ORIGINAL ARTICLE

The P Wave Time-Frequency Variability Reflects Atrial Conduction Defects before Paroxysmal Atrial Fibrillation

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Background: The study of atrial conduction defects associated with the onset of paroxysmal atrial fibrillation (PAF) can be addressed by analyzing the P wave from the surface electrocardiogram (ECG). Traditionally, signal-averaged ECGs have been mostly used for this purpose. However, this alternative hinders the possibility to quantify every single P wave, its variability over time, as well as to obtain complimentary and evolving information about the arrhythmia. This work analyzes the time progression of several time and frequency P wave features as potential indicators of atrial conduction variability several hours preceding the onset of PAF.

Methods: The longest sinus rhythm interval from 24-hour Holter recordings of 46 PAF patients was selected. Next, the 2 hours before the onset of PAF were extracted and divided into two 1-hour periods. Every single P wave was automatically delineated and characterized by 16 time and frequency metrics, such as its duration, absolute energy in several frequency bands and high-to-low-frequency energy ratios. Finally, the P wave variability over each 1-hour period was estimated from the 16 features making use of a least-squares linear fitting. As a reference, the same parameters were also estimated from a set of 1-hour ECG segments randomly chosen from a control group of 53 healthy subjects age-, gender-, and heart rate-matched.

Results: All the analyzed metrics provided an increasing P wave variability trend as the onset of PAF approximated, being P wave duration and P wave high-frequency energy the most significant individual metrics. The linear fitting slope α associated with P wave duration was $(2.48 \pm 1.98) \times 10^{-2}$ for healthy subjects, $(23.8 \pm 14.1) \times 10^{-2}$ for ECG segments far from PAF and for $(81.8 \pm 48.7) \times 10^{-2}$ ECG segments close to PAF $p = 6.96 \times 10^{-22}$. Similarly, the P wave high-frequency energy linear fitting slope was $(2.42 \pm 4.97) \times 10^{-9}$, $(54.2 \pm 107.1) \times 10^{-9}$ and $(274.2 \pm 566.1) \times 10^{-9}$, respectively ($p = 2.85 \times 10^{-20}$). A univariate discriminant analysis provided that both P wave duration and P wave high-frequency energy could discern among the three ECG sets with diagnostic ability around 80%, which was improved up to 88% by combining these metrics in a multivariate discriminant analysis.

Conclusion: Alterations in atrial conduction can be successfully quantified several hours before the onset of PAF by estimating variability over time of several time and frequency P wave features.

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In recent years, the P wave analysis from electrocardiogram (ECG) recordings has become a useful tool for gathering information about the atrial conduction defects that predispose patients to paroxysmal atrial fibrillation (PAF).¹ Indeed, averaged P wave duration has been accepted as the most reliable noninvasive marker of atrial conduction. Its prolongation from signal-averaged ECG recordings has been associated with history of atrial

fibrillation (AF),² development of arrhythmias after bypass surgery,³ and progression from paroxysmal to persistent AF.⁴ In addition, other investigations have also underscored the relevance of P wave morphology analysis in PAF prediction.² Thus, the signal-averaged P wave spectral analysis has revealed an interesting ability to discern between PAF patients and healthy subjects,^{5–7} to quantify the effects of low-dose Sotalol in PAF patients,⁸

and to stratify the risk of recurrence of arrhythmic episodes over a time period of 1 year in PAF patients.⁹ However, P wave averaging needs a wide sequence of waves to sufficiently reduce the ECG background noise,¹⁰ thus hindering the interesting possibility to quantify every single P wave and its variability over time.

Although not completely understood, the transition from sinus rhythm to PAF is often associated with progressive atrial electrophysiological alterations that may cause discontinuous propagation of the sinus impulses.¹¹ This work thus hypothesizes that the study of time and frequency features associated with every single P wave, as well as their progression over time, could provide new and clinically relevant information about the atrial conduction defects taking place several hours before the onset of PAF. To this respect, understanding of the pathophysiological mechanisms underlying PAF as well as assessing atrial electrophysiological properties using easily available noninvasive tools are essential for further improvement of PAF patient-tailored treatment strategies.⁹

METHODS

Study Population

All the subjects attending the Hospital Emergency Department with symptoms of palpitations, dizziness, chest pains, and breathlessness over a 6-month period (November 2010–April 2011) were screened and underwent Holter monitoring for 24 hours. Once PAF was diagnosed, every arrhythmic patient without structural heart disease, hyperthyroidism, or pulmonary disease was enrolled in the study. The final database consisted of 46 patients. Remark that none of them had previous history of AF. Therefore, any patient was under antiarrhythmic drug treatment at the time of the study. Expert cardiologists annotated AF episodes, defined by irregular ventricular response and absence of P waves.¹² The mean number of arrhythmic events per patient was 2.9 ± 1.8 , with an average duration of 4.1 ± 2.2 hours. The shortest episode duration was 59 minutes. Finally, 53 healthy volunteers, without previous history of arrhythmia or structural heart disease and recruited during the same time period, were used as a control set. In order to avoid possible confounding effects in the study, these healthy

individuals were age-, gender-, and heart rate-matched to the PAF patients, i.e., no statistically significant differences were found in terms of their mean values. The demographic and clinical characteristics of all the studied subjects are presented in Table 1.

P Wave Preprocessing

For every PAF patient, a 24-hour Holter recording was acquired on a Medilog FD12 recorder (Schiller, Switzerland) with a sampling rate of 1000 Hz. The longest sinus rhythm interval was selected and the 2 hours before the onset of PAF were extracted and divided into two 1-hour periods. This division aimed to evaluate the proposed approach ability to quantify P wave variability over time. 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 1 hour away from the episode onset and will be named as ECG segments far from PAF. With regard to the control group, an ECG segment of 1 hour in length was randomly chosen from the Holter recording of every healthy subject enrolled in the study.

Once the ECG segments were defined, P waves were automatically detected from lead V₁ and their boundaries delineated making use of a previously published automatic delineation algorithm.¹³ The greatest advantages of automatic P wave delineation are related to measurement reproducibility and quality.¹⁴ Nonetheless, P wave detection and delineation for all the recordings under study was 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. Finally, less than 4% of all the analyzed P waves were removed from the study. This set of P waves has been named as unedited data.

On the other hand, it is well known that AF is often preceded by premature atrial beats.¹⁵ In fact, the identification of a wide number of premature atrial complexes in the ECG has proved to be a successful predictor of imminent PAF onset.¹⁶ However, it has also been observed that the frequency of these ectopic beats is considerably decreased as the distance to the episode onset increases.^{17,18} Thus, in order to study the effect of this kind of beats on the proposed P wave variability time course, they were identified and removed from the analyzed time series. For that

Table 1. Baseline Demographic and Clinical Characteristics of the Studied Database

	PAF Patients (N = 46)	Healthy Subjects (N = 53)	P
Age (years)	63.2 ± 10.2	61.9 ± 9.1	> 0.05
Gender (M/F)	18/28	21/32	> 0.05
Height (m)	1.68 ± 0.11	1.70 ± 0.12	> 0.05
Weight (kg)	69.3 ± 9.8	70.3 ± 10.1	> 0.05
Heart rate (beats/min)	68.4 ± 7.1	64.2 ± 4.2	> 0.05
Respiratory rate (breaths/min)	13 ± 1	13 ± 1	> 0.05
QRS duration (ms)	82.3 ± 20.2	79.4 ± 19.7	> 0.05
PQ duration (ms)	164.1 ± 1.6	162.9 ± 24.5	> 0.05

purpose, the algorithm proposed by Hickey et al.¹⁹ was used. This filtered set of P waves was named as edited data.

Time Analysis of the P Wave

As stated in the Introduction, the most widely studied P wave time feature is its duration (P_{dur}).² In this study, the duration of every single P wave was computed as the distance between the P wave offset and onset, expressed in seconds, such as Figure 1A shows. Similarly, the variability in the series of distances between the peak of successive P waves (PP_k) was also quantified, as can also be appreciated in Figure 1A. This parameter provides information about the atrial depolarization variability. Moreover, a recent work has proved its notable ability to identify the onset of PAF and to reveal additional information than that carried by the RR series variability.²⁰

Frequency Analysis of the P Wave

The P wave spectral analysis has proved its ability to identify fragmentation in atrial conduction, which is an accepted indicator of PAF onset.^{2,11} Indeed, whereas the spectral content of a normal P wave is considered to be of low frequency, below 20 Hz,²¹ high frequency components can be displayed in fragmented P waves.^{5,6} Thus, several spectral metrics were considered to estimate the P wave high frequency content in order to identify its fragmentation. In this line, for every P wave a baseline was first constructed by linear interpolation between the amplitudes at its inception and termination and was removed by subtraction. Next, the P wave spectral content, $S(f)$, was obtained by means of a fourth-order autoregressive estimation. This parametric approach was preferred, instead of

traditional fast Fourier transform-based methods, because higher frequency resolution is achieved when short-duration signals (e.g., a P wave) are only available.²² Then, P wave energy was quantified by cumulative summation of the energies contained in frequency bands ranging from 20, 30, 40, 60, and 80 Hz up to 150 Hz, such as in previous works.⁵⁻⁸ These energies were expressed as absolute values P_{20} , P_{30} , P_{40} , P_{60} and P_{80} , respectively) and as energy ratios defined by

$$PR_F = \frac{P_F}{1 - P_F} = \frac{\sum_{f=F\text{Hz}}^{150\text{Hz}} S(f)}{\sum_{f=10\text{Hz}}^{F\text{Hz}} S(f)}, \quad (1)$$

where F was set to 20, 30, 40, 60, and 80 Hz (PR_{20} , PR_{30} , PR_{40} , PR_{60} , and PR_{80}).⁵⁻⁸ A graphical computation of these metrics is displayed in Figure 1B.

Although the P wave spectral content has been widely analyzed from frequencies near to zero up to 150 Hz,⁵⁻⁸ a recent work has revealed statistically significant differences among healthy subjects and PAF patients from higher frequency energies. Indeed, Vassilikos et al.⁹ defined the low (50–90 Hz), medium (100–150 Hz), and high (160–200 Hz) frequency bands and the maximum energy in each one of them was computed. These three metrics were also analyzed in this work, being referred to as *MLF*, *MMF*, and *MHF*, respectively. Their computation from a graphical point of view can be appreciated in Figure 1B.

Finally, the last analyzed parameter from the frequency domain was the median frequency (f_m), which is a simple index that summarizes the whole spectral content. It was defined as the frequency dividing the P wave spectral content, from 10 up to 150 Hz, in two parts having the same amount

Figure 1. Graphical summary about how each analyzed P wave (A) time and (B) frequency feature has been defined and computed.

of power, such as Figure 1B shows. The index has also been widely used in previous works.⁵⁻⁸ It is interesting to note that this index has proven previously a significant ability to differentiate among P waves with normal and abnormal morphology.²³ Indeed, uniform conduction during atrial activation provided low values of f_m , whereas the presence of high-frequency components due to nonuniform conduction and randomly varying activations were reflected by high values of this feature. Nonetheless, remark that in this case the authors computed the median frequency from the P wave wavelet decomposition.²³

Estimation of the P Wave Variability over Time

Given the relatively low amplitude of the P wave in the ECG with respect to the background noise,²⁴ this noise had to be removed before estimating the P wave variability. For that purpose, data series obtained from the single wave-to-wave analysis associated with each feature were

divided into segments of 10 samples. Then, 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 were rejected. As the endmost step, the parameter variability time course in every 1-hour ECG interval was estimated by using the least-squares method in order to fit a linear model to the data, see Figure 2. Thus, a positive value of the fitting line slope (α) suggests increasing variability and, therefore, higher dispersion in the data. Contrarily, a negative value would involve decreasing variability, thus reaching more stable values. Finally, constant values of the parameter over the studied time period could be represented by a value of α close to zero.

Statistical Analysis

Shapiro-Wilks and Levene tests proved that the fitting line slope α distribution was normal and homoscedastic for all the studied parameters. As

Figure 2. Example of the unedited P wave high-frequency energy (P_{80}) variability time course associated to (A) a healthy subject, (B) a patient far from PAF, and (C) a patient close to PAF.

a consequence, results were expressed as mean $\pm$ standard deviation for all the ECG segments belonging to the same group and statistical differences among the α distributions for the three ECG segment groups were tested by a one-way ANOVA test. In addition, a Student's *t*-test was used to analyze the difference between pairs of groups. In both cases, a statistical significance P value lower than 0.05 was considered as significant.

In order to analyze the prognostic value of the P wave variability over time, the ability of each single parameter for discerning among the three considered groups was assessed by means of a stratified two-fold cross-validation approach. The optimal discriminant threshold between pairs of groups was obtained by using a receiver operating characteristic curve. Thus, the α value providing the highest percentage of ECG segments correctly classified was used to determine the corresponding threshold. Moreover, a multivariate discriminant analysis was also performed to explore how the association of several parameters could improve discrimination among groups. Variable selection was performed by a forward stepwise approach including, at each step, the feature maximizing the Lawley-Hotelling trace.

RESULTS

No significant differences in the demographic and clinical characteristics between the considered PAF patients and healthy subjects were noticed, such as Table 1 shows. Indeed, values of age, sex, height, weight, heart rate, respiratory rate, QRS duration, and PQ duration from both groups were comparable.

Variability of the P Wave Time-Frequency Features

Mean and standard deviation of the slope α associated with the analyzed parameters from the unedited P waves of the three considered ECG segment groups are shown in Table 2. For all the parameters, α presented an increasing trend from healthy ECG segments to those far from PAF and, next, to those close to PAF. As an example, Figure 3 displays representative ECG segments showing P waves for a healthy subject as well as AF patients far from PAF and close to PAF. As can be observed, a higher variability occurs in P_{dur} as the onset of PAF approximates.

Table 2. Mean and Standard Deviation of the Fitting Line Slope α Computed from the Analyzed Time and Frequency Parameters for the Unedited P Waves of the Three Considered Groups of ECG Segments

Feature	ECG Segments from Healthy Subjects	ECG Segments Far from PAF	ECG Segments Close to PAF	P
$\alpha(P_{dur})$	$2.48 \times 10^{-3} \pm 1.98 \times 10^{-3}$	$2.38 \times 10^{-2} \pm 1.41 \times 10^{-2}$	$8.18 \times 10^{-2} \pm 4.87 \times 10^{-2}$	6.96×10^{-22}
$\alpha(P_{Pk})$	$1.17 \times 10^{-2} \pm 1.02 \times 10^{-2}$	$1.49 \times 10^{-1} \pm 2.76 \times 10^{-1}$	$5.36 \times 10^{-1} \pm 6.97 \times 10^{-1}$	7.28×10^{-15}
$\alpha(P_{20})$	$1.26 \times 10^{-7} \pm 5.08 \times 10^{-7}$	$1.92 \times 10^{-6} \pm 4.10 \times 10^{-6}$	$6.83 \times 10^{-6} \pm 1.28 \times 10^{-5}$	7.57×10^{-18}
$\alpha(P_{30})$	$4.34 \times 10^{-8} \pm 1.41 \times 10^{-7}$	$7.44 \times 10^{-7} \pm 1.18 \times 10^{-6}$	$3.41 \times 10^{-6} \pm 6.60 \times 10^{-6}$	7.85×10^{-19}
$\alpha(P_{40})$	$2.16 \times 10^{-8} \pm 5.82 \times 10^{-8}$	$4.05 \times 10^{-7} \pm 6.51 \times 10^{-7}$	$2.01 \times 10^{-6} \pm 3.99 \times 10^{-6}$	1.34×10^{-17}
$\alpha(P_{60})$	$7.33 \times 10^{-9} \pm 1.64 \times 10^{-8}$	$1.55 \times 10^{-7} \pm 2.83 \times 10^{-7}$	$7.90 \times 10^{-7} \pm 1.62 \times 10^{-6}$	9.26×10^{-19}
$\alpha(P_{80})$	$2.42 \times 10^{-9} \pm 4.97 \times 10^{-9}$	$5.42 \times 10^{-8} \pm 1.07 \times 10^{-7}$	$2.74 \times 10^{-7} \pm 5.66 \times 10^{-7}$	2.85×10^{-20}
$\alpha(P_{R20})$	$4.90 \times 10^{-6} \pm 9.31 \times 10^{-6}$	$3.14 \times 10^{-5} \pm 5.66 \times 10^{-5}$	$1.55 \times 10^{-4} \pm 5.64 \times 10^{-4}$	6.67×10^{-14}
$\alpha(P_{R30})$	$2.07 \times 10^{-6} \pm 3.95 \times 10^{-6}$	$1.09 \times 10^{-5} \pm 1.57 \times 10^{-5}$	$6.43 \times 10^{-5} \pm 2.10 \times 10^{-4}$	7.49×10^{-16}
$\alpha(P_{R40})$	$1.01 \times 10^{-6} \pm 1.39 \times 10^{-6}$	$5.97 \times 10^{-6} \pm 7.76 \times 10^{-6}$	$3.45 \times 10^{-5} \pm 1.02 \times 10^{-4}$	2.59×10^{-17}
$\alpha(P_{R60})$	$4.55 \times 10^{-7} \pm 6.36 \times 10^{-7}$	$2.15 \times 10^{-6} \pm 2.81 \times 10^{-6}$	$1.29 \times 10^{-5} \pm 3.44 \times 10^{-5}$	2.32×10^{-15}
$\alpha(P_{R80})$	$1.61 \times 10^{-7} \pm 2.18 \times 10^{-7}$	$7.80 \times 10^{-7} \pm 1.01 \times 10^{-6}$	$4.42 \times 10^{-6} \pm 1.11 \times 10^{-5}$	1.85×10^{-15}
$\alpha(MHF)$	$1.33 \times 10^{-11} \pm 2.60 \times 10^{-11}$	$3.78 \times 10^{-10} \pm 8.01 \times 10^{-10}$	$1.66 \times 10^{-9} \pm 3.48 \times 10^{-9}$	7.05×10^{-19}
$\alpha(MMF)$	$4.50 \times 10^{-11} \pm 8.88 \times 10^{-11}$	$1.06 \times 10^{-9} \pm 2.13 \times 10^{-9}$	$5.21 \times 10^{-9} \pm 1.08 \times 10^{-8}$	1.34×10^{-18}
$\alpha(MLF)$	$3.62 \times 10^{-10} \pm 9.73 \times 10^{-10}$	$6.01 \times 10^{-9} \pm 9.14 \times 10^{-9}$	$2.91 \times 10^{-8} \pm 5.73 \times 10^{-8}$	2.38×10^{-18}
$\alpha(f_m)$	$1.85 \times 10^{-4} \pm 2.83 \times 10^{-4}$	$1.91 \times 10^{-3} \pm 3.01 \times 10^{-3}$	$4.52 \times 10^{-3} \pm 9.01 \times 10^{-3}$	1.16×10^{-19}
P_{dur}	99.63 ± 21.10 ms	105.86 ± 24.15 ms	111.02 ± 19.26 ms	2.07×10^{-3}

The statistical significance P was obtained making use of a one-way ANOVA test. As a reference, the last row shows the P wave duration mean value for the three ECG segment groups.

Figure 3. Example of representative ECG segments corresponding to: (A) healthy subject, (B) PAF patient far from the arrhythmia onset, and (C) PAF patient close to AF onset. Note the evolving alteration in P wave duration as the onset approximates.

Similarly, Figure 2 displays the P_{80} variability time course, referred to as $\alpha(P_{80})$, for a healthy ECG segment together with intervals far from PAF and close to PAF from a diseased patient, respectively. Moreover, the slope α for all the metrics provided statistically significant differences among the three groups when a one-way ANOVA test was used, such as Table 2 also reflects. Similarly, statistically significant differences between ECG segments from healthy subjects and those far from PAF and between ECG segments far from PAF and those close to the onset of PAF were also noticed via a Student's t -test, such as Table 3 shows.

However, the highest differences among groups were observed from the P wave duration variability time course ($p = 6.96 \times 10^{-22}$; Table 2), thus confirming the relevance of this time feature in the identification of PAF patients. Furthermore, the slope α for some spectral parameters such as P_{80} and f_m also reported high statistical significance values (2.85×10^{-20} and 1.16×10^{-19} , respectively; Table 2). Indeed, similar distributions of α values from these three metrics were appreciated, such as Figure 4 displays.

On the other hand, it is worth noting that a very similar outcome was obtained for edited P

Table 3. Statistical Differences between Unedited P Waves of Pairs of ECG Segments Computed Making Use of a Student's *t*-test

Feature	ECG Segments from Healthy Subjects vs. ECG Segments Far from PAF	ECG Segments Far from PAF vs. ECG Segments Close to PAF
$\alpha(P_{dur})$	4.36×10^{-11}	1.04×10^{-10}
$\alpha(PP_k)$	2.81×10^{-7}	8.97×10^{-7}
$\alpha(P_{20})$	1.60×10^{-11}	3.37×10^{-7}
$\alpha(P_{30})$	1.31×10^{-13}	3.54×10^{-7}
$\alpha(P_{40})$	3.17×10^{-12}	2.75×10^{-7}
$\alpha(P_{60})$	2.12×10^{-12}	4.48×10^{-8}
$\alpha(P_{80})$	4.06×10^{-12}	1.09×10^{-9}
$\alpha(PR_{20})$	6.72×10^{-8}	1.71×10^{-7}
$\alpha(PR_{30})$	7.91×10^{-9}	1.06×10^{-8}
$\alpha(PR_{40})$	8.88×10^{-10}	3.81×10^{-8}
$\alpha(PR_{60})$	4.64×10^{-7}	2.80×10^{-8}
$\alpha(PR_{80})$	8.20×10^{-8}	2.35×10^{-8}
$\alpha(MHF)$	9.93×10^{-13}	1.75×10^{-8}
$\alpha(MMF)$	2.47×10^{-12}	1.02×10^{-8}
$\alpha(MLF)$	2.47×10^{-12}	2.89×10^{-7}
$\alpha(f_m)$	5.92×10^{-11}	2.46×10^{-8}
P_{dur}	2.89×10^{-3}	5.24×10^{-3}

As a reference, the last row shows the results associated with the P wave duration mean value pairs.

waves. Indeed, no statistically significant changes were observed in the mean and standard deviation values of α between edited and unedited P waves, although the amount of atrial premature contractions increased significantly from healthy subjects (0.07% of the analyzed beats) to ECG segments far from PAF (2.91%) and from these ones to ECG segments close to PAF (5.66%).

Finally, the P_{dur} mean value for the three analyzed ECG segment groups is also included in Tables 2 and 3 as a reference. Although a slight increase was found in average P wave duration from healthy ECG segments to those far from PAF and, next to those close to PAF, the revealed statistical differences were notably lower than those provided by the variability analysis of every time-frequency P wave feature.

Univariate Discrimination among the Studied Groups

The percentage of ECG segments correctly classified from the unedited P waves of each group as well as the global accuracy value, i.e., the ratio between the properly identified ECG segments for the three groups and the total number of analyzed ones, are presented in Table 4. In agreement with the aforementioned findings, the P wave duration variability time course revealed the highest global accuracy of 81.02%, discerning

correctly 91.45%, 69.58%, and 80.42% of ECG segments from healthy subjects, far from PAF and close to PAF, respectively. Nonetheless, the variability of the P wave spectral features P_{80} and f_m only classified incorrectly 2.9% and 4.8% of ECG segments less than this time metric, respectively. Moreover, the variability time course of the remaining P wave spectral parameters presented a higher global accuracy than $\alpha(PP_k)$, with improvements between 1.4 and 11.9%. For edited P waves, very similar results were appreciated. In this case, only negligible variations in the percentage of ECG segments correctly classified from each group as well as the global accuracy were observed in comparison with unedited P waves.

As before, the discriminant ability associated with the P_{dur} mean value is displayed in Table 4 for comparison. As expected in view of the previous results, every time-frequency P wave feature variability time course provided a better classification outcome.

Multivariate Discrimination among the Studied Groups

A model combining $\alpha(P_{dur})$ and $\alpha(P_{80})$ resulted when a stepwise discriminant analysis was applied to both edited and unedited data. Thus, in both cases the first feature to enter the discriminant

Table 4. Classification Results into ECG Segments from Healthy Subjects, Far from PAF, and Close to PAF Provided by the Fitting Line Slope α Computed for Each Single Parameter and Unedited P Waves

Feature	ECG Segments from Healthy Subjects	ECG Segments Far from PAF	ECG Segments Close to PAF	Global Accuracy
$\alpha(P_{dur})$	91.47%	69.58%	80.42%	81.02%
$\alpha(PP_k)$	78.17%	37.39%	69.78%	62.54%
$\alpha(P_{20})$	90.21%	69.19%	54.73%	74.47%
$\alpha(P_{30})$	83.88%	52.56%	74.91%	74.34%
$\alpha(P_{40})$	88.63%	53.23%	79.26%	73.96%
$\alpha(P_{60})$	86.44%	56.63%	74.91%	74.13%
$\alpha(P_{80})$	89.76%	65.67%	73.83%	78.12%
$\alpha(PR_{20})$	79.29%	62.93%	56.52%	66.90%
$\alpha(PR_{30})$	75.15%	48.09%	67.39%	64.14%
$\alpha(PR_{40})$	73.63%	46.98%	84.78%	68.97%
$\alpha(PR_{60})$	73.21%	47.84%	71.74%	64.83%
$\alpha(PR_{80})$	75.59%	41.59%	73.91%	64.32%
$\alpha(MHF)$	88.03%	56.41%	65.22%	71.03%
$\alpha(MMF)$	84.92%	52.33%	71.74%	71.74%
$\alpha(MLF)$	83.11%	47.84%	78.26%	70.81%
$\alpha(f_m)$	86.89%	60.71%	71.82%	76.21%
P_{dur}	72.39%	57.83%	54.94%	62.17%

The global accuracy obtained for each metric is also provided. As a reference, the last row shows the discriminant ability associated with the mean value of the P wave duration.

model was the P wave duration variability, which is in agreement with the highest discriminant ability presented by this parameter. Next, $\alpha(P_{80})$ was added to the model because it provided a discriminant ability greater than the remaining features when used in conjunction with $\alpha(P_{dur})$. This discriminant model outperformed the global accuracy of α for every single P wave feature. Indeed, for both edited and unedited data, it provided a global predictive ability of 88.07%, discriminating appropriately 85.87%, 76.09%, and 89.13% of ECG segments from healthy subjects, far from PAF and close to PAF, respectively. This fact implies an increase of 7.1% and 10% in the global discriminant ability with respect to the univariate results provided by $\alpha(P_{dur})$ and $\alpha(P_{80})$, respectively.

DISCUSSION

P Wave Variability before the Onset of PAF

In this study, a noninvasive assessment of the atrial conduction defects reflected as a P wave variability progression has been introduced for the first time. All the analyzed P wave time and frequency features evolved to increasing variabilities as the onset of PAF approximated, such as Figure 2 has shown. This finding is in line

with atrial electrophysiological alterations noticed before the onset of PAF. To this respect, the presence of decreased and different cell refractory periods in various atrial regions has proved to be common in patients prone to PAF. This fact can provoke overlapping between atrial depolarizations and possible premature atrial repolarization.^{3,25} Moreover, other intra- or intercellular factors, such as connections, ion channels, and regulatory proteins, have shown capability to cause the genesis of site-specific conduction delays.^{1,26} These delays together with the presence of structural abnormalities in atrial walls, such as fibrosis, may alter constantly the way through which the sinus beat travels across the atria.¹ Hence, this site-dependent inhomogeneous and intermittent atrial conduction results in a highly variable and fragmented atrial activation morphology over time,¹¹ which has been successfully quantified by the proposed methodology.

Moreover, it is remarkable to note that the proposed methodology is not sensitive to the effect of atrial premature contractions, because very similar results were appreciated for both edited and unedited P waves sets. This outcome could be explained by the fact that the proposed method estimates the P wave variability from the difference between the 90- and 10-quantiles of 10 sample-length segments, thus rejecting impulsive noise, artifacts, and the effect of a high part of atrial

Figure 4. Boxplots showing the distribution of the fitting line slope α associated with the most statistically significant features from ECG segments of (A) healthy subjects, (B) patients far from PAF, and (C) close to PAF for unedited P waves.

premature contractions. As a consequence, the variability time course estimated from the unedited P wave features could be considered as coming from normal P waves, thus reflecting reliably the electrophysiological changes occurring in the atria during the transition from sinus rhythm to PAF. This kind of noninvasive assessment of the P wave variability time course offers important advantages over invasive electrophysiological studies.⁶ First, the proposed methodology can provide information on the entire activation wave front, rather than on individual groups of cells that mainly contribute to the local recorded electrograms. In fact, a similar intraatrial approach would require an impractical number of recording points. Second, the information is gathered from the surface ECG and may, therefore, be obtained comfortably during patient follow-up or drug assessment. As a consequence, the P wave variability analysis opens possibilities for the development of long-term studies about the atrial conduction progression in PAF patients, which have never been addressed before.

The most significant variability over time was reported by the P wave duration. This result agrees with a wide variety of previous works which have also identified this metric as a successful indicator of atrial conduction defects.^{2, 11, 27} Nonetheless, the spectral feature P_{80} also revealed a highly significant ability to follow successfully P wave morphology progression before the onset of PAF. In accordance with this outcome, previous studies have shown that idiopathic PAF patients present significantly greater energy values at frequencies between 80 and 150 Hz than healthy individuals.^{5, 6} Moreover, in contrast to the P wave duration, it is worth noting that this spectral metric presents the additional advantage of not requiring an extremely precise identification of the P wave boundaries.²⁸ This aspect may be relevant when an accurate automatic P wave delineator is unavailable. In fact, the lack of standardized measurements of the P wave onset and offset and the fact that they are usually determined manually are limiting factors for the current use of the P wave duration in clinical practice.^{27, 29, 30}

Anyway, the multivariate discriminant analysis showed that the combination of $\alpha(P_{dur})$ and $\alpha(P_{80})$ was able to obtain an improved quantification of the P wave variability over time. In view of this result, it could be considered that P wave high-frequency energy analysis could provide additional

morphological information to the one revealed by its duration. This finding is clinically relevant because recent works have suggested that P wave duration alteration could not be considered as an unavoidable requirement for AF development¹. To this respect, previous works have shown that patients with lone PAF failed to demonstrate any remarkable P wave prolongation.³¹ Similarly, P wave duration has not been predictive of new-onset AF in patients with congestive heart failure.³²

Prognostic Value of the P Wave Variability Analysis

All the studied metrics revealed different rates of progression in the P wave variability over time, such as Figure 4 shows. Moreover, this progression provided to be more clinically relevant than the traditionally studied mean value of the P wave duration to predict the onset of PAF. Indeed, global accuracy values around 80% among the three considered ECG groups were only noticed by the variability analysis of several P wave features, such as $\alpha(P_{dur})$, $\alpha(P_{80})$ and $\alpha(f_m)$. The clinical importance of this novel finding is based on the fact that P wave variability analysis could be used to identify as early as possible the arrival of a new PAF episode. Further studies considering longer times before the onset of PAF could determine the maximum advance with which alterations in the atrial activation could be identified. Hence, early therapeutical approaches may be applied to avert future PAF events.⁹

Another interesting result of this study was that the P wave from healthy subjects did not show a substantial variability over time. This finding is in line with previous studies which demonstrated that P wave morphology was stable over a long time period in the majority of healthy subjects.³³ In fact, this information provided to be clinically useful to discern between healthy subjects and PAF patients in normal sinus rhythm. Indeed, the slope α for the most part of the analyzed P wave features identified appropriately more than 85% of the ECG segments from healthy individuals, see Table 4. Although a wide variety of authors have analyzed different time, frequency, and wavelet features from the signal-averaged P wave for that purpose, their diagnostic accuracy values were rarely higher than 75%.^{5-7,9} Hence, the P wave variability analysis introduced in this work can also play an interesting role to discover traces of PAF from the sinus

rhythm ECG, i.e., when AF is not occurring. This is a relevant clinical challenge, because PAF can sometimes be asymptomatic and not only a single episode may appear during long-time Holter monitoring.¹⁹ Another clinical application of the present methodology may be the evaluation of the AF risk in patients with sinus node disease receiving permanent pacemakers, those after coronary bypass grafting or valvular surgery and patients with valvular heart disease or severe left ventricular dysfunction. In all these cases, prophylactic anticoagulation might be considered if a high risk of AF is detected. Nonetheless, future prospective studies are required to validate the usefulness of P wave variability analysis for this purpose.

Study Limitations

The major limitation of this work could be its reduced study population. However, the studied databases of healthy subjects and PAF patients were representative enough and both groups were homogeneous in terms of confounding factors, such as age,^{34,35} gender,^{36,37} or heart rate.³⁸ To this respect, previous works have shown that P wave duration increases slightly with age^{34,35}, and that in men P wave is normally longer than in women.^{36,37} Additionally, it is well known that changes in autonomic tone may affect P wave duration through effects on either the conduction velocity or changes in atrial size or pressure that may arise from the associated change in heart rate.³⁸ However, it could be considered that the autonomic nervous system activity had no significant effects on the presented results because PAF patients and healthy subjects had similar heart and respiratory rates during the ECG recordings and the duration of the PQ segment was similar in both groups. On the other hand, only the P wave variability 2 hours before PAF onset has been assessed. Obviously, the development of studies considering wider time intervals before the arrhythmia starts seem to be clinically interesting, such as aforementioned. It is also mandatory to remark that only patients with no antiarrhythmic treatment were considered in the study. Hence, the obtained results could not be generalized for patients under antiarrhythmic drug treatment. Further analyses in this line will be required in the future, because the transition from sinus rhythm to PAF could suffer alterations depending on the antiarrhythmic treatment. Finally,

although some authors recommend evaluating the P wave in lead II,^{14,39} only lead V₁ was analyzed. However, this lead provides additional information concerning intraatrial conduction defects because it can reflect the posterior left atrial potential, unseen in the limb leads.⁴⁰

CONCLUSIONS

This work shows for the first time that alterations in atrial conduction 2 hours preceding the onset of PAF can be successfully quantified by estimating variability over time of several P wave time-frequency features. Clinical information from this noninvasive analysis could, on the one hand, improve our understanding of the electrophysiological mechanisms underlying PAF recurrences. On the other hand, this information may enable the identification of subjects at high risk of the arrhythmia, thereby creating the perspective of early application of tailored therapeutic strategies to avert future PAF events. Nonetheless, further prospective studies are required in the future.

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