

The Lagged Central Tendency Measure Applied to Assess P-wave Duration Variability Improves Paroxysmal Atrial Fibrillation Onset Prediction

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Abstract

The prediction of paroxysmal atrial fibrillation (PAF) onset is an interesting clinical challenge, because the chronification of this highly prevalent arrhythmia could be avoided. Recently, the quantification of the P-wave duration variability over time has revealed a promising ability to detect accurately the onset of PAF. However, the possible scale-dependent variations in this P-wave variability have not been studied yet. In the present work that variations have been analyzed by using a m-lagged central tendency measure (CTM). Thus, once P-waves were delineated, their time course variability was quantified by computing CTM for lags $m = 1, 2, \dots, 10$. Statistically significant differences between ECG segments one-hour far from the onset of PAF and those immediately before the onset were obtained for every lag. Although no great differences were observed among the CTM values obtained for the studied lags, a predictive ability increase of about 3.5% was observed for $m = 2$ compared with $m = 1$. This result suggests the existence of scale-dependent dynamics within the transition process from sinus rhythm to PAF.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice [1], with an increasing number of patients being affected worldwide [2]. It is expected that about 25 million people in Europe and North America will develop AF by the middle of the 21st century [3]. Clinically, AF can be presented in different forms [4]. It often starts as paroxysmal (self-terminating) and becomes more persistent with time. Paroxysmal AF (PAF) is defined as attacks of AF lasting from several seconds to less than 7 days, and spontaneously reverting to sinus rhythm. Persistent AF lasts more than 7 days, but responds to external interventions such as cardioversion or ablation, while permanent AF does not respond to therapy. In this last stage of the arrhythmia, both the patient and the

clinician make a joint decision to stop further attempts to revert AF, and only interventions to control the heart rate are pursued. Approximately, between 15 and 31% of PAF patients progress to persistent AF during a time period between 4 and 8 years [5, 6].

Even though PAF is self-limited, it can lead to serious complications, including decreased exercise capacity and quality of life, thromboembolic events or congestive heart failure [7, 8]. Furthermore, PAF recurrences are associated with increased cardiovascular morbidity and mortality [9]. Hence, once a PAF episode terminates spontaneously, the prediction on when a new one will start is a very relevant clinical challenge.

Intensive efforts have been carried out in the last decade to find out markers able to predict PAF onset from the electrocardiogram (ECG) [10]. The P-wave has been widely analyzed because it is the atrial depolarization result and, hence, characterization of alterations in its morphology may provide information about the underlying AF mechanisms [11]. Indeed, a prolonged P-wave duration is today a clinically accepted risk marker of AF [11]. Moreover, many authors have also associated P-wave prolongation with development of arrhythmias after bypass surgery [12] and progression from paroxysmal to persistent AF [13].

More recently, linear and non-linear estimations of the P-wave duration variability just before the onset of PAF have also provided a relevant ability to detect accurately this event [14, 15]. However, these analyses have not paid attention to the possible scale-dependent variations in the P-wave duration variability over time. Thus, the main goal of the present work is to assess whether the P-wave duration variability computed from different scales could reveal useful information able to improve the prediction of PAF onset. A lagged central tendency measure (CTM) is proposed because it can easily summarize the degree of variability in a time series for different time scales by using chaotic modeling [16].

2. Methods

2.1. Study population

The database consisted of 46 patients (18 men, mean age of 63.2 ± 10.2 years) suffering from idiopathic PAF, i.e., none of them suffered from heart disease, hyperthyroidism or pulmonary disease. Moreover, no patient was under anti-arrhythmic drug treatment at the time of the study. From the 24-h Holter ECG recording of each patient, expert cardiologists annotated AF episodes, defined by irregular ventricular response and absence of P-waves [17]. The number of arrhythmic events per patient was 2.9 ± 1.8 in average, with a mean duration of 4.1 ± 2.2 hours. The shortest episode duration was 59 minutes.

From each patient, the longest sinus rhythm interval in the recording was selected and the two hours preceding the onset of PAF were analyzed. To evaluate the ability of CTM to follow P-wave alterations in different lags, the interval under study was divided into two one hour-length segments. The first set of segments comprised the hour immediately before the onset of PAF, which will be referred to as ECG segments close to PAF. The second set comprised those segments one hour away from the episode onset and will be named as ECG segments far from PAF.

2.2. Computation of the P-wave duration

Following previous recommendations about time and amplitude resolutions for appropriate P-wave analysis [18], the 24-h Holter recordings were acquired with a sampling rate of 1000 Hz and 16-bit resolution over an amplitude range of ± 10 mV. Moreover, although three leads were recorded (II, aVF, and V1), only V1 was considered in the study because the P-waves were larger in this lead.

The lack of a standard definition of the P-wave onset and offset motivated the use of an automatic delineator based on the phasor transform to determine the P-wave fiducial points [19]. This algorithm has been validated making use of databases manually annotated by expert cardiologists, providing sensitivity of 99.27% and positive predictivity of 98.75% in the P-wave detection [19]. Furthermore, the algorithm is able to delineate the P-wave with notably reduced location errors. Indeed, even in the presence of noise provoking a remarkable P-wave distortion, the delineator provided location errors lower than 8 ms [19]. The difference between the automatically detected P-wave onset and offset was defined as its duration.

2.3. Lagged central tendency measure

CTM is a quantitative measure of variability computed from a difference plot [16, 20]. Given a time series $x[n]$ and a lag m , the m -order difference plot corresponds to the

graph $x[n+m+1] - x[n+m]$ versus $x[n+1] - x[n]$. This plot is centered around the origin such that selecting a circular region of radius ρ , CTM is computed by counting the number of points that fall within the radius and dividing by the total number of points. In this way, a low CTM value indicates a large amount of dispersion and a high value indicates concentration near the centre [20]. Variability of the P-wave duration over time was characterized by computing CTM from lags of $m = 1, 2, \dots, 10$.

From a strictly mathematical point of view, given N data points from a time series $x[n]$, $N - m - 1$ would be the total number of points in the scatter plot. Then, m -lagged CTM can be computed as

$$CTM(m) = \frac{\sum_{i=1}^{N-m-1} \delta_m[i]}{N - m - 1}, \quad (1)$$

where

$$\delta_m[i] = \begin{cases} 1, & \text{if } \sqrt{d_m[i]} < \rho, \\ 0, & \text{otherwise.} \end{cases} \quad (2)$$

$d_m[i]$ being the i -th point module, defined as

$$d_m[i] = (x[i+m+1] - x[i+m])^2 + (x[i+1] - x[i])^2. \quad (3)$$

Although the radius ρ is critical in determining the outcome of CTM, no guidelines exist for optimizing its value. Hence, it is usually chosen depending upon the character of the data. In the present study an approach similar to the developed in previous works was used [20, 21]. Thus, for each studied lag CTM was first computed from radius of $\rho = 10, 11, 12, \dots, 200$ ms. Then, for each considered ρ statistical differences between ECG segments far from PAF and close to PAF onset were assessed by means of a U Mann-Whitney test. Finally, the optimal selected radius was determined as the one providing the lowest statistical significance (p -value).

2.4. Performance assessment

The ability of CTM computed from every lag m to discriminate between ECG segments far from PAF and close to PAF was evaluated by means of a ROC curve. This plot is the result of plotting the fraction of true positives (TP) out of positives (sensitivity) against the fraction of false positives out of the negatives ($1 - \text{specificity}$) at various threshold settings. Sensitivity was here considered as the percentage of ECG segments close to PAF which were correctly classified. In a similar way, the rate of the ECG segments far from PAF properly identified was considered as the specificity. The optimal threshold was selected as those that provided the highest percentage of ECG segments correctly classified (i.e. accuracy).

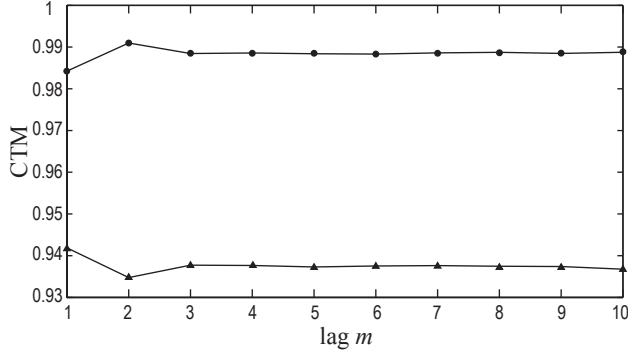


Figure 1. Mean CTM computed for different lags from the ECG segments far from PAF (●) and close to PAF (▲).

3. Results

After computing CTM from every lag, the radius ρ providing the highest statistical differences between ECG segments far and close to PAF ranged from 70 to 75 ms. Once the optimal radius for every lag was chosen, Figure 1 shows its influence on CTM within each group of segments. To this respect, ECG segments far from PAF presented mean CTM values higher than those close to PAF for every lag. However, the lowest differences between groups were noticed for $m = 1$. In this case the mean and standard deviation of CTM were 0.984 ± 0.015 for ECG segments far from PAF and 0.948 ± 0.112 for those close to PAF. Contrarily, CTM for $m = 2$ yielded the highest distance between groups. Thus, values of 0.991 ± 0.014 and 0.935 ± 0.105 were respectively obtained.

Differences between $m = 1$ and $m = 2$ were seen for higher lags. Nonetheless, it should be noted that these differences were not too large. Indeed, a *U* Mann-Whitney test provided statistically significant differences between both groups for every lag. Moreover, Figure 2 does not show very dissimilar m -order difference plots from lags of $m = 1, 2$ and 10 for typical ECG segments far from PAF and close to PAF. Only a slight trend towards a more circular plot was observed for $m \geq 2$.

In line with these findings, no great differences were observed from classification results into ECG segments far from PAF and close to PAF, such as Figure 3 displays. In fact, the maximum distance among sensitivity and specificity values was only about 8%. Nonetheless, an accuracy increase from 80.43% to 83.70% for $m = 1$ and $m = 2$ was also noticed. For higher lags accuracy was 81.52%.

4. Discussion and conclusions

According with a previous work where one-lagged CTM was studied [15], a notable progression in the P-wave duration variability over the two hours preceding the onset

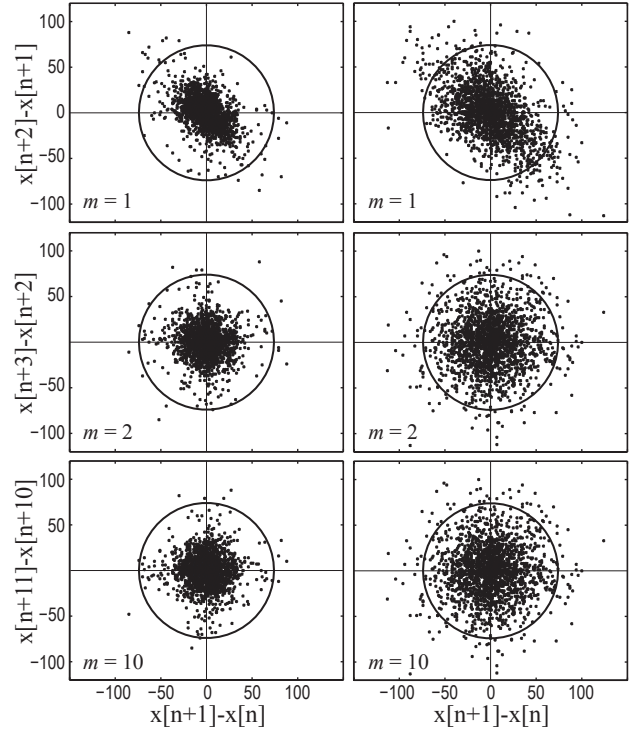


Figure 2. Illustrative example of difference plots for lags $m = 1, 2$ and 10 from a typical ECG segment far from PAF (left column panels) and another ECG segment close to PAF (right column panels).

of PAF was successfully quantified from every lag. As expected, a higher variability was also seen when the arrhythmia onset approximated (see Figure 1). Thus, CTM values closer to unity were observed for the ECG segments far from the onset of PAF. Although no great differences were observed among the CTM values obtained from the studied lags, an accuracy increase of about 3.5% was observed when $m = 2$ was used instead of $m = 1$ (see Figure 3). Moreover, slightly changed difference plots were also noticed for $m \geq 2$ compared with $m = 1$ (see Figure 2). These results suggest that the transition from sinus rhythm to PAF may be a process with a scale-variant structure. This suggestion seems to be coherent with the highly inhomogeneous and fragmented atrial conduction preceding the onset of PAF [11].

The early use of pacing and drug treatments may prevent the recurrence of subsequent PAF episodes, thus yielding electrical stabilization and avoiding that PAF turns into persistent AF [5]. Hence, given this clinical interest, further studies are required to validate more robustly the obtained findings. To this respect, the analysis of a wider database would be desired to assess the reproducibility of the results.

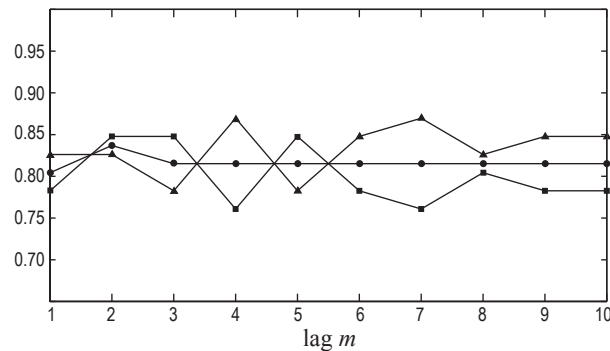


Figure 3. Classification results (accuracy ●, sensitivity ▲ and specificity ■) obtained from CTM as a function of the considered number of lags.

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