Joint Entropy for Spatial Information Retrieval from Orthogonal Heart Planes Improves Catheter Ablation Outcome Prediction in Persistent Atrial Fibrillation

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Abstract

Predictability of catheter ablation (CA) outcome in persistent atrial fibrillation (AF) is still an open issue. Predictors in previous studies are mainly computed in only one ECG lead, and neglect relevant information from the other ones. In this study we investigate the role of interlead relationships on the 12*-lead ECG in CA outcome prediction.*

Stepwise CA was performed in 36 *AF patients. Standard ECG was acquired at the beginning of the procedure. Spatial relationships are assessed by joint entropy (JE) in each possible pair of leads on an ECG subset (I, II +* V_1*-*V_6*). JE quantifies the amount of information about AF patterns observed on two distinct leads. Clinical outcome prediction is assessed by area under curve (AUC).*

Our analysis reveals that the best prediction is obtained for pairs combining a frontal and a horizontal lead, as confirmed by the corresponding AUC values, e.g. leads I-V_3*, AUC=*0.95*. Conversely, contributions from the same heart plane seem not to sufficiently characterize AF complexity content, thus yielding a less accurate prediction performance (e.g., leads* V_1*-*V_5*, AUC=*0.63*).*

Higher JE values denote a higher amount of interlead global information and render a more organized AF activity, which is more likely to be successfully treated by CA. Simultaneous analysis by JE of pairs of standard ECG leads from orthogonal heart planes enriches AF content characterization and enhances outcome prediction for CA.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. [1]. However, the mechanisms of its genesis and perpetuation have not been elucidated yet. Several theories have been but forward in order to explain such phenomena. Some studies state that AF is triggered by one or multiple fibrillatory reentrant sources, the so called ectopic foci [2]. Other lines of investigation rather focus on the role of self-sustaining wavelets and re-entrant circuits [3]. Yet, understanding where AF sources are located and how the arrhythmic wavefront propagates throughout the heart would help determining the degree of chronification of the disease and selecting a patient-tailored therapy in a more effective way [3, 4]. However, a unique definition of AF spatio-temporal complexity has not been provided yet, and several measures have been put forward in order to quantify the level of chronification. Several factors contribute to AF complexity, including age, additional pathologies and effects of atrial remodeling due to disease chronification.

Standard 12-lead electrocardiogram (ECG) is widely employed as a non-invasive and cost-effective diagnostic tool. Its multilead character can be exploited for describing heart electrical activity at different leads' orientations so as to have a deeper understanding of this arrhythmia.

In [5–7] some noninvasive measures of AF organization are assessed on surface recordings. Nevertheless, the analysis is limited to a single lead, therefore the spatial diversity typical of multilead recordings is neglected. In [8] an attempt to study AF spatial variability is also made on vectocardiograms in the frequency domain. However, all these studies only focus on AF pattern temporal variability and its repetitiveness throughout the recording. Furthermore, no clinical correlation with AF therapy has been established. By contrast, relevant clinical information could be provided by surface ECG spatial variability, thus allowing for a more accurate and complete AF wavefront characterization, thanks to the different positions of the ECG leads.

The main goal of this work is providing a novel interpretation of AF pattern diversity in terms of spatial correlation between different ECG leads. Indeed, we demonstrate that

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valuable clinical information about AF treatment can be obtained by examining the ECG at different orientations and planes and investigating interlead relationships. We assume that a more irregular and unpredictable AF activity reflects on more fragmented patterns, whereas a more organized wavefront propagates in a more structured manner as seen by multiple leads. AF content can be effectively characterized at different planes through proper information theory (IT) indices. Typically employed in telecommunications [9, 10], such theory is applied to AF analysis for the first time as far as we are aware. We demonstrate that looking at orthogonal ECG leads enables a more complete characterization of this arrhythmia, and such information can help selecting the most suitable therapy. Our work focuses on radiofrequency catheter ablation (CA), and demonstrates that AF spatial information improves the quality of ablation prediction outcome.

2. Methods

2.1. Atrial activity signal extraction

Since we are mainly interested in AF interlead spatial correlation and we neglect the temporal variability, ventricular activity is suppressed by removing the QRS complexes from the input multilead ECG signal. R waves are automatically detected by the Pan-Tompkins algorithm [11]; Q wave onset and T wave offset are determined through the Woody's method [12]. Noise is removed through a fourth-order zero-phase type II Chebyshev bandpass filter with -3 dB attenuation between 0.5 and 30 Hz, as AF dominant frequency ranges between 3 and 12 Hz. Moreover, power line interference, baseline wander and high frequency noise (e.g., myoelectric artifacts) are effectively removed. TQ intervals are finally mean-corrected and concatenated, thereby representing the atrial activity (AA) signal in an $(L \times N)$ matrix $\mathbf{Y}_{\mathrm{AA}}$:

$$\mathbf{Y}_{\mathrm{AA}} = [\mathbf{y}_{\mathrm{AA}(1)} \cdots \mathbf{y}_{\mathrm{AA}(\mathrm{N})}] \in \Re^{L \times N} \tag{1}$$

where vector $\mathbf{y}_{\mathrm{AA}}(n) = [y_1(n), \ldots, y_L(n)]^{\mathrm{T}}$ represents the multilead AA signal at sample index n, L is the number of leads used, and N the number of samples of the AA signal $y_\ell(n)$ for each lead $\ell = 1, 2, \ldots, L$. In this study, we examine a subset of $L = 8$ ECG leads which are linearly independent from each other, namely, I, II, V_1-V_6.

2.2. Information theory background

IT theory tries to model and quantify the amount of information exchanged between two systems, i.e., the level of uncertainty of the message transmitted [13]. From a mathematical point of view, we consider a generic continuous random variable (r.v.) X that can take on any value from a domain $\mathcal{X}$, and that is characterized by a probability distribution (pdf) function $p(x)$, $x \in \mathcal{X}$.

We define the marginal entropy $H(X)$, which quantifies the amount of information carried by X:

$$H(X) = -E\{\log p(x)\} = -\int_{x \in \mathcal{X}} p(x) \log p(x) dx. \tag{2}$$

Entropy is always positive ($H(X) \geq 0$). The higher its value, the higher the rate of information provided, the lower the uncertainty about the message exchanged. As all the IT measures, it is conventionally expressed in bits, thus logarithm function is computed in base 2. Moreover, $H(X)$ is a functional of the pdf $p(x)$, therefore it does not depend on the actual values taken by X, but only on their probabilities.

Just as with probabilities, entropy definition can be extended to a bidimensional domain by introducing another r.v. Y with values in $\mathcal{Y}$ and probability density $p(y)$. If their joint probability distribution $p(x, y)$ is known, the joint entropy (JE) can be expressed as:

$$JE = H(X; Y) = -\int_{x \in \mathcal{X}} \int_{y \in \mathcal{Y}} p(x, y) \log p(x, y) dx dy \tag{3}$$

In our application, AF spatial information is evaluated in terms of mutual information observed in pairs of ECG leads and quantified by the JE index. Furthermore, we merely focus on two variables. Indeed, the multidimensional counterpart of the JE descriptor introduced in Eq. (3) is not a direct extension of the bidimensional definition and intervariable relations are more difficult to evaluate [14].

2.3. Assessment of AF spatial distribution on standard ECG

The JE index is computed through the algorithm presented in [14] as in Eq. (3). Accordingly, AA signal amplitude PDF is determined first. In the ECG subset presented in Sec. 2.1, all the possible pairs of leads are examined, i.e., $\frac{L!}{2!(L-2!)} = 28$ combinations, since our goal is investigating the JE descriptive power and its variability across ECG leads. For a couple of N-sample AA signals $y_{\ell,1}$ and $y_{\ell,2}$, ℓ, $\ell = 1, \ldots, L$, $L = 8$, their 2-D histogram is determined in the range of values $[y_{\ell,k_{\mathrm{MIN}}} - \frac{\delta}{2}, y_{\ell,k_{\mathrm{MAX}}} + \frac{\delta}{2}]$, $k = 1, 2$, where $\delta = (N)^{-\frac{1}{2}}$ is the histogram bin width. By convention, if $p(x) = 0$, we set $p(x) \log p(x) = 0$. JE predictive power is evaluated by the receiving operator analysis (ROC), yielding the area under curve (AUC) index: the closer its value to 1, the more accurate prediction.

Our methods are tested on a database of 36 standard ECG signals acquired right before CA. Each ablation has been performed with the aid of Prucka Cardiolab and Biosense CARTO electrophysiology measurement sys-

tems at the Cardiology Department, Princess Grace Hospital, Monaco. More precisely, $n_S = 29$ subjects experience durable SR restoration by CA in the long-term follow-up (8 ± 4 months), whereas the remaining ones ($n_F = 7$) do not. CA effects are studied through the ECG/Holter-documented sustained AF recurrence (> 30 s) starting from at least 6 months after CA performance [15].

Moreover, we compare the JE index with some classical ECG descriptors of AF in the same pairs of ECG leads. We thus examine the mean amplitude $\widetilde{D}(\cdot)$ of the fibrillatory waves (f-waves) in the mentioned subsets of the rank-1 approximation to the 2-lead AA signal through principal component analysis (PCA) as in [16]. To the same end, the mean NMSE introduced in [7], denoted $\overline{NMSE}(\cdot)$, is computed in the same leads. The index is tuned as in [17].

Single-lead perspective is also investigated. Accordingly, we computed the marginal entropy $H(\cdot)$ in each lead of the aforementioned ECG subset. Another single-lead non-linear measure, i.e., sample entropy $Sampen(V_1)$, is also determined in V_1. Setting parameters are tuned as in [18], thus the length of the AA sequences to be compared is $L_S = 2$ and the threshold for accepting matches is equal to 0.1σ, where σ is AA standard deviation in V_1.

3. Results

The AUC values related to the JE index prediction performance are reported in Table 1 for each couple of ECG leads. Similarly, ROC analysis outcome for conventional marginal entropy $H(\cdot)$ is shown in Table 2.

Table 1. ROC analysis for CA outcome prediction in each pair of ECG leads: comparison of the JE index with other ECG descriptors. Leads examined are underlined by the symbol $\times$.

Leads	$JE(\cdot)$	$\widetilde{D}(\cdot)$	$\overline{NMSE}(\cdot)$	I	II	V_1	V_2	V_3	V_4	V_5	V_6
[I V_3]	0.95	0.84	0.67	X				X			
[I V_4]	0.94	0.88	0.62	X					X		
[I V_2]	0.93	0.63	0.78	X			X				
[II V_4]	0.93	0.68	0.72		X				X		
[II V_3]	0.91	0.83	0.70		X			X			
[I V_5]	0.91	0.62	0.92	X						X	
[II V_6]	0.89	0.74	0.78		X						X
[I V_6]	0.89	0.74	0.78	X							X
[I V_1]	0.89	0.65	0.59	X		X					
[II V_2]	0.89	0.84	0.59		X		X				
[II V_5]	0.89	0.60	0.84		X					X	
[V_3 V_4]	0.79	0.75	0.54					X	X		
[V_2 V_6]	0.79	0.75	0.64				X				X
[V_4 V_6]	0.78	0.70	0.85						X		X
[II V_1]	0.76	0.68	0.68		X	X					
[V_2 V_4]	0.76	0.76	0.55				X		X		
[V_4 V_5]	0.74	0.72	0.72						X	X	
[V_3 V_6]	0.74	0.77	0.74					X			X
[V_2 V_3]	0.74	0.75	0.64				X	X			
[V_3 V_5]	0.72	0.75	0.59					X		X	
[V_1 V_3]	0.72	0.66	0.59			X		X			
[V_2 V_5]	0.72	0.80	0.62				X			X	
[I II]	0.71	0.85	0.53	X	X						
[V_1 V_4]	0.71	0.66	0.54			X			X		
[V_1 V_2]	0.70	0.68	0.67			X	X				
[V_5 V_6]	0.70	0.39	0.75							X	X
[V_1 V_6]	0.70	0.58	0.72			X					X
[V_1 V_5]	0.63	0.61	0.67			X				X	

Table 2. AUC estimation in marginal entropy $H(\cdot)$.

Lead	I	II	V_1	V_2	V_3	V_4	V_5	V_6
AUC	0.93	0.82	0.58	0.73	0.70	0.67	0.61	0.56

4. Discussion

Our study demonstrates the ability of the JE measure to characterize AF content in preferential electrical planes, in particular those which are more relevant for CA outcome prediction. Therapy effects can be properly quantified if the pair of ECG leads is properly chosen. The higher the JE value, the higher the amount of information observed in two leads. This evidence is confirmed by our investigation, underlining that JE is globally higher when ECG leads belonging to different planes are taken into account in all the subjects, regardless of CA outcome (e.g., $JE = 4.68 \pm 0.64$ in I-V_3, $JE = 4.99 \pm 0.70$ in V_3-V_4, p value$= 0.05$). The index is not too sensitive to amplitude variations. Even though JE values depend on the r.v. scale, classification results are not significantly affected. Indeed, amplitude scaling invariance properties are verified by comparing the JE values computed on the original signal with those obtained on the same signals normalized between 0 and 1 through the relation $\overline{y}_{\ell,k} = \frac{y_{\ell,k} - y_{\ell,\mathrm{MIN}}}{y_{\ell,\mathrm{MAX}} - y_{\ell,\mathrm{MIN}}}$, where $y_{\ell,\mathrm{MIN}} = \mathrm{MIN}\{y_{1,\mathrm{MIN}}, y_{2,\mathrm{MIN}}\}$ and $y_{\ell,\mathrm{MAX}} = \mathrm{MAX}\{y_{1,\mathrm{MAX}}, y_{2,\mathrm{MAX}}\}$. The most discriminative signal components are clearly emphasized when information about AF comes from different planes and orientations of the heart electrical vector. Results in Table 1 confirm that procedural AF termination can be effectively assessed by the JE index when a frontal lead is examined in combination with a precordial lead, as proved by the related high AUC values. By contrast, contributions coming from the same planes seem not to be relevant to CA outcome prediction, or they poorly cluster the groups of patient. Moreover, conventional measures of AF content, such as mean AA amplitude and spatio-temporal complexity, are not able to provide such directional characterization of CA outcome, and prediction performance is globally quite poor, regardless of the couple of leads selected. Analysis results in Table 2 also demonstrate the lack of robustness of the single-lead assessment of entropy, as prediction results are variable and strongly influenced by the electrode chosen. The single-lead index $Sampen(V_1)$ is not capable neither to highlight significant differences between the categories of interest (AUC$= 0.70$). This evidence highlights that limiting our analysis to only one electrode could neglect useful predictive information coming from the other ones. Moreover, AF characterization in V_1 seems relatively incomplete. This idea is also supported by results

in Table 1, showing that it does not have a predominant role in AF therapy outcome assessment, but other leads seem to be more descriptive (e.g., AUC$= 0.95$ in I-V_3; AUC$= 0.89$ in I-V_1). Apart from JE, all the features examined are not able to quantify AF spatial content in orthogonal electrodes. Yet, our analysis shows the potential role of AF spatial information in therapy management, as the higher JE, the higher the amount of information carried by the heart electrical wavefront at orthogonal planes, the more likely AF termination by CA (e.g., in leads I-V_3, AUC$= 0.95$, AF termination: 7.17 ± 0.82, Non AF termination: 5.43 ± 1.69, p value: $3.45 \cdot 10^{-5}$).

5. Conclusions

Our research demonstrates that IT measures are able to emphasize AA signal predictive features and enhance ECG spatial variability. Moreover, they enhance AF content at orthogonal angles and orientations of the heart electrical activity, thus enriching disease characterization. The higher the JE index, the higher the amount of information shared by two ECG leads, which correlates with more organized AF forms, more likely to be terminated by CA. To our knowledge, the IT indices are applied to AF analysis and therapy management for the first time. A more detailed analysis of some IT theoretical properties should be carried out, in particular for potential extensions to more than two leads. Moreover, physiological interpretation of such measures needs to be investigated in more detail. Finally, further attention should be paid to some tuning parameters, in particular those related to AA signal histogram. Despite these limitations, our investigation corroborates the role of interlead spatial information as a descriptor of AF content on standard ECG, with no need for signal temporal characterization. It opens new perspectives for AF complexity evaluation and therapy assessment through ECG analysis.

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