Analysis of Inter-atrium Differences in Paroxysmal and Persistent Atrial Fibrillation Using Principal Component Analysis

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Abstract

The pathophysiological mechanisms of Atrial Fibrillation (AF) are not entirely clear yet, and there is no full explanation for the development and evolution of the arrhythmia. The goal of this study is to find inter-atrium differences in electrophysiological behavior between persistent and paroxysmal AF. The database analyzed contains intra-cardiac records from 14 patients with paroxysmal AF and 10 with persistent AF. Dominant Frequency and Sample Entropy measurements showed that in the paroxysmal group there was a left-to-right gradient. These differences were enhanced after the extraction of the main components with Principal Component Analysis. These findings may be interpreted as a possible evolutionary path from paroxysmal to persistent AF, with a higher irregularity in the left atrium in paroxysmal AF and non- significant differences in persistent AF.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, with a prevalence rising nearly to 10% in the elderly [1]. AF is an arrhythmia originated at the atria and is considered to be due to the coexistence of multiple re-entrant atrial wavelets which are often initiated by arrhythmogenic foci located at the pulmonary veins [2, 3].

It is classified as either paroxysmal, where the episode terminates spontaneously, persistent, where cardioversion (electrical or pharmacological) or ablation is required for termination, or permanent, where cardioversion is unsuccessful (or not indicated) usually when the arrhythmia is long-standing.

The activation patterns during AF have traditionally been described as disorganized or random [2, 4, 3]. Furthermore, the anatomy and electrophysiological characteristics of the atria are likely to constrain the patterns of wave propagation, resulting in some degree of underlying spatiotemporal order, mainly in the left atrium [5, 6, 7]. Analyses of intra-cardiac recordings of the arrhythmia in the frequency domain have demonstrated multiple narrowband peaks, often with a single dominant peak [8, 9]. The presence of a dominant peak suggests that a substantial portion of the atria is activated at that frequency, potentially in a spatially ordered manner. However, the spatial patterns of wave propagation remain unknown, and the entropy measurement as a regularity index of atrial electrical activity can be helpful to quantify its organization. We had two principal aims: (1) to characterize regional atrium differences of paroxysmal and persistent AF with entropy measurements of time series and (2) to use spectral analysis to determine the regional atrial electrical activity frequency content, especially in relation to the dominant frequency in both groups.

2. Materials

AF intracardiac recordings were registered in 24 patients diagnosed as AF by specialists (10 persistent and 14 paroxysmal AF). A 24-pole catheter (Orbiter, Bard Electrophysiology, 2-9-2 mm electrode spacing) was inserted through the femoral vein and positioned in the right atrium with the distal dipoles into the coronary sinus to record left atrial electrical activity as well. The medium and proximal electrodes were located spanning the right atrial peritricuspid area, from the coronary sinus ostium to the upper part of the interatrial septum. Using this catheter, 12 bipolar intracardiac electrograms from the right atrium (RA) and left atrium (LA), were digitally recorded at 1 kHz sampling rate (16 bit A/D conversion; Polygraph Prucka Cardio-Lab, General Electric).

3. Methods

3.1. Preprocessing process

In order to reduce noise and interferences two different types of preprocessing steps were applied: a commonly used filter and Principal Component Analysis.

3.1.1. Traditional filtering

These signals, without any influence of ventricular activation, were band-pass filtered using a 40-250-Hz third-order Butterworth filter. The resulting filtered waveforms rectified were filtered once more using a 20-Hz low-pass third-order Butterworth filter. This filtering process enhances the periodicity or non-periodicity of the signals. This algorithm was previously proposed to take a complex waveform and transform it to a series of atrial activations while diminishing the effects of changing electrogram morphology and/or amplitude [10, 11].

3.1.2. Principal component analysis

Principal Component Analysis (PCA) is a popular data processing and dimension reduction technique [12]. The objective is to find a linear transformation of the original signals, ordered by high proportion of the variation of the old variables, in a set of new uncorrelated variables, the principal components (PCs). PCA was done via the singular value decomposition (SVD) of the data matrix. This method detects and extracts signals from noisy original data.

In detail, let the data $\mathbf{X}$ be a $n \times p$ matrix, where n and p are the number of observations and the number of variables, respectively. Without loss of generality, assume the column means of $\mathbf{X}$ are all 0. Suppose we have the SVD of $\mathbf{X}$ as

$$\mathbf{X} = \mathbf{UDV^T} \tag{1}$$

where $\mathbf{U}$ are the PCs of unit length, and the columns of $\mathbf{V}$ are the corresponding loadings of the PCs. The variance of the i^{th} PC, is d_i^2, with d_i being the i^{th} element in the diagonal of $\mathbf{D}$. Usually the first q ($q < p$) PCs are chosen to represent the data, thus a great dimensionality reduction can be achieved.

3.2. Parameter extraction

3.2.1. Dominant frequency

The dominant atrial frequency was determined from the power spectral density of the signals. This was computed from the Welch's periodogram, with a 4s length Hamming window and a 50% overlapping between adjacent windowed segments [13]. Atrial wavelets were identified by comparing the main frequency with the range of frequencies of the atrial activity.

The dominant atrial frequency was obtained for both, the original filtered electrograms and the PCs. In addition, several analysis based on LA and RA regions were performed separately.

3.2.2. Sample entropy

The activation patterns behind the electrical activity of the heart during AF have often been characterized as random phenomena. Entropy measures have been recently used to the analysis of complex physiological time series, particularly to quantify the regularity of the wavefront in cardiac tissues.

In this study, we have used Sample Entropy (SampEn) [14] to characterize the organization of the actrial activity. This parameter is a similar but less biased measure than the Approximate Entropy (ApEn), introduced by Pincus to quantify the regularity of finite length time series [15].

From $B_i^m(r)$ as $(N-m-1)^{-1}$ times the number of vectors $x_m(j)$ within *r* of $x_m(i)$, where *j* ranges from *1* to *N-m*, and $j \neq i$ to exclude self-matches. We then defined $B^m(r) = (N-m)^{-1} \sum_{i=1}^{N-m} B_i^m(r)$. Similarly, it is defined $A_i^m(r)$ as $(N-m-1)^{-1}$ times the number of vectors $x_{m+1}(j)$ within *r* of $x_{m+1}(i)$, where j ranges from *1* to *N-m* ($j \neq i$), and set $A^m(r) = (N-m)^{-1} \sum_{i=1}^{N-m} A_i^m(r) \cdot B^m(r)$ is then the probability that two sequences will match for *m* points, whereas $A^m(r)$ is the probability that two sequences will match for *m+1* points. The parameter SampEn, expressed by the equation 2, is equal to the negative of the natural logarithm of the conditional probability that sequences close to each other for *m* consecutive data points $B^m(r)$ will also be close to each other when one more point is added to each sequence $A^m(r)$, fixing a threshold value *r*. Larger SampEn values indicate greater independence, less predictability, and hence greater complexity in the data.

$$SampEn(m, r, N) = -ln \frac{A^m(r)}{B^m(r)} \tag{2}$$

For the study discussed in this paper, SampEn is estimated using the widely established parameter values of *m=2*, and $r = 0.25\sigma$, where σ represents the standard deviation of the original data sequence, as suggested by Pincus [15]. We have used SampEn as a characterization of activation patterns in determined atrial areas, where LA and RA regions were performed separately.

4. Results

4.1. Filtered bipolar electrogram results

Frequency domain analysis was applied to these recordings to determine the dominant frequency (DF) of the atrial waveforms. In addition the Sample Entropy (SampEn) of the time series was calculated as a index of regularity. In the paroxysmal group, there was a left-to-right atrial DF gradient trend, with the DF lowest at the LA, and highest in the RA (5.65 ± 0.34 vs. 6.00 ± 0.23Hz, respectively; p=0.05), and in the persistent group, there was no statistically significant difference between the DF recorded from the LA and RA (5.80 ± 0.36 and 5.89 ± 0.22 Hz, respectively; p=0.12) (Figure 1).

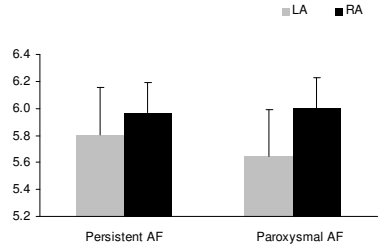
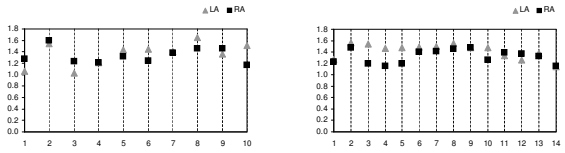


Figure 1. Maximal Frequency gradient across atrial chambers of filtered dipole electrode recording time series across all subjects. Bars represent $mean \pm SD$ for each group

In addition, the measurements of entropy showed a greater difference between atria in the paroxysmal group (1.37 ± 0.21 in the LA vs. 1.30 ± 0.16 in the RA, p=0.01)(Figure 4.1), than in the persistent group (1.36 ± 0.20 in the LA vs. 1.33 ± 0.17 in the RA, p=0.60) (Figure 4.1).



(a)Persistent AF (b)Paroxysmal AF

Figure 2. SampEn of filtered dipole electrode recording time series from LA and RA regions

4.2. Principal component analysis results

In order to emphasize the differences, Principal Component Analysis (PCA) was applied to the intra-atrial dipoles of LA and RA separately, and as result, the differences were increased. The DF from PCA decomposition reached a significance of p=0.007 in the paroxysmal group (5.78 ± 0.49 Hz in the LA vs. 6.29 ± 0.30Hz in the RA), as distinct from highly similar values observed in the persistent AF group (6.10 ± 0.41Hz in the LA vs. 6.20 ± 0.32Hz in the RA, p=0.622) (Figure 3).

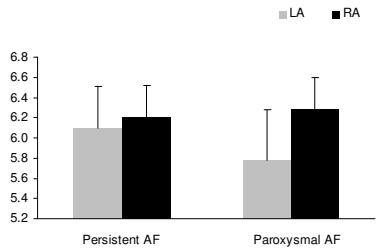
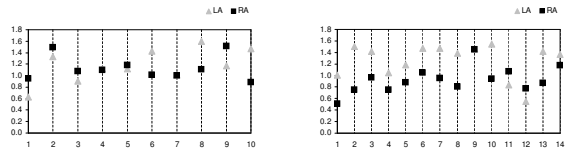


Figure 3. Maximal Frequency gradient across atrial chambers of PCs from dipole electrode recording time series across all subjects. Bars represent $mean \pm SD$ for each group

In addition, the application of SampEn to the PCA components showed more marked differences between paroxysmal (1.21 ± 0.23 in the LA vs. 1.01 ± 0.25 in the RA, p=0.001)(Figure 4.2) and persistent AF (1.18 ± 0.25 in the LA vs. 1.13 ± 0.24 in the RA, p=0.66) (Figure 4.2).



(a)Persistent AF (b)Paroxysmal

Figure 4. SampEn of PCs from dipole electrode recording time series from LA and RA regions

5. Discussion and conclusions

In the present work, it has been observed the capability of PCA as a preprocessing stage to capture the atrium waveform exempt from noise and other interferences that are present in the original signals but appear much reduced in the selected principal components. As a consequence, the frequency analysis and the regularity index measurements are more reliable and the results become more consistent.

Although the exact mechanisms of the alteration of the atrial rate during AF remain to be fully understood, animal and human studies have shown that activity during AF is more rapid in the LA than in the RA [8, 16, 17]. These

studies suggest that high-frequency sources in the LA act as triggers and or drivers for some types of AF. However in some patients, it is possible to observe the presence of foci of rapid electrical activity in areas outside the pulmonary veins. About this theory, an important and novel finding reported by Lin [18] is that the highest dominant frequency is not always in the LA but shifts to the RA when AF is initiated in the superior vena cava. It corroborates the results obtained from this study, where it is observed that inside of paroxysmal and persistent groups there are patients that follow a opposite trend with a ascendent frequency gradient from RA to LA, providing further evidence about the inhomogeneity of AF patients.

In addition, the results of entropy analysis show a more irregular activity in LA compared with RA, that arrives to be statistical significant in the paroxysmal group. As well it is possible to observe in Figures 4 and 2 the heterogeneity between patients, and the enhancement of the differences between LA and RA after PCA application. These findings may be interpreted as a possible evolutionary path from paroxysmal to persistent AF. This inhomogeneous atrium behavior during paroxysmal AF may play an important role in the arrhythmia maintenance.

Our results identify transient periods of wave propagation changing over space and time, that characterizes both chambers in different types of AF. The detailed mechanisms by which this occurs require further study, and multisite mapping would be helpful to further elucidate the reason for which this difference of organization occurs.

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