician expertise remains of main importance during CFAE-based ablation.

Acknowledgements

The work described in this paper is part of the research portfolio supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, UK. Financial support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil, Grant. N. 200251/2012-0, TPA; Grant. N. 200598/2009-0, JLSJr).

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