Beat-to-beat analysis of P waves in patient with atrial fibrillation history

Valentina D.A. Corino[1], Federica Censi[2], Marianna Tesoro[1], Ivan Corazza[3], Elisa Reggiani[3], Giuseppe Boriani[4], Luca T. Mainardi[1]

[1] Politecnico di Milano, Milan, Italy
[2] Italian National Institute of Health, Rome, Italy
[3] University of Bologna, Bologna, Italy
[4] AOU Policlinico di Modena, Modena, Italy

Abstract

P wave morphology has been shown to be modified in patients with paroxysmal atrial fibrillation (AF) and in healthy subjects of different age. These changes are commonly evaluated in the signal averaged ECG, thus in average P waves. Aim of this study is to assess beat-to-beat variations in P wave characteristics. Five-minute 12-lead ECG were recorded from 10 healthy subjects (C group), 10/10 patients with/without an AF recurrence (R/NR groups), after electrical cardioversion. Principal component analysis was performed on a beat-to-beat basis. The dynamic of the first three eigenvalues series and the beat-to-beat variability of the first three principal components (PCs) morphology were analyzed by calculating the distance between the average morphology over all the beats acquired and the morphology identified on each beat for the first three PCs. Most of the indexes were statistically different between C group and the patients with history of AF, highlighting higher regularity of the eigenvalues series as well as more similar PCs in healthy subjects. In addition, the series of the first eigenvalues was significantly less regular in R group compared NR group (Reg: 0.029 ± 0.020, 0.062 ± 0.033, $p<0.05$, R vs NR group).

1. Introduction

Although the wide diffusion, the mechanisms behind initiation, maintenance and termination of atrial fibrillation (AF) episodes are not completely understood [1].

After treatment for restoration of sinus rhythm, atrial fibrillation may recur. A predictor for maintenance of sinus rhythm is fundamental to anticipate the onset of new AF episodes and prevent the risks for the patients and reduce the social and economic burden of AF treatment and management. To prevent the onset of new AF episodes, the understanding of the pathophysiological mechanisms underlying AF and the assessment of atrial electrophysiological properties are essential. Now available non-invasive diagnostic tools may be used for further improvement of patient monitoring and for the development of patient-tailored treatment strategies.

One of the most commonly and widely accepted risk marker for atrial conduction disturbances and predisposition to AF is P wave prolongation. A more complete and extensive analysis of the P wave morphology could help characterize the heterogeneous propagation of sinus impulses in the atria [2]. This analysis may help identifying the mechanisms predisposing to the arrhythmia, playing a role in the early loss of sinus rhythm in patients subjected to electrical cardioversion (EC) or ablation of the pulmonary veins.

The aim of this study is to analyze the beat-to-beat variability of the atrial depolarization route during sinus rhythms which may reflect the degree of atrial remodeling and thus might be associated with the success probability of AF cardioversion and ablation.

2. Methods

2.1. Study protocol

Five-minute 12-lead ECG were recorded (2044 Hz) from 10 healthy subjects (control group, C group), 10 patients with an AF recurrence (R group) and 10 patients without recurrence (NR group), after electrical cardioversion (EC). The protocol included an ECG recording after 3 and 6 months after EC. The recurrence was defined if an AF episode occurred in the six months following the EC.

The study conforms to the Declaration of Helsinki, and was approved by the Ethics Committee of Policlinico di Modena (Italy). All patients gave their written informed consent for the procedures related to the study.
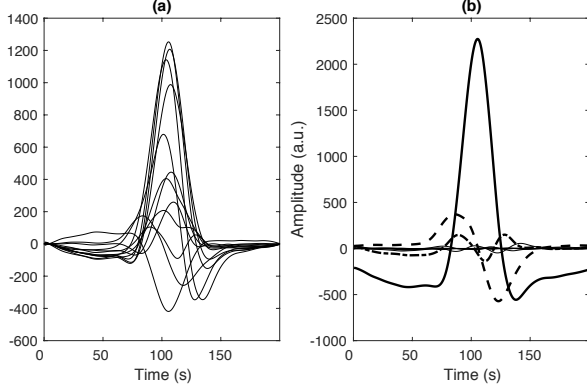
Figure 1. (a) Twelve-lead P waves for one beat and (b) the corresponding PCs (the solid line is the first PC, the dashed line is the second PC and the dotted line is the third PC) for a subject of the control group.
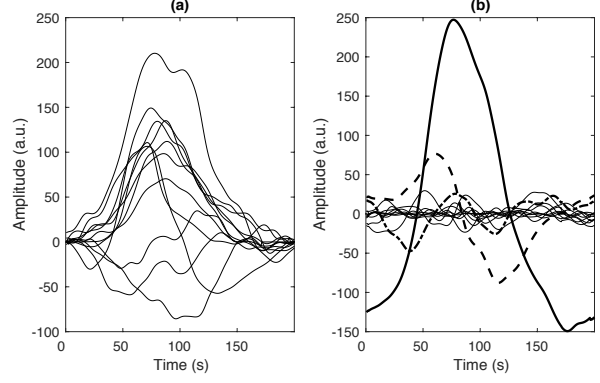

Figure 2. (a) Twelve-lead P waves for one beat and (b) the corresponding PCs (the solid line is the first PC, the dashed line is the second PC and the dotted line is the third PC) for a patient of the R group.

2.2. P wave pre-processing

Every lead signal was pre-processed and analysed to extract P waves. The first step is to isolate the P waves from the acquired signals: after detecting the R-wave (using an algorithm similar to that proposed by Pan and Tompkins [3]), P waves are extracted in a 200-ms long window (410 samples) starting 300 ms before the R-wave. Two pre-processing algorithms were applied to the P waves to exclude those affected by noise. First, the cross-correlation between each P wave and a template, defined as the median of all the P waves, was computed and the waves with a maximum cross-correlation lower than 0.95 were excluded from further analysis. Secondly, P waves with an amplitude greater than 0.3 times the maximum of the median P wave were excluded.

2.3. P wave variability

Principal component analysis (PCA), implemented through an algorithm based on by Singular Value Decomposition, was performed on a beat-to-beat basis. The PCA transforms the P waves to mutually independent components, where each principal component (PC) is a linear combination of the original 12 leads. The first three PCs were studied on a beat-to-beat basis by assessing i) the dynamic of the first three eigenvalues series (L1, L2, L3) and ii) the similarity of PCs among beats.

2.3.1. Eigenvalues series analysis

The first-three eigenvalues beat-to-beat series were analyzed by calculating four indexes: the standard deviation (SD), the coefficient of variation (CV), the linear predictability (LP) [4] and the regularity index (REG) [6, 7].

The CV is defined as the ratio between the SD and the mean of the series.

The LP is a linear index, defined as the percentage of series power which can be explained by self prediction when the series, $x(n)$, is modelled by an autoregressive model of p-order.

$$x(n) = \sum_{k=1}^{p} a_k x(n-k) + \eta(n) \tag{1}$$

where n is the discrete time index, the a_k's are the model coefficients, and η is a white noise process of variance σ_η^2 feeding the model. The actual sample differs from its model prediction thus generating the prediction error.

$$e(n) = x(n) - \hat{x}(n) = x(n) - \sum_{k=1}^{p} a_k x(n-k) \tag{2}$$

The LP index is then defined as:

$$LP = \left(1 - \frac{\sigma_e^2}{\sigma_x^2}\right) \times 100 \tag{3}$$

where σ_x^2 represents the variance of the signal and and σ_e^2 the variance of the prediction error.

REG is based on the conditional entropy and it is defined as the degree of recurrence of a pattern in a signal. The conditional entropy represents the amount of information carried by the most recent sample of a normalized realization of the series when its past L-1 samples are known. CE is defined as:

$$CE_L = - \sum_{J=1}^{M} p(\mathbf{x}_{L-1}^J) \sum_{i=1}^{N} p\left(x_i | \mathbf{x}_{L-1}^J\right) \log\left(p\left(x_i | x_{L-1}^J\right)\right) \tag{4}$$

where $\mathbf{x}_{L-1}^J$ represents the J-th pattern of length L-1, $p(\mathbf{x}_{L-1}^J)$ its probability and $p(x_i / \mathbf{x}_{L-1}^J)$ the conditional

probability of the sample x_i given the pattern $\mathbf{x}_{L-1}^J$, i.e., the probability of finding x_i when the J-th pattern $\mathbf{x}_{L-1}^J$ is encountered. Using Eq. 4 over short data series can cause an unreliable estimate of CE, as, when the conditioning pattern is found only once in the series, CE decreases to zero. Therefore, the corrected conditional entropy (CCE) is introduced to perform a reliable measure over short data series. CCE takes into account the percentage of patterns of length L found only once in the series. The minimum value of the CCE is taken as a measure of signal complexity: the larger the index, the less predictable the processes. The CCE is normalized by the Shannon entropy of the series to derive an index independent of the different probability distribution of the processes, thus obtaining NCCE. Finally, an index of regularity (the opposite of complexity) is defined as REG=1- min (NCCE(L)).

REG tends to zero if the series is an unpredictable process and tends to one if the series is a periodic signal and it assumes intermediate values for those processes that can be partially predicted by the knowledge of the past samples.

2.3.2. Distance of PCs

Let's define as $\mathbf{X_{i,k}} = [\mathbf{X_{i,k}(1)}, \mathbf{X_{i,k}(2)}, \ldots, \mathbf{X_{i,k}(N)}]$ the i–_th_, N samples, Principal Component (PC) vector obtained by PCA of the P–waves of the k–_th_ beats. A measure of distance between succesive PCs is obtained by computing following figure

$$D(i)_k = \arccos\left(\frac{\mathbf{X_{i,k}X_{i,k+1}^T}}{\|\mathbf{X_{i,k}}\|\,\|\mathbf{X_{i,k+1}}\|}\right) \qquad (5)$$

which measures the angle between the two vectors $\mathbf{X_{i,k}}$ and $\mathbf{X_{i,k+1}}$ and ranges from 0 (when vectors are parallel, i.e. maximally similar) to $\frac{\pi}{2}$ (when vectors are orthogonal, i.e. highly dissimilar). The measure is performed on each couple of successive beats and the average value $D(i) = E_k[D(i)_k]$ is taken as representative for the subject.

A second measure of distance is computed between each PC and the median value computed across all beats. The following quantify is computed

$$Dm(i)_k = \arccos\left(\frac{\mathbf{X_{i,k}M_i^T}}{\|\mathbf{X_{i,k}}\|\,\|\mathbf{M_i}\|}\right) \qquad (6)$$

where $\mathbf{M_i}$ is the median across the i-th PCs. The average value $Dm(i) = E_k[Dm(i)_k]$ is taken as representative for the subject.

2.4. Statistical analysis

A one-way ANOVA was applied to compare the parameters in the three groups. An unpaired t-test or Wilcoxon test with Holm correction was then applied for comparison between C vs. R, C vs. NR, R vs. NR.

A p-value <0.05 was considered statistically significant.

3. Results

Figures 1 and 2 show the twelve P waves for one beat and the corresponding PCs for a subject of the control group and a patient of the recurrence group, respectively. It can be noted that the first three PCs contain most of the atrial information in both subjects. However, the PCs are longer in the patient with history of AF.

Table 1. Explained variance for the first three PCs in the three analyzed groups.

Param	Control	Recurrence	Non-Recurrence
EV1	72 ± 9	64 ± 6	70 ± 8
EV2	25 ± 8	17 ± 4†	19 ± 4†
EV3	3 ± 3	5 ± 1†	6 ± 2†

EV1, EV2, EV3: explained variance of the first, second and third PC.
†$p < 0.05$ case vs. control group;
* $p < 0.05$ R vs. NR groups.

In both cases, the first PC, the one with the most energy, is much higher than the remaining components. On average, the explained variance of the first PC is more than 60% for all three groups, as shown in Table 1. In the following, we therefore present results for the first PC only. From Table 1, it can be noted that that the explained variance of the second PC is significantly higher in the subjects of the C group compared to the patients with AF history. On the contrary, the explained variance of the third PC is significantly higher in the patients with AF history than in the subjects of the C group.

Table 2. Mean $\pm$ SD values of the parameters computed on the first PC.

Param	Control	Recurrence	Non-Recurrence
D(1)	0.045 ± 0.014	0.147 ± 0.033†	0.149 ± 0.053†
Dm(1)	0.034 ± 0.011	0.114 ± 0.026†	0.113 ± 0.039†
SD	41 ± 18	115 ± 41†	114 ± 26†
CV	0.012 ± 0.006	0.033 ± 0.015†	0.033 ± 0.010†
LP	28 ± 13	44 ± 26	23 ± 10
REG	0.064 ± 0.040	0.029 ± 0.020	0.062 ± 0.033*

†$p < 0.05$ case vs. control group;
* $p < 0.05$ R vs. NR groups.

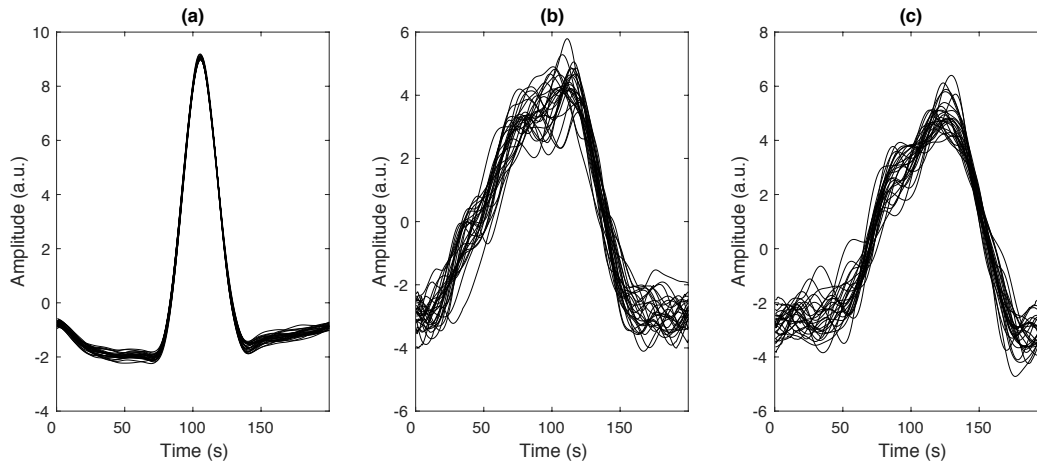Figure 3 shows the first PC over many beats for a subject

Figure 3. The first PC over many beats for (a) a subject of the C group, (b) a patient of the R group and (c) a patient of the NR group.

of the C group, for a patient of the R group and for a patient of the NR group. It can be observed that the variability in the morphology of the PC is much higher in the R and NR patients.

Table 2 summarizes the overall results. Both indexes assessing the morphology variability (D(1) and Dm(1)) are significantly higher in the patients with history of AF (R and NR groups) when compared with healthy subjects of the C group.

When assessing the variability of the eigenvalues series by means of SD and CV, significantly higher linear variability is present in the patients with history of AF. LP could not differentiate among groups. REG is the only index able to differentiate between R and NR groups, being the eigenvalues series of patients not presenting a recurrence significantly more regular than those with recurrence. Interestingly, the REG index of eigenvalues series of the NR group is similar to that of the C group.

4. Conclusions

In this study we showed that the analysis of beat-to-beat P waves variability may provide significant results in the characterization of normal and AF subjects. The analysis of shape similarity confirms recent findings on the capability in discriminating healthy subjects from patients with AF history [5], even if in this paper the similarity of waveforms is computed using different methods.

Another important result is obtained from the postprocessing of the eigenvalues series. In particular, the REG index is significantly different in patients with an AF recurrence from patients maintaining sinus rhythm after EC. This results evidences that R patients have a more irregular beat–to–beat oscillation than NR groups, likely evidencing a more unstable atrial activation pattern.

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Address for correspondence:

Valentina D.A. Corino
Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, via Golgi 39, 20133, Milan, Italy
valentina.corino@polimi.it