NONLINEARITY CHARACTERIZATION AND ENTROPY ANALYSIS OF INTRACARDIAC ATRIAL ELECTROGRAM SIGNALS

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Abstract: *The main objective of this paper is to identify evidences of nonlinear components in persistent atrial fibrillation electrograms (persAF). Firstly, an exploratory data analysis using linear approaches (autocorrelation and spectral analysis) was performed to assess the behaviour of the AF electrograms. Secondly, a nonlinear characterization using surrogate data analysis was performed with a complementary return map comparison. Finally, Approximate Entropy (ApEn) was considered as an analysis tool of system complexity to measure disorganization over time for different AF behaviours. From our results, (1) we identified strong evidence of nonlinear components negating the null hypothesis, (2) lower ApEn values were associated with organized and periodic AF activations and higher entropy values were associated with the increase of electrogram complexity and (3) ApEn response of longer window segments showed a general AF behaviour while shorter windows (1s and 2s) help identifying dynamical atrium electrical changes.*

Keywords: *atrial fibrillation, nonlinear component signals, contact mapping.*

Introduction

AF is characterized by very fast uncoordinated atrial activation with serious consequence on the atrial mechanical function. Its presence, especially in long-term (persAF), promotes pronounced electrical and structural atrial substrate remodelling and atrium enlargement with fibrosis [1], therefore contributing for its recurrence [2]. Simultaneous mechanisms are primarily responsible for persAF (focal triggers and multiple re-entrant wavelets), and the treatment via ablation is still a challenging subject, in particular the problem of locating sites for successful ablation [1].

Diagnose and characterization of the underlying AF substrate through the measurement of local electrical activations contributes to the understanding of AF mechanisms, trigger areas and AF paths of propagation. Clinical studies have concentrated their efforts basically on Fourier analysis of the atrial electrograms (tracking dominant frequency), complex fractionated electrograms (CFE) and complex sinus rhythm electrograms [3-5].

The use of linear modelling techniques employed in the majority of AF studies neglects the possible presence of nonlinear components [6], which may have a clinical impact. Recently, nonlinear analysis (dimension and entropy correlation) of the epicardial AF signals was applied showing evidence of an underlying non-linear mechanism for different types of AF [7]. In addition, nonlinear spatiotemporal interactions and changing characteristics of nonlinear parameters were observed by Mainardi *et al.* [8] and Censi *et al.* [9].

In this study we first aimed to perform an exploratory data analysis (EDA) using linear techniques to assess the behaviour of the AF electrograms. For this analysis we hypothesized that AF signals may present well defined periodic activation components (such as a marked dominant frequency) or complex fractionated electrical activations (several frequency components). The EDA was based on the autocorrelation function (ACF) and spectral analysis. The ACF response allows identifying periodic patterns or non-randomness in the data [10] and its first zero crossing reflects the decorrelation time scale of the signal. Spectral analysis is a complementary tool used to identify the frequency components of AF signals with periodic activations components. Secondly, we aimed to expand the analysis by performing a nonlinear characterization using surrogate data analysis and return maps of raw and surrogate signals to highlight the possible presence of nonlinearity. Finally, we applied a nonlinear metric, Approximate Entropy (ApEn), as an analysis tool of system complexity to measure disorganization for different AF behaviours.

Methods

Signals were recorded simultaneously over 30s by five bipolar contact electrodes on a decapolar catheter placed on the coronary sinus (CS) from 10 patients who had persistent AF. Bipolar atrial electrograms were sampled at 1 kHz and band-pass filtered between 30 Hz and 250 Hz resulting signals containing mainly components of local electrograms depolarization [11].

Exploratory Data Analysis (EDA) – the linear characteristics of the AF electrograms were obtained using Autocorrelation Function (ACF) and Spectral Analysis.

Autocorrelation Function (ACF): the ACF is defined according to Eq. 1 and measures how strong is the similarity, on average, of a time series with itself at delay lag τ [10, 12]. Varying the delay (τ = T, 2T, …, mT, where T is the sampling period) is useful to evaluate the randomness, periodicity and the amount of memory present in a data set.

$$ACF(\tau) = \mathrm{E}[f(t)*f(t-\tau)] \quad (1)$$

Spectral Analysis: power spectrum analysis was performed for each individual site using the fast Fourier transform (FFT) with an antileakage hamming window and zero padding. The signals were split into windows of 1s, 2s, 4s, 7s, 10s, 15s and 30s.

Nonlinear Characterization – as part of nonlinearity characterization, surrogate data analysis method and return map evaluations were performed [13-14]. Approximate Entropy (ApEn) was the nonlinear metric used to test the null hypothesis and measure the complexity behaviour.

A useful method for nonlinear characterization of time series is using a set of surrogate data. The electrograms (original time series, $f(t)$) were converted to the frequency domain and their phase was randomly shuffled without changing the spectrum amplitude. Inverse Fourier transform was then applied in the "modified" signals returning them to the time domain, resulting in a "new" signal, called 'surrogate' (surrogate time series, $g(t)$). Two linear metrics of both signals, their two first statistical moments, the mean and the variance, are obtained and it is assumed that the phase mixing process does not change these metrics [13].

The Approximate Entropy (ApEn) is considered a nonlinear metric [14] for the null hypothesis H_0 given by

$$ApEn[f(t)] = ApEn[g(t)] \quad (2)$$

where $ApEn[f(t)]$ and $ApEn[g(t)]$ are respectively the Approximate Entropy of $f(t)$ and of $g(t)$.

In this analysis, if H_0 is rejected then the existence of nonlinear components should be considered.

A graphic exploratory data analysis can be also done with the time delay embedding plot, or return map, for the original and the surrogate data, i.e., the trace of $f(t)$ versus $f(t+\tau)$, where $\tau = T$. Since both series have the same linear statistical properties, the differences in shape when comparing both plots can be classified as being due to the influence of nonlinear components [15].

The ApEn of an atrial electrograms $S(t)$ is the negative natural logarithm of the probability that two similar sequences of m points remain similar at the next point (equation 5) [14, 16]. Low entropy values indicate low complexity in the time series. Two entropy input parameters must be defined: m is the length of a subset of S_i and r is a similarity criterion. Two subsets are considered similar if

$$\left|S_{i+k} - S_{j+k}\right| < r \quad (3)$$

for $0 < k < m$.

Consider P_m as the set of all patterns from S_N with length m. The relation $C_{i,m}(r)$ can now be defined by

$$C_{i,m}(r) = \frac{n_{i,m}(r)}{N-m+1} \quad (4)$$

where $n_{i,m}(r)$ is the number of patterns similar to $p_m(i)$ in P_m. The parameter $C_m(r)$ must be calculated as the average of all $C_{i,m}(r)$ for the entire P_m set. Finally, $ApEn(S_i,m,r)$ electrogram is shown below.

$$ApEn(S_i, m, r) = \ln \frac{C_m(r)}{C_{m+1}(r)} \quad (5)$$

For qualitative ApEn analysis, the first step is to determine the input parameters. This work considers $m = 2$ and $r = 0.2\sigma[S(t)]$, based on [14, 16]**.** It is also necessary to define an optimal subset length (window size) for entropy calculation which would not hide any short term or long term dynamics contained in the signal. The impact of ApEn response over different atrial window durations (1s, 2s, 4s and 7s) was also evaluated.

Results

ACF vs. Spectral analysis – two distinct ACF behaviours were identified (Fig. 1) and classified as: a well-defined periodicity and (2) non-periodic ACF, where no significant behaviour was identified and after an initial lag the ACF is usually close to zero.

In Fig. 1, the ACF plot (top) shows a periodic component with the first occurrence in τ=144 (fundamental) followed by τ=287 and τ=431 (fundamental periodicity of 0.1440 s or 6.95 Hz), which was quite close to the fundamental frequency (7.1 Hz). In Fig. 1(bottom), the ACF curve decays immediately crossing zero at lag 6 and then remaining close to a baseline. Its respective electrogram spectrum (not shown) is formed by multiple and unorganized frequency peaks showing lack of autocorrelation.

Surrogate data analysis - this work considers as a null hypothesis that the signal is formed basically by linear components and as a test for it, surrogate analysis was used to identify if there is evidence of the presence of nonlinear deterministic components. To verify this assumption, ApEn was then calculated over time (Fig 2a) in the same electrode positions and patients used in the return plot maps (Fig 2b-e). In figure 2(a) using different time windows. The round marks in black are referenced to the ApEn of the raw signals and the cross marks in grey to the surrogate signals. The results show that entropy values of raw and surrogate signals were totally divergent for all cases providing reason to reject the null hypothesis (Fig 2a). Raw signals had different entropy when compared with their correspondent surrogate signals, suggesting that nonlinear components were present in these signals. The differences between the raw and surrogate amplitude entropies for the entire

population was significant different (p value <0.005).

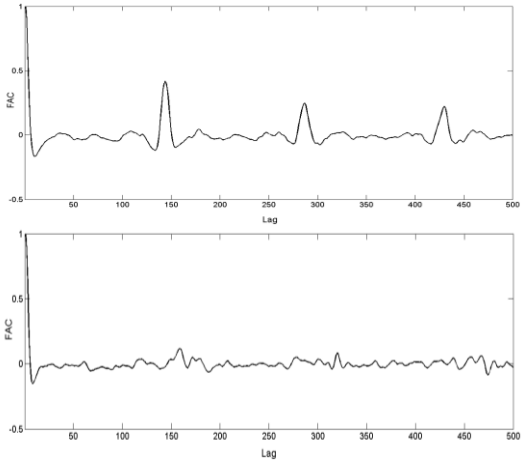

Fig. 1: Autocorrelation Function (ACF) for 7s atrial electrograms: periodic and non-periodic ACF.

For Fig. 2b return plots of raw electrograms and their surrogates are presented with segments sizes of 1s and 2s respectively. It can be seen from the maps that the raw signals had considerable changes when compared with their correspondent surrogate signals also giving reason to reject the null hypothesis. As consequence, it is appropriate to affirm that AF bipolar electrograms from persistent AF patients used in this study showed strong evidences of presence of nonlinear components.

Approximate Entropy Analysis - from our results, two different points can be highlighted: (1) the effect of the entropy value over organized or complex and electrograms atrium activations and (2) the effect of the window size choice over ApEn response.

Firstly, it was identified in Fig. 3 that lower ApEn values were associated with organized atrial activations (strong periodic component) and the increase of electrogram complexity (consequent loss of activation periodicity) reflected in higher entropy values. Figure 3a shows a single AF electrogram with organised atrium activations and the ApEn increased to 0.49 when other electrogram showed both organised and complex behaviours. Fig. 3c highlights that higher values of ApEn were intrinsically related with the increase of complexity or electrogram fractionation.

Moreover, a significant factor that influences entropy response is the selection of the electrograms' window size used to calculate the ApEn. With different windows, a single or multiple patterns can be considered. For example, segments with higher entropies (segment 6s from figure 4a and segment 17s from figure 4b) showed to have a smooth response with longer windows (longer than 4s. 7s window is not shown here), as expected. These results highlight that with the increase of the length of the window, the entropy values are associated with an overall AF behaviour response while shorter windows help to identify dynamical atrial electrical electrogram changes (1s and 2s).

Evaluating entropy analysis as a diagnostic tool for identifying complexity in AF electrograms, we noted that in 42 of the 50 cases (84%) ApEn were correctly correlated with the complex or periodic and organized activations. In 7 bipolar electrograms (14%) ApEn values remained high during the entire 30s recording. Further analysis showed the presence of a range of high frequency components in the electrograms influencing the entropy response. Additionally, we had one bipolar signal with periodic behaviour of one or two atrial activations per second (ApEn=0.28±0.0551). The changes of entropy were more related with the difference of activations per second instead the "complexity".

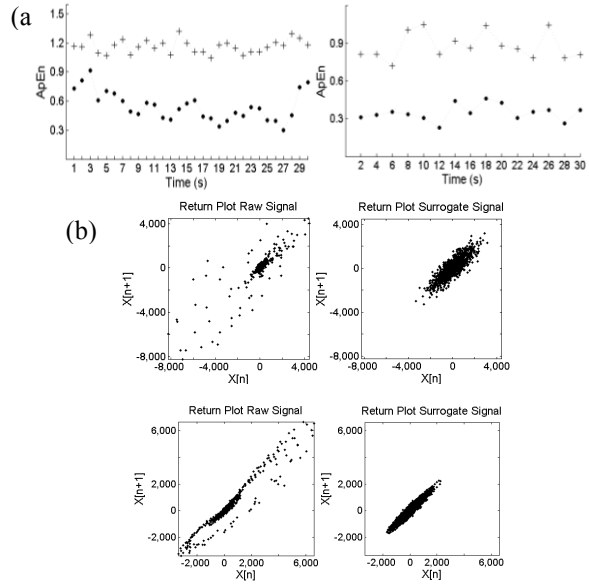

Fig. 2: (a) ApEn from signals using different window sizes. The marks in grey are from the surrogate and in black from the raw signal. The respective return plots are also presented in (b).

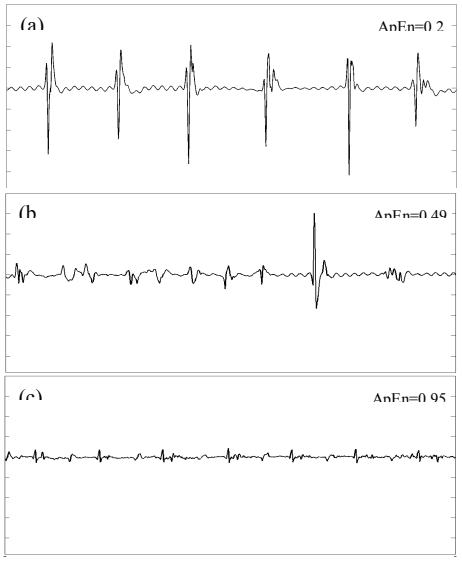

Fig. 3: Entropy Analysis of different behaviours of AF electrograms: (a) well defined atrial activations with clear and strong periodic component, (b) presence of both well-defined atrial activations and fractionated electrograms and (c) high fractionated AF electrograms.

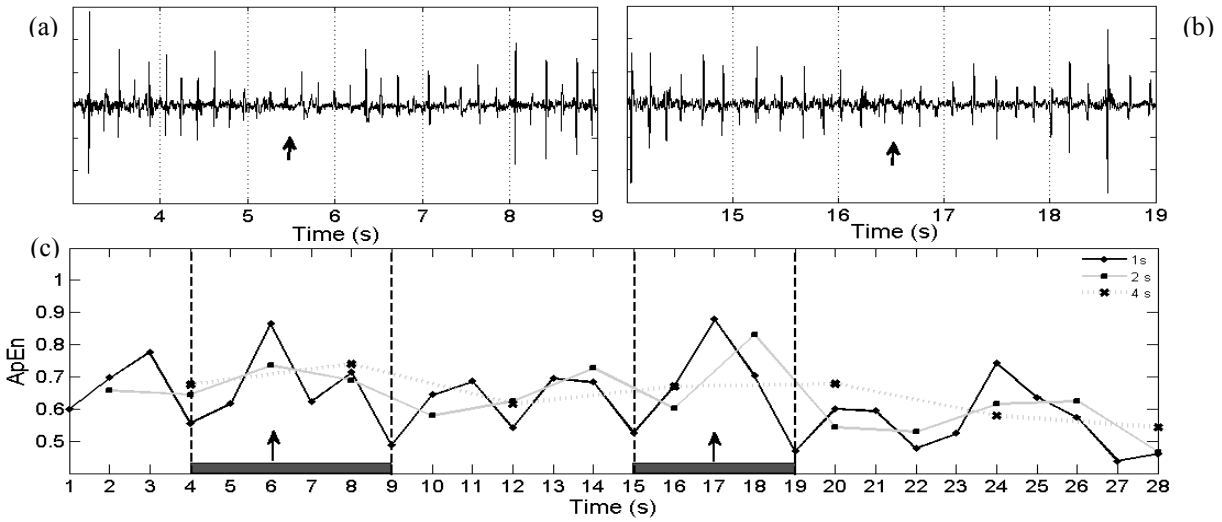

Fig. 4: Atrial electrograms recording over two different time segments, (a)-(b), and (c) their respective ApEn response: (a) 4 s to 9 s and (b) 15 s to 19 s. (c) ApEn calculated for windows of 1 s, 2 s and 4 s.

Discussion

From the linear exploratory data analysis (EDA) we observed a periodic ACF with periodicity response matching the dominant frequency of the atrial electrograms and a non-periodic ACF formed by multiple and unorganized frequency peaks.

We expanded the study by performing a nonlinear characterization of AF electrograms signals using surrogate data analysis and return maps on raw and surrogate signals [13]. We showed evidence of the presence of nonlinear components in bipolar electrograms in persAF and this highlights a serious limitation in applying linear techniques to persAF electrograms. We also considered ApEn, as an analysis tool of system complexity to measure disorganization for different AF behaviours and lower ApEn values were associated with organized AF activations and higher entropy values with the increase of electrograms complexity. The selection of the window segment length also influences the ApEn response with longer segments showing a general AF behaviour while shorter windows helped identifying dynamical atrium electrical changes (1 s and 2 s).

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