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Morphological variability of the P-wave for premature envision of paroxysmal atrial fibrillation events

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Abstract
The present work introduces the first study on the P-wave morphological variability two hours preceding the onset of paroxysmal atrial fibrillation (PAF). The development of non-invasive methods able to track P-wave alterations over time is a clinically relevant tool to anticipate as much as possible the envision of a new PAF episode. This information is essential for further improvement of preventive and patient-tailored treatment strategies, which could avert the loss of sinus rhythm. In this way, risks for the patients could be minimized and their quality of life improved. Recently, the P-wave morphological analysis is drawing increasing attention because differences in morphology can reflect different atrial activation patterns. Indeed, the P-wave morphology study has recently proved to be useful for determining the presence of an underlying pathophysiological condition in patients prone to atrial fibrillation. However, the P-wave morphology variability over time has not been studied yet. In this respect, the present work puts forward some parameters related to the P-wave shape and energy with the ability to quantify non-invasively the notable atrial conduction alterations preceding the onset of PAF. Results showed that P-wave fragmentation and area presented higher variability over time as the onset of PAF approximates. By properly combining these indices, an average global accuracy of 86.33% was achieved to discern between electrocardiogram segments from healthy subjects, far from a PAF episode and less than one hour close to a PAF episode. As a consequence, the P-wave morphology long-term analysis seems to be a useful tool for the non-invasive envision of PAF onset with a reasonable anticipation. Nonetheless, further research is required to
corroborate this finding and to validate the capability of the proposed P-wave metrics in the earlier prediction of PAF onset.

Keywords: atrial fibrillation, electrocardiogram, morphological analysis, P-wave, variability

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice, increasing its incidence with age (Go et al. 2001, Fuster et al. 2011). It affects about 1% of patients younger than 60 yr and about 8% of patients older than 80 yr (Fuster et al. 2011). This arrhythmia may appear as paroxysmal AF (PAF), featuring episodes of AF that terminate spontaneously after some seconds, minutes, hours or even days. In contrast, persistent AF requires external intervention to restore sinus rhythm, whereas permanent AF cannot be converted to sinus rhythm or its termination is not recommended (Gallagher and Camm 1998)

Although the mechanisms leading to the initiation, self-termination or maintenance of this arrhythmia have been under intensive investigation, their whole comprehension is still an open issue for the scientific community (Fuster et al. 2011). It is unknown why AF is self-terminating in certain individuals but not in others, or why the duration of PAF episodes varies from patient to patient and from episode to episode (Petrutiu et al. 2007).

Within this context, once a PAF episode terminates spontaneously, the early prediction of the next PAF episode onset still remains as an unsolved clinical challenge. Although AF itself does not represent a life-threatening condition, it increases the risk of stroke by approximately five-fold, is responsible for approximately 15–20% of all strokes (Hughes et al. 2008, Verheugt 2013) and is associated with a high risk of cardiovascular morbidity (Wolf et al. 1978) and mortality (Kannel et al. 1982). In addition, given that AF leads to electrophysiological changes within the atria, such as electrical, contractile and structural remodeling that reduce the probability of AF termination (Wijffels et al. 1995), the early use of pacing and drug treatments before a PAF episode may prevent the arrhythmia’s recurrence. In this way, patient’s electrical stabilization could be yielded, thus avoiding that PAF degenerates into persistent or permanent AF (Al-Khatib et al. 2000).

Previous works have shown that most PAF episodes are initiated by the presence of rapidly firing atrial ectopic foci (Hassaguerre et al. 1998, Tsai et al. 2000). Given that their occurrence results in premature atrial depolarizations (Kolb et al. 2001), the identification of a wide number of premature atrial complexes in the electrocardiogram (ECG) has proved to be a successful predictor of imminent PAF onset (Thong et al. 2004). However, it has also been noticed that the frequency of these ectopics is considerably decreased as the distance to the episode onset increases (Shin et al. 2006, Vikman et al. 1999). As a detrimental consequence, a feasible prediction would only be possible just before the arrhythmia’s onset, which is too late for the application of an efficient prophylactic therapy (Dimmer et al. 1998, Hogue et al. 1998).

Similarly, a wide variety of methods analyzing the heart rate variability in terms of different time, frequency and complexity parameters have also provided relevant changes few minutes prior to the onset of PAF (Vikman et al. 1999, Shin et al. 2006, Tuzcu et al. 2006, Hickey et al. 2004, Chesnokov 2008, Mohebbi and Ghassemian 2011, 2012). The objective of these works was to assess the autonomic nervous system role in the initiation of PAF, because previous findings suggested that an increased vagal tone could predispose to arrhythmia development (Vikman et al. 1999, Shin et al. 2006, Tuzcu et al. 2006). Furthermore, they also presented the drawback of requiring complex combinations of metrics extracted from the RR series
Recently, the assessment of P-wave morphology has gained increasing interest to identify the risk of AF development (Platonov 2012). P-wave morphology on the ECG is the result of a complex interplay of factors as right atrial depolarization, left atrial depolarization and shape and size of atrial chambers (Platonov 2012). Hence, differences in morphology can reflect different activation patterns, including conduction defects (Platonov 2008), and have been analyzed to determine the presence or absence of an underlying pathophysiological condition in patients prone to AF episodes. Indeed, the evaluation of different P-wave morphological aspects have shown a good ability to identify successfully traces of PAF from the sinus rhythm ECG (Carlson et al 2001, Ishida et al 2010, Clavier et al 2002, Vassilikos et al 2011) and to stratify the risk of long-term AF development (Censi et al 2007, De Bacquer et al 2007, Holmqvist et al 2009). In addition, the P-wave morphology study has revealed to bear a prognostic value for prediction of clinical outcome beyond the AF context, including acute myocardial infarction (Mehta et al 1997) or heart failure-related death (Holmqvist et al 2010).

Nonetheless, it is interesting to note that in most of the previous works such a type of morphological features have been computed from the signal-averaged P-wave (Carlson et al 2001, Ishida et al 2010, Censi et al 2007, Holmqvist et al 2009). In this way, drawbacks derived from the relatively low P-wave amplitude, with respect to background noise, can be partially palliated and subtle P-wave shape changes can be appropriately quantified (Censi et al 2008). On the other hand, although a beat-to-beat P-wave analysis has been developed in other studies, only reduced time intervals lower than 1 min-length were considered (Clavier et al 2002, Vassilikos et al 2011, De Bacquer et al 2007). Hence, not too much attention has been previously paid to the P-wave morphology time course during tens of minutes or even hours. Therefore, this work focuses on quantifying P-waves morphological variability during the two hours preceding the onset of PAF. This study represents an initial step in the global aim of determining the earliest reliable anticipation able to predict the onset of a PAF episode through the atrial electrical activity non-invasive study.

The remainder of the paper is organized as follows. Section 2 describes the used database, whereas section 3 presents the preprocessing applied to the P-wave and how its morphological variability over time is quantified. Section 4 summarizes the obtained results, which are then discussed in section 5. Finally, section 6 presents the concluding remarks.

2. Materials

The database consisted of 46 patients (18 men, mean age of 63.2 ± 10.2 yr) suffering from PAF and 53 healthy individuals, age- and gender-matched to the PAF patients (21 men, mean age of 61.9 ± 9.1 yr). None of the PAF patients were under antiarrhythmic drug treatment at the time of the study and suffered from heart disease, hyperthyroidism or pulmonary disease. 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 (Bollmann et al 1999). The number of arrhythmic events per patient was 2.9 ± 1.8 in mean, with an average duration of 4.1 ± 2.2 hr. The shortest episode duration was 59 min. From each patient, the longest sinus rhythm interval in the recording was selected and the two hours segment preceding the onset of PAF was analyzed. To evaluate the proposed method ability in following P-wave features over time, 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 as ECG segments close to PAF. The second set comprised those segments one hour away from
the episode and will be named as ECG segments far from PAF. Finally, to obtain a control set, an ECG segment of one hour in length was randomly chosen from the Holter recording of each healthy subject. It is interesting to note that none of these subjects had presented any previous history of arrhythmia or structural heart disease.

Following previous recommendations about time and amplitude resolutions for the appropriate P-wave analysis (Censi et al. 2012), the Holter recordings were acquired with a sampling rate of 1000 Hz and 16-bit resolution over an amplitude range of ± 10 mV. Although three leads were recorded (II, aVF, and V1), only V1 was considered in the study because P-waves were larger in this lead.

3. Methods

3.1. Signal preprocessing

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 (Martínez et al. 2010). This algorithm has been validated making use of databases manually annotated by expert cardiologists, providing a sensitivity of 99.27% and a positive predictivity of 98.75% in the P-wave detection. 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 (Martínez et al. 2010). Briefly, the algorithm first preprocesses the original ECG \( y[n] \) by applying a forward/backward filtering strategy to remove the baseline wander and high frequency noise. The power-line interference is reduced by an adaptive filtering based on the LMS algorithm. It is interesting to note that the bidirectional filtering has proved to preserve the P-wave fiducial points (Censi et al. 2009, Clavier et al. 2002). Next, each instantaneous preprocessed ECG sample \( \tilde{y}[n] \) is converted into a phasor with magnitude \( M[n] \) and phase \( \varphi[n] \), such that \( PT[\tilde{y}[n]] = M[n]e^{j\varphi[n]} \). Given that the maximum instantaneous phase variation in the ECG is found on the QRS complexes, these waves were located as the segments exceeding a threshold in \( \varphi[n] \). Next, the corresponding R-peak was marked as the maximum magnitude point within the segment. Thereafter, an adaptive windowing, relative to the R-peak position, was used to detect the presence of the P-wave in each beat. When a P-wave was found, the P-peak was marked as the maximum value within the seek window. Around this peak, two 75 ms windows were established and the local minima within them, detected by the first derivate of \( \varphi[n] \), were provided as the P-wave onset \( (n_o) \) and offset \( (n_e) \). Then, the P-wave was extracted from the ECG as

\[
u[n] = (y[n_o], y[n_o + 1], \ldots, y[n_e]) \quad \text{for } n = 1, 2, \ldots, L; \tag{1}\]

\( L \) being its total length in samples. Obviously, this index will be slightly different for every P-wave, because each one will have a different length. More details on the algorithm can be found in Martínez et al. (2010). Finally, a baseline was constructed by linear interpolation between the amplitudes at inception and termination of the P-wave and was removed by subtraction. After this processing, the P-wave is referred to as \( \tilde{w}[n] \).

It has to be remarked that ectopic beats are early heart beats remarkably different to the normal beat morphology. Indeed, to detect accurately their ECG fiducial points, some previously proposed automatic delineation algorithms required the application of special detection rules (Ghaffari et al. 2009, Arzeno et al. 2008, Martínez et al. 2004). In contrast, the previously described algorithm does not need to differentiate between normal and ectopic beats for their proper delineation (Martínez et al. 2010). Thus, both normal beats and atrial premature
complexes were considered in the same way to estimate the P-wave morphology variability over time. Finally, note that the P-wave detection and delineation for all the recordings under study were visually supervised by expert cardiologists. In this process, P-waves masked by the end of the preceding T-wave or notably distorted by noise were discarded. However, less than 4% of the all the analyzed P-waves were finally removed from the study.

3.2. P-wave morphological variability over time

Once every P-wave was delineated and preprocessed, several morphological features were computed for its characterization. Hence, given that previous works have suggested that inhomogeneous intra- and inter-atrial electrical conduction predisposes to the development of AF (Sovilj et al. 2010, Vassilikos et al. 2011), maximum and minimum conduction velocities during the atrial depolarization were estimated as Sovilj et al. (2010)

\[ v_{\text{max}} = \max_{n=2,3,...,L} (\tilde{w}[n] - \tilde{w}[n-1]) \quad \text{and} \]
\[ v_{\text{min}} = \min_{n=2,3,...,L} (\tilde{w}[n] - \tilde{w}[n-1]), \]

respectively. Moreover, the dispersion in the propagation velocity during the depolarization process was also obtained as

\[ v_{\text{disp}} = v_{\text{max}} - v_{\text{min}}. \]  

On the other hand, altered and fractioned atrial activity seems to be reflected as the appearance of bumps in the P-wave normal Gaussian shape (Censi et al. 2007), which could provoke even phase changes in lead V1 (Ishida et al. 2010). Hence, to identify this morphological alteration prior to the onset of PAF, the arc length of each P-wave (\( P_{al} \)) was computed as

\[ P_{al} = \sum_{n=2}^{L} \sqrt{1 + (\tilde{w}[n] - \tilde{w}[n-1])^2}. \]

Given that this parameter measures the rectified P-wave length, it can be useful to discern between normal and abnormal P-waves with similar duration, such as figure 1 shows for two typical examples. Indeed, as can be appreciated in both cases, normal and abnormal P waves present the same duration, but the arc length is notably higher for the wave with abnormal morphology.
Some additional parameters related to the P-wave amplitude were also used to quantify other possible alterations in the atrial depolarization preceding the onset of PAF. Thus, the normalized root mean square value and the area of the P-wave were computed as

\[
P_{\text{rms}} = \sqrt{\frac{1}{L} \sum_{n=1}^{L} \tilde{w}[n]^2},
\]

and

\[
P_{\text{area}} = \sum_{n=1}^{L} \left| \tilde{w}[n] \right|,
\]

respectively. These indices have been previously associated with the amount of electrical mass depolarized in each atrial beat, reporting a notable decrease after catheter-based ablation of pulmonary veins (Van Beeumen et al. 2010) and after external electrical cardioversion (Stafford et al. 1998). Finally, taking into account that the P-wave amplitude could affect directly to its arc length as well as to its energy, their relationship was analyzed by normalizing the two previous parameters with respect to the rectified P-wave length, such that

\[
P_{\text{energy}} = \frac{P_{\text{rms}}^2}{P_{\text{al}}},
\]

and

\[
P_{\text{area}} = \frac{P_{\text{area}}}{P_{\text{al}}},
\]

respectively.

On the other hand, the variability of these parameters over the one hour-length recordings was estimated in the same way as in a previous work, in which variability time course of temporal P-wave features was successfully assessed (Martínez et al. 2012). In this case, only parameters related to the P-wave timing were assessed without studying morphological features. This method allowed a remarkable noise reduction in the analysis, which is required given the relatively low P-wave amplitude in the ECG with respect to the background noise (Censi et al. 2008). Briefly, data series obtained wave-to-wave for each analyzed parameter were divided into segments of ten samples. Next, the variability within each segment was computed as the difference between the 90- and 10-quantiles. In this way, outliers originated by impulse noise or artifacts could be rejected. As the endmost step, the parameter variability time course was estimated by using the least-squares method in order to fit a linear model to the data. Thus, a positive value of the fitting line slope (\(\alpha\)) suggests increasing variability and, therefore, higher dispersion in the data. In contrast, a negative value indicates decreasing trend in the data variability, thus reaching more stable values. Finally, constant values of the parameter over the studied time period could be represented by a value of \(\alpha\) close to zero.

3.3. Performance assessment

The performance of each single parameter variability to discriminate between ECG segment groups was evaluated by means of a stratified two-fold cross-validation. Thus, the database was first partitioned into two equally sized folds, rearranging the data to ensure that each fold is a good representative of the whole. Subsequently, two iterations of training and validation were performed, such that within each iteration a fold of the data was held out for validation whereas the other was used for learning. For each learning set, two receiver operating characteristic (ROC) curves were used to obtain discriminant thresholds between ECG segments close to PAF and far from PAF onset and between ECG segments far from PAF onset and from healthy subjects. Each ROC was created by plotting the fraction of true positives out of positives versus the fraction of false positives out of negatives at various threshold setting. The \(\alpha\) value...
Table 1. Classification results into ECG segments from healthy subjects, far from PAF and close to PAF provided by the slope \( \alpha \) computed for each single parameter. The global accuracy obtained for each metric is also provided.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Healthy subjects</th>
<th>Far from PAF</th>
<th>Close to PAF</th>
<th>Global accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \nu_{\text{max}} )</td>
<td>90.01%</td>
<td>86.95%</td>
<td>55.22%</td>
<td>42.17%</td>
</tr>
<tr>
<td>( \nu_{\text{min}} )</td>
<td>90.58%</td>
<td>87.96%</td>
<td>45.00%</td>
<td>35.87%</td>
</tr>
<tr>
<td>( \nu_{\text{disp}} )</td>
<td>90.60%</td>
<td>88.60%</td>
<td>40.22%</td>
<td>35.87%</td>
</tr>
<tr>
<td>( P_{\text{a}} )</td>
<td>96.62%</td>
<td>89.98%</td>
<td>79.57%</td>
<td>68.75%</td>
</tr>
<tr>
<td>( P_{\text{rms}} )</td>
<td>86.82%</td>
<td>83.82%</td>
<td>58.26%</td>
<td>52.39%</td>
</tr>
<tr>
<td>( P_{\text{area}} )</td>
<td>90.72%</td>
<td>87.76%</td>
<td>70.22%</td>
<td>60.91%</td>
</tr>
<tr>
<td>( P_{\text{energy}} )</td>
<td>86.42%</td>
<td>82.94%</td>
<td>51.52%</td>
<td>40.65%</td>
</tr>
<tr>
<td>( P_{\text{area}} )</td>
<td>89.05%</td>
<td>86.58%</td>
<td>55.43%</td>
<td>46.09%</td>
</tr>
</tbody>
</table>

providing the highest percentage of ECG segments correctly classified, that is, the accuracy, was selected as optimum threshold. Thereafter, these two thresholds were used to determine from the test set the number of ECG segments correctly classified for each group and the global accuracy, i.e., the ratio between the correctly classified ECG segments and the total number of analyzed ones. Finally, these values were averaged for the two iterations.

Moreover, a decision tree was assembled to investigate non-monotonic relationships among single parameters, thus improving group classification. The used stopping criterion for the tree growth was that each node contained only observations of one class or fewer than 20\% of all the observations. Moreover, the impurity-based Gini index was used to look for the best parameter and its threshold for the splitting of each node (Breiman 1984). As for the single metrics, the decision tree classification performance was also assessed making use of a stratified two-fold cross-validation strategy.

3.4. Statistical analysis

Both Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess \( \alpha \) distribution normality for each single parameter, whereas homocedasticity was verified with Levene’s test. For the metrics meeting parametric test assumptions, statistical differences among \( \alpha \) distributions for the three ECG segment groups were tested by a one-way ANOVA test, the \( t \)-Student’s test being used to focus on the difference between pairs of groups. On the contrary, differences between ECG segment groups for non-normal and non-homoscedastic features were assessed by non-parametric Kruskal–Wallis and U Mann–Whitney tests, respectively. In all the cases, a statistical significance (\( p \)) value lower than 0.05 was considered as significant.

4. Results

In order to obtain a reliable performance estimation, a stratified two-fold cross-validation was run five times for each single parameter, ten learning and ten test sets being analyzed. Thus, the number of ECG segments correctly classified for each group as well as the global accuracy value presented in table 1 were averaged for the corresponding ten folds. As can be appreciated, all the parameters reached a notable ability to identify ECG segments from healthy subjects, the accuracy being higher than 82\% in all the cases. However, ECG segments far from PAF and close to PAF were only identified by \( P_{\text{a}} \) and \( P_{\text{area}} \) with an accuracy higher than 60\% and 70\%, respectively. Hence, these parameters presented the highest predictive
abilities. Indeed, the P-wave arc length variability reported the highest global accuracy for the test sets, which was around 80%. Moreover, it reached a discriminant ability of 94.48% and 86.96% between ECG segments from healthy subjects and PAF patients and between ECG segments far from PAF and close to PAF, respectively. The second parameter with higher predictive power was the P-wave area, reporting a global accuracy slightly above 75% for the test sets. The remaining metrics provided a more limited discriminant ability, presenting a global classification outcome lower than 70%.

In agreement with these results, the most statistically significant differences among ECG segment groups were also noticed for \( \alpha \) values computed from the P-wave arc length and area, such as table 2 shows. Nonetheless, it is worth noting that remarkable differences among groups were observed for all the analyzed parameters, the statistical significance always being lower than 0.01. A very similar behavior was observed when the differences between pairs of groups were evaluated. However, it has to be remarked that parameters related to the propagation velocity during atrial depolarization provided statistically non-significant differences between ECG segments far from PAF and close to PAF. On the other hand, it can also be appreciated in table 2 how \( \alpha \) values presented an increasing trend, for all the parameters, from ECG segments for healthy subjects to ECG segments far from PAF and, next, to ECG segments close to PAF.

Finally, the decision tree provided that the optimal combination of parameters was also achieved by the P-wave arc length and area. As for single parameters, this classifier performance was validated by running five times a stratified two-fold cross-validation. For every learning set, the same decision structure based on the P-wave arc length and area and similar splinting values for the nodes were observed. Figure 2 shows the obtained decision tree corresponding to one of the iterations. As can be seen, ECG segments from healthy subjects were identified by the \( \alpha \) values closer to zero for the P-wave area. In contrast, higher values of \( \alpha \) were noticed both for P-wave area and arc length as the onset of PAF approximates. On the other hand, the global accuracy achieved by this classifier for the test sets improved more than 6% and 10%, in average, the one presented by the P-wave arc length and area as single classifiers, respectively. Indeed, the decision tree showed an averaged global accuracy of 86.33%, discerning appropriately 95.42%, 79.29% and 83.98% of ECG segments from healthy subjects, far from PAF and close to PAF, respectively. In addition, an accuracy of 95.42% was achieved in the discrimination between ECG segments from healthy subjects and patients suffering from PAF with a false positive rate lower than 5.52%.

5. Discussion

The time in advance with which a PAF episode onset can be predicted is today a relevant clinical challenge. This information could be useful in the development of tailored preventive treatments to avert the loss of normal sinus rhythm (Ishida et al 2010). To the best of our
Table 2. Mean and standard deviation of the slope $\alpha$ computed from the analyzed parameters for the three considered ECG segment groups. The statistical significance obtained from the three ECG segment groups is also presented.

<table>
<thead>
<tr>
<th>Feature</th>
<th>ECG segments from healthy subjects</th>
<th>ECG segments far from PAF</th>
<th>ECG segments close to PAF</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{max}$</td>
<td>$6.54 \times 10^{-7} \pm 2.25 \times 10^{-6}$</td>
<td>$6.40 \times 10^{-6} \pm 1.20 \times 10^{-5}$</td>
<td>$1.26 \times 10^{-5} \pm 2.66 \times 10^{-5}$</td>
<td>$2.01 \times 10^{-3}$</td>
</tr>
<tr>
<td>$V_{min}$</td>
<td>$7.43 \times 10^{-7} \pm 4.07 \times 10^{-6}$</td>
<td>$6.58 \times 10^{-6} \pm 1.05 \times 10^{-5}$</td>
<td>$1.58 \times 10^{-5} \pm 3.12 \times 10^{-5}$</td>
<td>$6.32 \times 10^{-4}$</td>
</tr>
<tr>
<td>$V_{disp}$</td>
<td>$9.28 \times 10^{-7} \pm 2.36 \times 10^{-6}$</td>
<td>$1.16 \times 10^{-5} \pm 2.13 \times 10^{-5}$</td>
<td>$2.72 \times 10^{-5} \pm 5.76 \times 10^{-5}$</td>
<td>$1.12 \times 10^{-3}$</td>
</tr>
<tr>
<td>$P_d$</td>
<td>$2.69 \times 10^{-3} \pm 2.40 \times 10^{-3}$</td>
<td>$2.50 \times 10^{-2} \pm 1.79 \times 10^{-2}$</td>
<td>$8.31 \times 10^{-2} \pm 5.19 \times 10^{-2}$</td>
<td>$2.15 \times 10^{-25}$</td>
</tr>
<tr>
<td>$P_{rms}$</td>
<td>$4.29 \times 10^{-6} \pm 1.15 \times 10^{-5}$</td>
<td>$4.58 \times 10^{-5} \pm 5.32 \times 10^{-5}$</td>
<td>$1.45 \times 10^{-4} \pm 1.66 \times 10^{-4}$</td>
<td>$2.18 \times 10^{-10}$</td>
</tr>
<tr>
<td>$P_{area}$</td>
<td>$4.64 \times 10^{-4} \pm 1.28 \times 10^{-3}$</td>
<td>$4.74 \times 10^{-3} \pm 4.97 \times 10^{-3}$</td>
<td>$1.80 \times 10^{-2} \pm 1.92 \times 10^{-2}$</td>
<td>$3.03 \times 10^{-12}$</td>
</tr>
<tr>
<td>$P_{energy}$</td>
<td>$1.27 \times 10^{-8} \pm 3.73 \times 10^{-8}$</td>
<td>$2.72 \times 10^{-7} \pm 4.94 \times 10^{-7}$</td>
<td>$9.40 \times 10^{-7} \pm 1.94 \times 10^{-6}$</td>
<td>$2.68 \times 10^{-4}$</td>
</tr>
<tr>
<td>$P_{area}$</td>
<td>$3.70 \times 10^{-6} \pm 8.61 \times 10^{-6}$</td>
<td>$4.34 \times 10^{-5} \pm 5.05 \times 10^{-5}$</td>
<td>$1.29 \times 10^{-4} \pm 1.27 \times 10^{-4}$</td>
<td>$1.54 \times 10^{-10}$</td>
</tr>
</tbody>
</table>
knowledge, there is only one recent work that has tried to assess the P-wave evolution over time (Martínez et al., 2012). In that study, the time course of P-wave features, defined as temporal distances among its fiducial points, were studied in depth. The P-wave duration variability over time provided the highest statistical differences among groups of ECG segments as well as the best classification results. Discriminant abilities slightly higher than 90% and 80% between ECG segments from healthy subjects and PAF patients and between ECG segments far from PAF and close to PAF were achieved, respectively (Martínez et al., 2012).

Hence, the present work is the first study analyzing the P-wave morphological variability over time. It has been shown that the rectified P-wave length variability over time provided the highest statistical differences between groups of ECG segments and the best classification results from all the analyzed P-wave morphological features. Although the $P_d$ global accuracy for the three considered ECG segment groups was similar to those reported by the P-wave duration variability, that is around 80% (Martínez et al., 2012), the arc length provided a considerably higher ability in discerning between ECG segments from healthy subjects and PAF patients (94.48%) and between ECG segments far from PAF and close to PAF onset (86.96%). Moreover, a notably wider database and a more robust statistical analysis has been carried out in the present study than in the previous aforesaid work, in which P-wave duration variability was analyzed (Martínez et al., 2012).

Results also indicated that P-wave morphological features showed an increased variability trend as the PAF onset approximated. Therefore, they can be identified as potential risk indicators of PAF. This outcome is in agreement with the intermittently disturbed conduction observed in the atrial tissue susceptible to PAF (Dilaveris and Gialafos, 2001). Electrophysiological and geometrical abnormalities in the atria result in a nonuniform and anisotropic atrial conduction, which plays a major role in the initiation of reentry (Dilaveris and Gialafos, 2001). Moreover, other intra- or inter-cellular factors can cause the genesis of site-specific conduction delays (Papageorgiou et al., 1996, Platonov, 2012), which together with the presence of structural abnormalities in the atrial walls may alter constantly the way through which the sinus beat travels across the atria (Platonov, 2012). This site-dependent inhomogeneous atrial conduction results in a highly variable P-wave morphology. To this respect, highly fractionated atrial endocardial electrograms have been observed in patients close to the onset of PAF (Dilaveris and Gialafos, 2001).

In line with the present work, other authors have also suggested a greater P-wave morphology alteration when AF onset approximates. Thus, Censi et al. (Censi et al., 2007) reported more fragmented P-waves, modeled by a linear combination of Gaussian functions, in patients with higher risk of developing PAF. In a similar way, P-wave complexity after coronary artery bypass grafting, estimated by singular value decomposition (Gang et al., 2004) or wavelet analysis (Vassilikos et al., 2003), resulted higher in those patients who developed postoperative AF compared to those others who did not. Finally, Barbosa et al. (Benchimol-Barbosa et al., 2006) introduced the P-wave spectral turbulence analysis. They found that the higher the atrial electrical activity fragmentation, the higher the AF recurrence after electrical cardioversion. However, none of these methods was specifically designed nor used to track the P-wave morphological evolution over time, as the one presented here.

Remark that delays in atrial conduction velocity can provoke a similar increase both in the P-wave duration and its rectified length. However, as shown in figure 1, the arc length has the ability to discern between waves of similar duration remarkably different in morphology. Thus, high values of the rectified P-wave length can be due to the presence of bumps on its waveform, such as indicated in the examples of figure 1. Overall, it can be considered that the P-wave arc length could provide additional morphological information to the one revealed by the P-wave duration. Nonetheless, future studies are required to analyze the relationship between P-wave
duration and P-wave arc length, as well as the possible complementary information carried by them.

The second group of interesting parameters after Pставил were those related to the P-wave energy. Thus, the P-wave area variability over time presented the second highest global accuracy for the test sets, around 75%. However, its normalization by the arc length did not provide any remarkable improvement in the group classification, thus suggesting a non-relevant overlapping between them provoked by variations in the P-wave amplitude. Indeed, a statistically non-significant correlation between the variability of these parameters was noticed. In contrast, their nonlinear combination through a decision tree increased the global accuracy above 86% for the test sets, which is indicative of a notable complementarity in their information. In addition, this discriminant model based on the $P_{\text{area}}$ and $P_{\text{al}}$ also identified appropriately more than 98% of the ECG segments from healthy subjects with a false positive rate lower than 6%. This result is very interesting, because discovering traces of PAF from the sinus rhythm ECG, i.e. when PAF is not occurring, is also a relevant clinical challenge (Hickey et al. 2004).

Regarding the P-wave energy, previous works have reported higher energy values for PAF patients than for healthy subjects in the signal-averaged P-wave (Stafford et al. 1995). Similarly, within PAF patients, higher energy values have been observed in those patients with an increased number of episodes (Vassilikos et al. 2011). Additionally, some authors have also reported that the P-wave energy is reduced by treatment with antiarrhythmic drugs, whose main action on atrial muscle is to lengthen the refractory period without affecting conduction velocity, thus suggesting that this metric may be a non-invasive marker of atrial refractoriness (Stafford et al. 1998). Obtained results for the metrics $P_{\text{area}}$, $P_{\text{nrms}}$, $P_{\text{energy}}$ and $P_{\text{narea}}$ are strongly coherent with this finding, given that the heterogeneity of the cell refractory periods in different atrial regions, as aforementioned, could be the origin of the noticed increasing variability in the P-wave energy as PAF onset approximates. Nonetheless, it has to be noted that previous works computed the P-wave energy in the frequency (Stafford et al. 1995) or wavelet (Vassilikos et al. 2011) domains. In contrast, the present work quantified P-wave energy from the time domain.

Finally, some limitations merit consideration. First, the present work was a retrospective study with a limited sample size. Larger prospective studies are needed to further validate the proposed P-wave morphological features. Second, the P-wave morphological variability two hours before the onset of PAF has only been assessed. Thus, extended studies considering wider time intervals before the onset of PAF would be developed in future works. Finally, although some authors recommend evaluating the P-wave in lead II (De Bacquer et al. 2007, Clavier et al. 2002), only lead V1 was analyzed. However, this lead provides additional information concerning intra-atrial conduction defects because it can reflect the posterior left atrial potential, unseen in the limb leads (Passman et al. 2001).

6. Conclusions

Morphological variations of the P-wave features two hours preceding paroxysmal atrial fibrillation (PAF) onset have been analyzed for the first time in the present study. Results have shown that the higher the variability in the P-wave fragmentation and area, the higher the risk of PAF onset. This finding is in agreement with the intermittently disturbed conduction observed in the atrial tissue preceding the onset of PAF. As a consequence, the P-wave morphology long-term analysis has proved to be a useful tool for the non-invasive envision of PAF onset with a reasonable anticipation. However, extended studies considering wider time intervals before the onset of PAF would be desirable in future works.
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