On Predicting the Spontaneous Termination of Atrial Fibrillation Episodes Using Linear and Non-Linear Parameters of ECG Signal and RR Series

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Abstract

In this study, surface ECG signals recoded during Atrial Fibrillation (AF) episodes have been investigated to detect signs of spontaneous termination and to derive an automatic classifier of terminating (T) and non-terminating (N) AF events. The ECG signals consisted in Holter recordings coming from the 2004 Computers in Cardiology Challenge database. A set of features have been extracted from the ECG signals and the related RR interval series including both linear and non-linear indexes. In the training dataset, we observed a prolonged dominant atrial cycle length (DACL) passing from N to T accompanied by an increased of residual ECG (rECG) power. Concerning the RR interval variability a reduction of mean RR interval and Regularity (R) and an increase of Approximated Entropy (ApEn) have been documented. These features were used to train a feed-forward neural network which was employed for the automatic classification of the Challenge test set. Score of the classifier was encouraging: 26/30 episodes were correctly classified..

1. Introduction

The occurrence of spontaneous re-organization has been observed in the electrical activities of different atrial sites preceding the termination of atrial fibrillation (AF) episodes [1]. In addition, we reported the presence of changed patterns in the series of atrial activations during organized and non-organized atrial rhythm [2] as well as during drug administration [3]. It could be therefore argued that these signs of re-organization may also appear on surface ECG recordings.

In the past, the analysis of the residual ECG signal (i.e. the ECG signal in which the ventricular activities, the QRST complexes, have been cancelled through beat averaging techniques) has been proposed to characterize atrial activities [4][5]: residual ECG evidences marked changes during AF, after infusion of drug or throughout various atrial rhythms. In particular, the Dominant Atrial Cycle Length (DACL), which may be obtained by spectral analysis of the residual ECG signal (rECG), has been related to atrial refractoriness and therefore to the probability of maintenance of AF.

Aim of this study is to assess the presence of subtle changes in the surface ECG signals (related to the regularization of atrial sites activity) that could be used to predict the end of the AF episodes. To accomplish this, we selected a set of linear and non-linear parameters aimed at measuring glimpse of re-organization in atrial activities. The parameters were extracted from rECG and the related RR interval series. The set includes: Entropy based measures (Approximated Entropy, Regularization and Synchronization indexes), spectral analysis parameters (frequency and amplitude of fibrillation waves) and a model-based index (level of predictability). These features were computed on the data set of the 2004 Computers in Cardiology Challenge and used to classify terminating (T) and non-terminating (N) episodes of AF.

2. Methods

2.1. Processing of ECG signals

Extraction of the residual ECG was obtained through beat-to-beat subtraction of an averaged QRST complex [4][5].

Despite the 2004 Challenge dataset already contained QRS annotations, ventricular beats were mainly misclassified, leading to a serious source of cancellation errors. Moreover, refined QRS locations were necessary for the entropy measures. Thus, a slightly modified version of OSEA, a freely available ECG library [6], was employed to detect and classify beats. QRS onsets and widths were further refined by means of a second publicly available software, ECGPUWAVE [7]. Then, on a lead-by-lead basis, separate average templates were built for QRS and T waves. To take into account morphological changes and minor variations in the electrical axis induced by respiration, subtraction of the templates was performed after a warping procedure and subsequent templates were connected via linear interpolation. With the assumption that during fibrillation atrial and ventricular activities are highly independent, the resulting rECG includes atrial activity only. The rECG was finally low-pass filtered and sub-sampled (32 Hz) to reduce the computational burden in the estimation of the non-linear parameters.

2.2. rECG Features

Features extracted from rECG included linear indexes obtained through spectral analysis and non-linear metrics based on Entropy measurements.

Spectral analysis of rECG was performed using the Welch methods (Hanning window: 128 points, overlap: 32 pt, zero-padding: 512 pt). Then, for each lead we computed: Frequency (fibrillatory rate) and Amplitude (A) of the spectrum's peak in the range 3.8-8 Hz; Total Spectral Power (P); Spectral width (W) intended as the width of the main spectral peak at 75% of its maximum amplitude.

The Non-linear parameters included two indexes: Regularity (R) and Synchronization (S), which we have successfully applied for the analysis of endocavitary atrial signals [2]. They were selected because they can capture information about randomness/regularity (or, in general, the "complexity") of the analyzed signals. The idea is that the fewer are the circulating "mother" wavelets in the presence of a spatially organized atria, the higher is the regularity and the predictability of the rECG. Conversely, when the number of circulating wavelets is increased in a highly fragmented atrium or when the main fibrillatory wave is vanishing, a reduced regularization and predictability in the signal is expected.

The regularity (R) index is defined as the degree of recurrence of a pattern in a signal and it is based on the measurement of the Conditional Entropy (CE). Values of CE close to zero mean high regularity, while CE increases in presence of White Noise (WN). An estimate of CE can be obtained from the Shannon Entropy according to:

$$CE(L) = -\sum_{L} p_L \log p_L + \sum_{L-1} p_{L-1} \log p_{L-1}$$

where p_L is the probability of a given sequence $s_L=(s(i),\ldots,s(i,-L+1))$ among the whole $(M=N-L+1)$ sequences. In order to overcome the problems in the consistency of the estimate of CE the Corrected Conditional Entropy (CCE) may be computed [8]. For a given process x, the regularity index is then defined as:

$$R = 1 - \min\left(\frac{CCE(L)}{E(x)}\right)$$

where the CCE(L) function is normalized to the process Entropy, E(x), in order to obtain an index which is independent from the process distribution. R ranges between 0 and 1, leading to 0 in presence of WN and to 1 in presence of a periodic process.

Similarly, we can obtain a non-linear synchronization (S) index. From the observation of two processes, x and y, their Mutual-Conditional Entropy (MCE) is defined as

$$MCE(L)_{y/x} = E(y,\ x_{L-1}) - E(x_{L-1})\,.$$

MCE measures the amount of information in y which may be predicted from the observation of x. From the simultaneous measurements of $MCE_{y/x}$(L) and $MCE_{x/y}$(L) follows an index of non-linear Synchronization (S)[8] defined as:

$$S = 1 - \min\left(\frac{MCCE_{x/y}(L)}{E(x)}, \frac{MCCE_{y/x}(L)}{E(y)}\right).$$

S tends to zeros in presence of completely uncoupled systems and to 1 for fully synchronized processes.

2.3. RR Features

RR interval series were analysed using standard time-domain parameters of Heart Rate Variability (HRV). We computed the mean RR (RRm), standard deviation (RRsd), and RMSSD [9].

In addition, non-linear parameters were measured, including Regularity and Approximated Entropy (ApEn) indexes [10].

Finally, a model-based index of predictability has been considered [2]: the series of RR intervals was modelled with a p-order Autoregressive (AR) model and we computed the standard deviation of the model prediction error (σ_e). The "level of predictability" index is defined as:

$$LP = (1 - \sigma_e / \sigma_{RR}) \cdot 100$$

where σ^2_{RR} is the variance of the RR series. The index LP measures the percentage of power which may be predicted by the model. In fact, it tends to 100 when the standard deviation of $e(n)$ tends to zero.

2.4. Neural network Classification

To automatically select a separation surface between the two classes N and T in the multidimensional parameter space, we used a non linear classifier implemented through a feed-forward neural network

(NN) with a single hidden layer [11] and two outputs, O_1 and O_2, each associated with one of the classes. During the training phase, we set (O_1=1, O_2=0) for N while (O_1=0, O_2=1) for T. Being J the number of hidden units, and I the number of input features, the output for each class was described by the non linear mapping

$$y = g\left(\sum_{\mathrm{j}}^{\mathrm{J}} W_{\mathrm{j}} \cdot h\left(\sum_{i}^{I} w_{ji} x_i\right)\right)$$

where w_{ji} are the coefficients from inputs to hidden layers while W_j link hidden layers to outputs. We selected h to be the hyperbolic tangent and g the sigmoid function, being the target output in the interval [0 1]. Weights W_j and w_{ji} were estimated through back-propagation on the train set, minimizing the mean squared error between predicted and actual outputs.

The complexity of the classifier implemented by the neural network in terms of separation boundaries depends on the number of hidden units. The more the hidden units the more complex will be the separation boundary, but also the more the overfitting. Having only few training records it is not possible to apply effectively cross-validation and early stopping techniques to reduce overfitting so we used an ensemble approach to select the classifier complexity. We trained an ensemble of network having from 1 to 6 hidden neurons and we used the majority vote to combine the results of networks, which had a perfect classification on the training set.

	N	T
DACL (ms)	156 ± 16	196 ± 15[§]
A (μV^2/Hz)	3.22 ± 0.52	3.67 ± 0.55*
P (μV^2)	4.35 ± 0.21	4.15 ± 0.22*
W (Hz)	0.60 ± 0.21	0.55 ± 0.23
R	0.13 ± 0.16	0.12 ± 0.05
S	0.07 ± 0.04	0.05 ± 0.02

Table 1. Mean values ± SD of the features computed on the rECG signals obtained from the training set. N: non-terminating episodes, T: terminating. § p< 0.0001; *p<0.001;

3. Results

3.1. ECG Signal

Table 1 summarizes the results obtained from the analysis of the training set on the rECG data. For the sake of conciseness, data from the two leads are grouped together.

The DACL was significantly prolonged passing form non-terminating (N) to terminating (T) episodes (the main frequencies decreased from 6.48 ± 0.67 vs. 5.14 ± 0.40), in agreement with previous studies on spontaneous

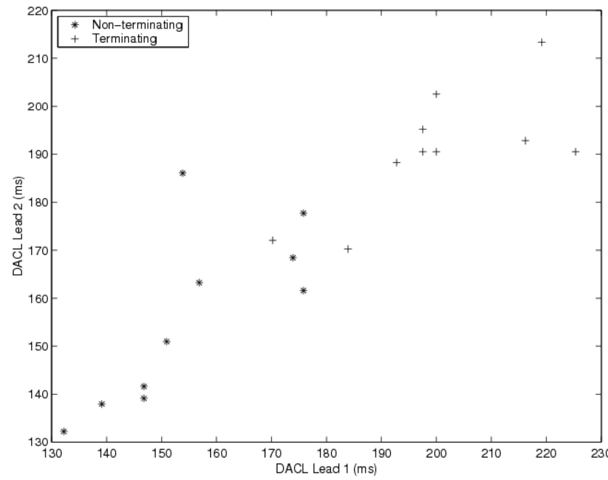

Figure 1. Scatter plot of the DACL parameters estimated for each of the two rECG leads. It is evident the separation between N episodes (which tend to be located in the lower left corner) and T ones (mainly located on the upper right).

termination of AF [12]. In addition, both total power and main-peak amplitude increased passing from N to T. Concerning non-linear indexes, no significant changes have been documented: only the synchronization index shows a tendency toward reduction in terminating events (p<0.06, ns). Statistical significance was assessed using the Student *t*-test.

In order to investigate the potential application of these indexes for the classification N and T events, we analyzed their distributions into the parameter space. By selecting an appropriate projection, the indexes show the tendency to group into two clusters, corresponding to N and T episodes, respectively. The most straightfull case has been observed for DACL. It can be noticed that DACL < 170 ms is always associated to N events, while longer values (> 190 ms) are indicative of T episodes.

Similar clustering have been observed for A and P values (data not shown). Even in this case, data coming for N and T episode show the tendency toward separation except for a few areas of uncertainty.

3.2. RR series

Table 2 summarizes the results obtained for the analysis of the RR interval variability signals.

The mean RR interval decreased passing from N to T episodes, while the other HRV parameters did not show significant changes. Interestingly, non-linear indexes evidence the existence of different dynamics passing from N to T episodes: ApEn was increased, while R decreased.

These findings, when associated to the reduction of S, observed on rECG, suggest that termination of atrial fibrillation could be associated to the vanishing of a main fibrillatory waves and to the fragmentation of atrial conduction.

3.3. Classification results

The first experiment in classification has been obtained by removing 10 records classified as S from the Computer in Cardiology training set. The training procedure obtained a perfect classification on the training set for networks having 2, 3, 4, and 6 neurons in the hidden layer. Networks with 1 and 5 neurons misclassified one record in the training set thus they were not used in the classifier ensemble. By using the majority vote between these classifiers we obtained 24/30. To increase the number of patterns in the training dataset we introduced also the 10 S-records and we arbitrarily classified them as T. We performed the same training procedure and we obtained 26/30. Thus the classifier performance could be improved by the use of more training data even from S patients.

	N	T
RRm (ms)	807 ± 177	650 ± 215*
RRstd (ms)	166 ± 56	155 ± 70
RMSSD (ms)	228 ± 78	185 ± 77
LP	4.38 ± 2.85	4.61 ± 3.27
R	0.181 ± 0.098	0.104 ± 0.056*
ApEn	0.545 ± 0.103	0.646 ± 0.152*

Table 2. Mean values ± SD of the features computed on the RR interval series obtained from the training set. N: non-terminating episodes, T: terminating. *p<0.05;

4. Discussion and conclusions

In this study, we analysed the ECG signals and the RR interval series during AF episodes. We observed that they carry information on the spontaneous termination of AF. In particular DACL and rECG spectral powers increased in T events, while regularity and ApEn of the RR interval series were reduced. Among the studied features, DACL was the most sensitive and specific in detecting T event. However, the computation of this parameter strongly depends on the quality of the residual ECG signal. RR interval series were easier to extract but they were less reliable in discriminating between T and N events. Finally, the performances of the NN classifier (26/30) were probably limited by the exiguous number of cases in the training set.

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