THE SPATIO-TEMPORAL BEHAVIOR OF ATRIAL ELECTROGRAM FRACTIONATION IN PERSISTENT ATRIAL FIBRILLATION

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Abstract: The temporal behavior of atrial electrograms (AEGs) during persistent atrial fibrillation (persAF) remains poorly understood. In the present work, we investigated the temporal behavior of consecutive AEGs and the consistency of complex fractionated atrial electrograms (CFAEs) with the CARTO (Biosense Webster) criterion. 797 bipolar AEGs were exported from NavX (St. Jude Medical) with three segment lengths (2.5 s, 5 s and 8 s) from 18 patients undergoing persAF ablation. Three 2.5 s consecutive segments were created from the 8 s AEGs. CFAE classification was applied offline to all cases following the CARTO criterion. CFAEs were defined as AEGs with the interval confidence level (ICL) ≥4. Moderate correlation was found in AEG classification between the consecutive segments (segment 1 vs 2: Spearman's correlation ρ=0.74, Kappa score κ=0.62; segment 1 vs 3: ρ=0.72; κ=0.62; segment 2 vs 3: ρ=0.75; κ=0.68), resulting in different CFAE maps. AEGs with 5 s generated AEG classification more similar to 8 s (ρ=0.96; κ=0.87) than 2.5 s vs 5 s (ρ=0.93; κ=0.84) and 2.5 s vs 8 s (ρ=0.90; κ=0.78). The results suggest that consecutive 2.5 s AEGs resulted in different ablation target identification, which would affect the ablation strategy and contribute to the conflicting outcomes in AEG-guided ablation of persAF. CARTO criterion should be revisited in clinic and consider AEGs with longer duration for consistent CFAE classification in persAF.

Keywords: Atrial fibrillation, fractionation, catheter ablation, electrophysiology mapping, stability.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia found in clinical practice. Although pulmonary vein isolation (PVI) has been proved effective in treating patients with paroxysmal AF, the identification of critical areas for successful ablation in patients with persistent AF (persAF) remains a challenge due to an incomplete understanding of the mechanistic interaction between relevant atrial substrate and the initiation and maintenance of AF [1]. Atrial electrograms (AEGs) with low amplitude and multiple activations were thought to represent such atrial substrate, with structural and electric remodeling induced by sustained AF. Complex fractionated atrial electrograms (CFAEs) have been introduced as markers of such atrial sites and, therefore, targets for ablation [2]. CFAE-guided ablation has become broadly used as an adjunctive therapy to PVI for persAF, however the low reproducibility of outcomes and recent evidences that ablation additional to PVI does not improve the ablation outcome motivated intense debate whether CFAEs truly represent AF drivers [3].

The complex spatio-temporal dynamics of the underlying mechanisms of AF are still not fully understood, and that might be one of the reasons for the inconsistency in ablation outcomes in persAF patients [4]. Previous works have suggested that CFAEs have a high degree of spatial and temporal stability [5-8], and others suggested that the assessment of AEG fractionation requires a recording duration of 5 s at each site to obtain a consistent fractionation [9-11]. In the present study, we investigated the spatio-temporal behavior of AEGs considering consecutive AEGs with 2.5 s – as currently used by some systems – and also to investigate the consistency of AEG fractionation using different AEG segment durations.

Materials and methods

Electrophysiological Study – The population consisted of 18 patients (16 male; mean age 56.1 ± 9.3 years; history of AF 67.2 ± 45.6 months) referred to our institution for first time catheter ablation of persAF. Details of the clinical characteristics of the study subjects have been provided elsewhere [12]. All patients were in AF at the start of the procedure. Study approval was obtained from the local ethics committee (REC Reference 13/EM/0227) and all procedures were performed with full informed consent.

All antiarrhythmic drugs, except amiodarone, were discontinued for at least 5 half-lives before the start of the procedure. Details of the mapping procedure have been described previously [12]. Briefly, 3D LA geometry was created within Ensite NavX^{TM} (St. Jude Medical, St. Paul, Minnesota) [13] using a deflectable, variable loop circular pulmonary vein (PV) mapping catheter (Inquiry Optima, St. Jude Medical). PVI was performed with a point-by-point wide area circumferential ablation approach, followed by the creation of a single roof line (Cool Path Duo irrigated RF catheter, St. Jude Medical). No additional ablation targeting CFAE was performed in this study. Sequential point-by-point bipolar AEGs were collected from 15 pre-determined atrial regions before and after LA ablation [12]. All patients were in AF before and after ablation during signal collection.

Signal analysis – A total of 797 AEGs were recorded from the LA, 455 before and 342 after PVI, with a sampling frequency of 1200 Hz, and band-pass filtered within 30–300 Hz.

Each AEG was exported from NavX with three segment lengths (2.5 s, 5 s and 8 s). A validated offline MATLAB algorithm was used to compute the interval confidence level (ICL), the average complex interval (ACI) and the shortest complex interval (SCI) according the CARTO (Biosense Webster, Diamond Bar, California) criteria for CFAE classification for all AEGs [14]. ICL ≥ 4 was considered for CFAE detection [14].

Temporal consistency of AEG fractionation with different segment lengths – CFAE classifications performed in AEGs with different segment lengths have been analyzed to investigate the temporal consistency of AEG fractionation. ICL, ACI and SCI were measured for 2.5 s, 5 s and 8 s segments. Currently, ICL thresholding for CFAE classification as defined by CARTO is referred to a default 2.5 s segment length (ICL ≥ 4). Hence, there is no validated ICL threshold for CFAE classification using segment lengths longer than 2.5 s. Therefore, ICL calculated for the 5 s segment lengths was normalized by a factor of 2, while ICL calculated for the 8 s segments was normalized by 3.2 in order to make them comparable. Bland-Altman plots were created to assess the average difference (bias) from the three indices measured with the different segment lengths.

Temporal behavior of consecutive AEGs – Consecutive AEG segments were assessed to infer about AEG temporal behavior. For each AEG, the 8 s segments were divided in three consecutive 2.5 s segments, as illustrated in Figure 1B, accordingly: 0 to 2.5 s; 2.5 s to 5 s; 5 s to 7.5 s. Therefore, three consecutive segments with 2.5 s length were created for each one of the 797 AEGs, allowing the investigation of the temporal behavior in the same points. ICL, ACI and SCI were measured for each segment, and each segment was compared to the other. A best fit exponential was computed to estimate the time constant of stable AEGs according to Graphpad Prism 6's One Phase Decay best fit (©2014 GraphPad Software, La Jolla, California).

Statistical Analysis – Nonparametric paired multiple data were analyzed using the Friedman test with Dunn's correction. Spearman's correlation (ρ) was calculated to quantify the correlation between AEG classifications measured with different segment lengths (2.5 s, 5 s and 8 s), and the correlation between AEG classifications was measured within the three consecutive segments. The agreement of CFAE classification performed by ICL – either measured with different segment lengths (2.5 s, 5 s and 8 s) or within the three consecutive segments – was assessed by the Cohen's kappa (κ) score [15]. A Kappa score within range $0 \leq \kappa < 0.4$ suggests marginal agreement between two indices; $0.4 \leq \kappa \leq 0.75$ good agreement and; $\kappa > 0.75$ excellent agreement [15]. P-values of less than 0.05 were considered statistically significant.

Results

Temporal behavior of consecutive AEGs – Three types of AEGs were identified when investigating the consecutive segments, as illustrated in Figure 1A: 'stable CFAEs' as AEGs with ICL ≥ 4 in all assessed segments; 'stable non-CFAEs' as AEGs with ICL < 4 in all assessed segments and; 'unstable AEG' as AEGs with ICL varying to and from ICL ≥ 4 to ICL < 4 within the assessed segments. Each AEG segment also affect the resulting CFAE map as generated by ICL (Figure 1B), ACI and SCI (maps for both ACI and SCI omitted). Moderate correlation was found in the AEG classification performed by ICL, ACI and SCI, measured in consecutive segments. The correlation for ICL, ACI and SCI are shown on Table 1, as well as the agreement of CFAE classification performed by ICL between segments. The temporal behavior of CFAE classification within the three consecutive segments for each collected point is shown on Figure 2A. When comparing segment 1 versus 2, 47% of the total AEGs were labelled as stable CFAEs, while 35% were stable non-CFAEs, and 18% AEGs were unstable (Figure 2B). When comparing segment 2 versus 3, 49% of the total AEGs were labelled as stable CFAEs, 35% were stable non-CFAEs, and 16% AEGs were unstable. A total of 43% AEGs were stable CFAEs within the three segments, 30% were stable non-CFAEs and 27% were unstable. The temporal change of stable AEGs (CFAEs and non-CAFE) has been assessed (Figure 2C). In the first 2.5 s segment, all AEGs were considered stable since it was the first classification (797 AEGs). On segment 2, a total of 151 AEGs were classified as unstable, with 646 AEGs remaining stable. On the last segment, 62 additional AEGs changed their classification, with 584 remaining stable. An exponential best fit suggests a time constant (τ) of 2.8 s.

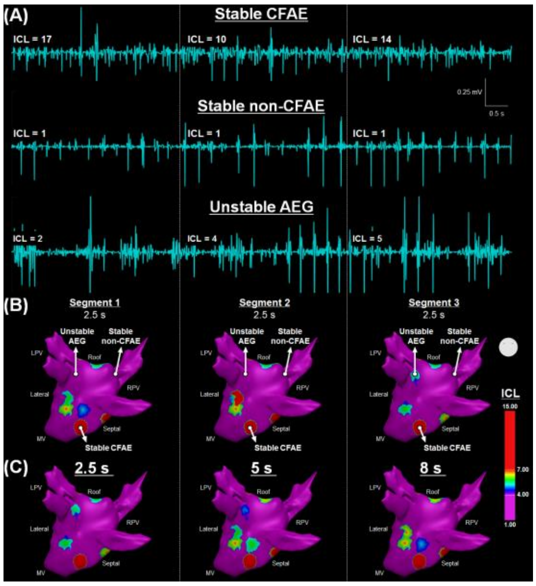

Figure 1: (A) The different types of AEGs from the consecutive segments. LA maps based on consecutive AEG segments (B) and different segment lengths (C).

Table 1: Spearman's correlation for ICL, ACI and SCI, and the Kappa score for the CFAE classification performed by ICL measured from the consecutive 2.5 s segments.

2.5 s segments	1 v 2	1 v 3	2 v 3	P value
Spearman's correlation (ρ)	0.74	0.73	0.75	<0.0001
	0.46	0.43	0.42	<0.0001
	0.55	0.52	0.57	<0.0001
Kappa score (κ)	0.61	0.62	0.68	<0.0001

Temporal consistency of AEG fractionation with different segment lengths – ICL measured with 2.5 s was significantly different than with 8 s (Figure 3A). The bias calculated from the Bland-Altman plots suggests a smaller average difference between ICL calculated with 5 s and 8 s when compared with the other segment lengths (2.5 s vs 5 s and 2.5 s vs 8 s, Figure 3B).

Different segment lengths had little influence on ACI, but significantly affected SCI (Figure 3A). The Bland-Altman plots also suggest smaller average difference between 5 s and 8 s for both ACI and SCI.

The AEGs with 5 s generated more similar AEG classification compared to 8 s (Table 2). Figure 1C illustrates the AEG classification map for ICL with different AEG durations.

Discussion

Despite much effort to understand atrial substrate properties during persAF, the dynamic nature of some AEGs continues challenging for electrophysiologists in search of critical sites for ablation [4].

The temporal behavior of AEGs during persAF – Previous works have suggested that CFAEs demonstrate a high degree of spatial and temporal stability by analyzing consecutive CFAE maps where the AEGs for each map are collected in different time instants [5-8]. Our results, however, suggest that ablation target identification using the CARTO criterion is dependent on the time instant that the AEGs are collected. Some AEGs have unstable temporal behavior, switching from fractionated to non-fractionated depending on the moment it is collected. This would affect the resulting CFAE map and, therefore, both ablation strategy and outcomes. Considering that the atrial substrate is anchored and should host "stable" fractionated activity, atrial regions represented by unstable AEGs should not be targeted during ablation as they might be a result of passive wave collision from distant AF drivers and, therefore, not a true representation of atrial substrate [12]. Ablation of those regions might create areas of slow or anisotropic conduction, thereby creating more pro-arrhythmogenic areas which would perpetuate the arrhythmia instead of organizing or terminating it [16].

The AEG Duration for Atrial Substrate Assessment – Previous work has investigated different segment lengths to consistently characterize CFAEs using NavX, since this system allows for different AEG duration recordings (1 s to 8 s) [9,10].

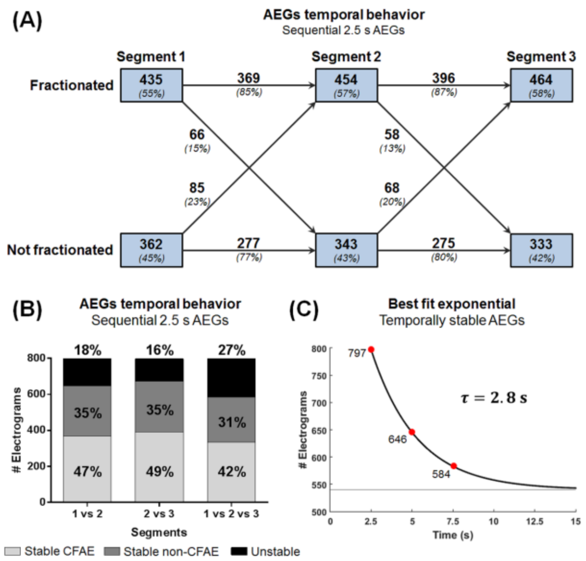

Figure 2: (A) The temporal behavior of CFAE classification within the three consecutive AEG segments with 2.5 s duration each. (B) CFAE classifications and AEG temporal behavior in all segments were mutually compared. (C) The temporal decay of stable AEGs.

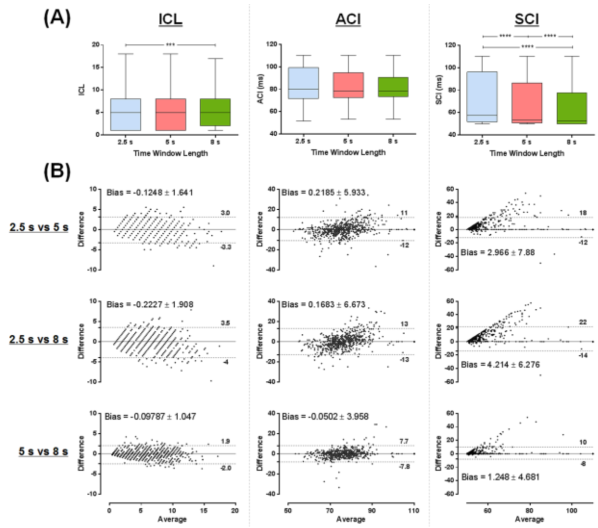

Figure 3: (A) The ICL, ACI and SCI measured with 2.5 s, 5 s and 8 s. B. Bland-Altman plots for ICL, ACI and SCI measured with 2.5 s, 5 s and 8-s. **** P<0.0001; *** P<0.001.

Table 2: Spearman's correlation for ICL, ACI and SCI, and the Kappa score for the CFAE classification performed by ICL measured from the different segment lengths (2.5 s, 5 s and 8 s).

AEG durations	2.5 v 5	2.5 v 8	5 v 8	P value
Spearman's correlation (ρ)	0.93	0.90	0.96	<0.0001
	0.89	0.85	0.93	<0.0001
	0.87	0.82	0.92	<0.0001
Kappa score (κ)	0.84	0.78	0.87	<0.0001

These data suggest AEG duration of 5 s or longer to consistently measure CFAEs using NavX algorithm. As CARTO inherently limits the AEG collection to 2.5 s, few studies accomplished an investigation for the 'best' segment length to assess fractionation, suggesting that 5 s or longer should be considered for proper AEG classification.[11]

Our results suggest that AEG duration of 2.5 s might not be sufficient to measure CFAEs consistently using CARTO criterion. If CFAEs were temporally consistent, it would be expected for the recording duration to have little influence in the CFAE classification and, ultimately, the CFAE map created with CARTO criterion measured with 2.5 s should not differ from maps created using 5 s or 8 s. Our results, however, suggest that longer segment lengths produce more consistent CFAE maps. Therefore, CARTO criterion should be revisited to consider recording durations longer than 2.5 s to measure AEG fractionation.

Conclusion

This study investigated the temporal behavior of AEGs collected during persAF and the temporal consistency of fractionation considering different AEG segment lengths. Three types of AEGs have been described by investigating consecutive AEGs: stable CFAEs, stable non-CFAEs and unstable AEGs. Consecutive 2.5 s AEGs resulted in different ablation target identification, and that would affect the ablation strategy and contribute to the conflicting outcomes in AEG-guided ablation in persAF. CARTO criterion should be revisited in clinic and consider AEGs with longer duration than 2.5 s for consistent CFAE detection in persAF.

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