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Chapter 2

Recent Advances in the Noninvasive Study of Atrial Conduction Defects Preceding Atrial Fibrillation

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Additional information is available at the end of the chapter

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Abstract

The P-wave represents the electrical activity in the electrocardiogram (ECG) associated with the heart's atrial contraction. This wave has merited significant research efforts in recent years with the aim to characterize atrial depolarization from the ECG. Indeed, the alterations of the P-wave main time, frequency, and wavelet features have been widely studied to predict the onset of atrial fibrillation (AF), both spontaneously and after a specific treatment, such as pharmacological or electrical cardioversion, catheter ablation, as well as cardiac surgery. To this respect, the P-wave prolongation is today a clinically accepted marker of high risk of suffering AF. However, given the relatively low P-wave amplitude in the ECG, its analysis has been most widely carried out from signal-averaged ECG signals. Unfortunately, these kind of recordings are uncommon in routine clinical practice and, moreover, they obstruct the possibility of studying the information carried by each single P-wave as well as its variability over time. These limitations have motivated the recent development of the beat-to-beat P-wave analysis, which has proven to be very useful in revealing interesting information about the altered atrial conduction preceding the onset of AF. Within this context, the main goal of this chapter is to review the most recent advances reached by this kind of analysis in the noninvasive assessment of atrial conduction alterations. Thus, the chapter will introduce and discuss the existing methods of the beat-to-beat P-wave analysis and their application to predict the onset of AF as well as its advantages and disadvantages compared with the signal-averaged P-wave analysis.

Keywords: atrial premature contractions, electrocardiogram, paroxysmal atrial fibrillation, P-wave, variability

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1. Introduction

Atrial fibrillation (AF) has been described as the arrhythmia of the twenty-first century given that it is the most commonly diagnosed sustained cardiac arrhythmia, affecting up to 1% of the general population and up to 15% of the population older than 70 years of age [1, 2]. Despite extensive research during the last decades, it is still unclear how AF starts and perpetuates itself [2]. Once AF appears, its usual evolution presents three different stages [3]. In the first one, named paroxysmal AF (PAF), patients present auto-limited episodes with a duration shorter than seven days, which terminate spontaneously without the need of medical intervention. However, approximately between 15 and 31% of PAF patients progress to permanent AF in four to eight years [4]. During this progression, recurrent episodes normally appear, but it is also still unknown why the duration of these episodes varies from patient to patient and from episode to episode [5]. Therefore, once a PAF episode has terminated spontaneously, the early prediction of the onset of the next PAF episode is a relevant clinical challenge. Such a prediction may minimize risks for AF patients and improve their quality of life, since a preventive therapy may be used to avoid recurrence of the arrhythmia. Thus, the maintenance of normal sinus rhythm may reduce symptoms, get better hemodynamics, and minimize the atrial remodeling, which increases the probability of recurrence of AF [6]. Moreover, the risk of suffering thromboembolic events can also be notably reduced [2].

The normal electrical conduction in the heart is generated by the sinoatrial node and is propagated throughout the right atrium and through the Bachmann's bundle to the left atrium, thus defining the P-wave in the electrocardiogram (ECG). However, when this progressive conduction is altered by accessory pathways, reentries, or conduction delays, the P-wave morphology will reflect this fact [7]. Currently, it is well known that both slowed conduction velocity as well as inhomogeneous cell refractory periods in several atrial regions are atrial electrophysiological alterations provoking and maintaining AF [8]. Such atrial conduction abnormalities result in prolonged and highly variable P-waves [9]. Thereby, the analysis of the P-wave has gained increasing interest in the last years [10].

Within this context, the noninvasive P-wave analysis has been performed, following two main recording approaches. On the one hand, it has been based on the standard 12-lead ECG [11]. On the other hand, some authors have based their studies on the P-wave vector magnitude obtained from Frank's orthogonal leads [12]. However, in both alternatives, only averaged-signal P-waves have been widely analyzed in order to minimize the shortcomings derived from the relatively low amplitude of this wave in the ECG [13]. Indeed, the duration of the averaged P-wave has been widely analyzed, and its prolongation has been associated with history of AF, development of arrhythmia after bypass surgery, and progression from paroxysmal to persistent AF [9]. Additionally, the fragmentation of the P-wave template has also been broadly studied from the spectral, gaussian, and wavelet domains [14, 15, 16]. In this case, a wide variety of features associated with the P-wave morphology have provided the ability to discern between PAF patients and healthy subjects [15, 16], to quantify the effects of different antiarrhythmic drugs [17], and to stratify the risk of recurrence of AF after electrical cardioversion [14], catheter ablation [18, 19], and coronary artery bypass grafting [20].

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However, recording of the signal-averaged P-wave is not today a common practice in the clinical routine [21]. Moreover, this kind of analysis does not allow to exploit the information contained in every individual P-wave. Indeed, consecutive P-wave averaging hinders the interesting possibility of characterizing every single P-wave as well as its variability across time. Furthermore, the ability of all the previously defined signal-averaged P-wave features to stratify the risk of PAF has also proven to be seriously reduced when long-term ECG recordings, longer than 30 minutes, with no more than two or three available leads are analyzed [22, 23, 24]. Hence, further studies are required to tackle the crucial issue about the minimum time gap required between the detection of P-wave feature alterations that potentially would provoke the onset of PAF. Within this context, recent works have introduced new alternatives able to assess the P-wave time and spatial variability from routine clinical recordings. Some of these methods have proven to accurately anticipate the risk of arrhythmia, at least 60 minutes before its onset, which is a relevant advance in turning clinically useful PAF risk predictors [25, 26, 27]. Overall, the purpose of this chapter is to describe the most recent advances presented in the literature for the noninvasive assessment of atrial conduction defects and how the information provided by these methods has allowed significant advances in the prediction of PAF onset from the surface ECG.

2. Analysis of atrial premature complexes

Several studies have shown that most PAF episodes are initiated by the presence of rapidly firing atrial ectopic foci [28, 29]. Given that their occurrence results in premature atrial depolarizations [30], the identification of a wide number of premature atrial complexes (PACs) in the ECG has proved to be a successful predictor of imminent PAF onset [31, 32]. To this respect, Thong et al. [31] defined an isolated PAC as those preceded and followed by two cycles of the prevalent rhythm. Moreover, they identified four separate categories of isolated PACs. First, Fig. 1(a) shows a PAC with sinus node reset. The sinus node is reset by the ectopic P-wave within normal conduction time, thus provoking that the next RR interval is within 100 ms of the prevalent one. Second, Fig. 1(b) shows an interpolated PAC. In this case, the sinus node is not reset and the corresponding QRS is located in a normal RR interval with no alteration of the prevalent rhythm. Third, Fig. 1(c) shows a PAC in which the sinus node reset has been delayed. A delay occurs in the path of electrical conduction to the sinus node, thus increasing the next RR interval by approximately 100 ms. Finally, Fig. 1(d) displays a PAC in which a full compensatory pause occurs. In this case, the PAC causes the AV junction to be refractory, thus doubling the RR interval compared with the prevalent one.

Making use of the database proposed by the Computers in Cardiology Challenge, which is freely available in PhysioNet [33], the authors compared the two provided ECG leads to detect rhythm changes. These rhythm changes were associated with the ECG intervals preceding the immediate onset of PAF, while those intervals more than 45 minutes far from a PAF episode were related to a normal rhythm. The authors counted the number of isolated PACs in categories 2–4 for each lead of every subject and followed the criteria presented in Fig. 2 to identify rhythm changes. Three or more consecutive PACs without any intervening long

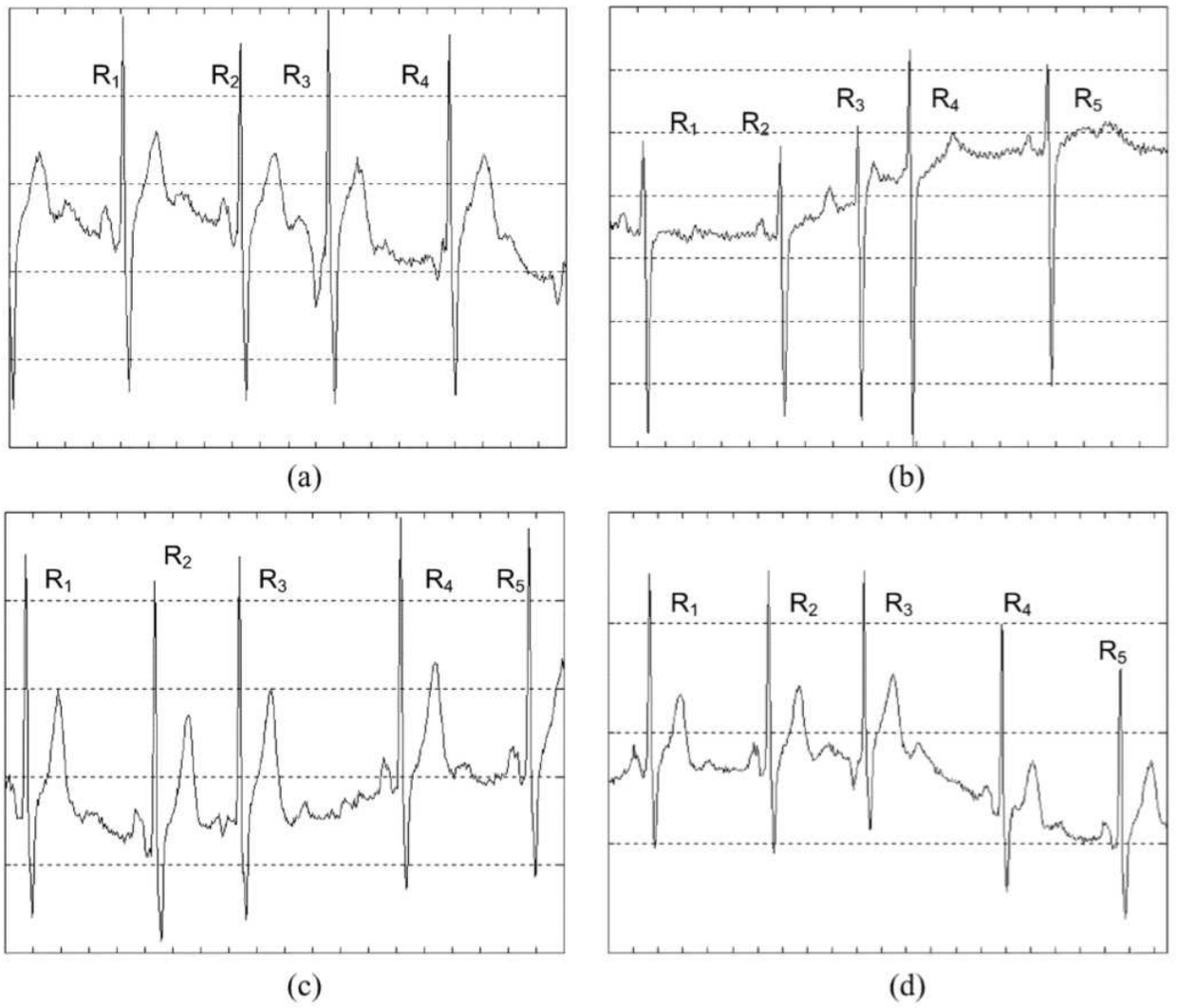


Figure 1. ECGs of various types of PACs according to Thong et al. [31]. (a) PAC with sinus reset, $R_3R_4 = R_1R_2$. (b) Interpolated PAC, $R_2R_4 = R_1R_2$. (c) PAC with delayed sinus node reset, $R_3R_4 > R_1R_2$. (d) PAC with full compensatory pause, $R_2R_4 = 2R_1R_2$. QRS of PACs are similar to other QRS. RR timing is used to differentiate the four types of PACs. Note inverted P-waves in (a), (c), and (d). Horizontal tick marks are 200 ms apart.

intervals were considered to meet the PAT criterion. Regarding the PAC test, if the difference in the number of PACs between the two leads of a subject was higher than or equal to two, a rhythm change was marked. Finally, to account for atrial bigeminies and trigeminies, changes in RR series higher than 70 ms were first detected. After, a 10-point boxcar filter was applied to the RR series and the averaged power of the filtered signal was computed. A change of rhythm was detected when the average power was higher than 0.95 and a difference between leads was higher than 1.5. Finally, the algorithm allowed to discern between ECG intervals far from PAF and close to PAF with an accuracy around 90%.

This result was greater than those achieved by other participants in the Computers in Cardiology Challenge, which proposed different algorithms to detect the presence of PACs. Thus,

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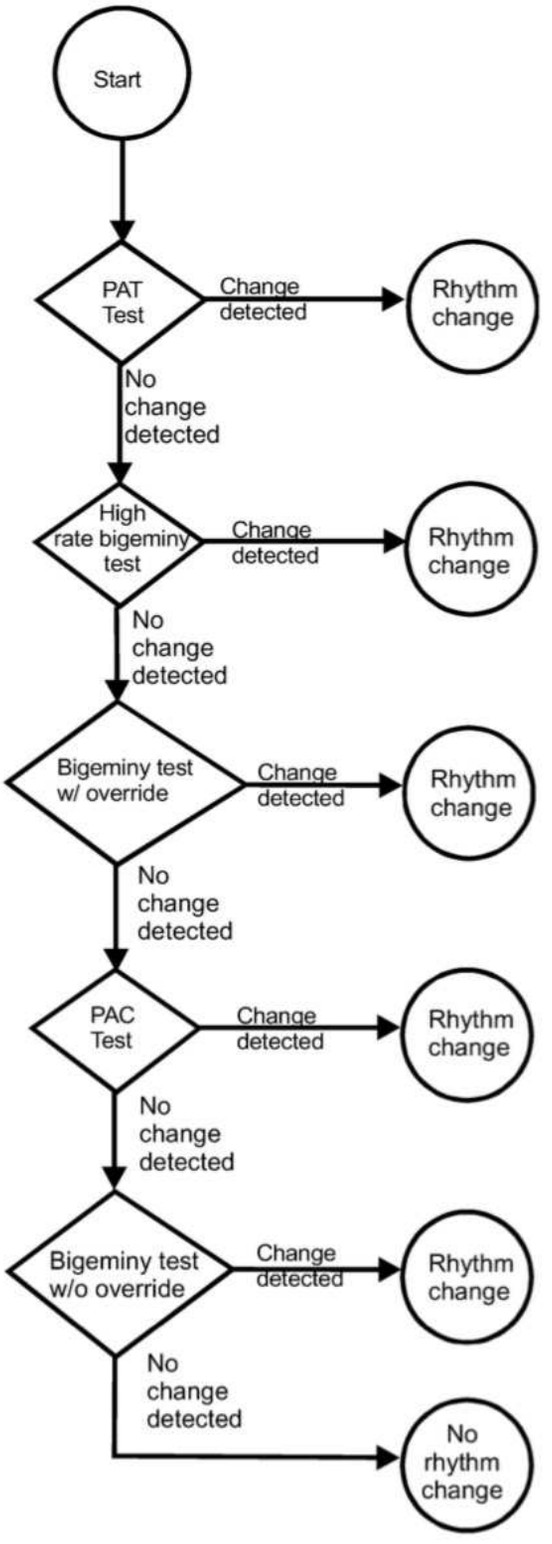


Figure 2. Flow diagram for the algorithm proposed by Thong et al. [31] to identify the onset of PAF.

Langley et al. [34] identified the potential ectopics from those provoking RR intervals shorter than 80% of their average. Next, those beats with an RR value exceeding ±10% of their mean

were considered as atrial, whereas those altering more than ±30% of that value were considered as ventricular. In [35], a morphological comparison among potential ectopic and normal beat was also considered. Finally, ectopic beats were considered as those with a QRS morphology similar to normal beats. In a similar line, Schreier et al. [36] considered that those beats with a very different morphology compared to their neighbors could cause the onset of PAF. On the other hand, symbolic analysis was applied to the RR series to identify acceleration and decelerations in the heart rate and associate them with the onset of PAF. Finally, Hickey et al. [32] identified APCs by using an algorithm based on two steps. First, a beat was flagged as a suspected APC if the RR interval preceding it was 15% shorter than a defined local moving average of the surrounding RR intervals. In the second stage, the area, width, and amplitude of the QRS were computed. If all these parameters differed more than 10% from a normal beat, they were confirmed as APCs. The first 100 beats from a regular sinus rhythm were used to compute the parameters associated with normal beats. This algorithm is based on the fact that ventricular ectopics present morphologies very different from normal beats. Although the accuracy of this algorithm to identify ECG intervals immediately before the onset of PAF was slightly lower than those presented by Thong et al.'s algorithm, its combination with information obtained from the RR series spectral analysis yielded a better outcome (i.e., an accuracy around 98%) [32]. Indeed, subjects with imminent PAF showed to have highly correlated low-frequency and high-frequency components in their heart rate. Thus, the authors suggested that sympathetic and parasympathetic autonomic activity may be coupled in these subjects [32].

3. Time course of the P-wave variability

3.1. Time characterization of the P-wave

The variability of features from the P-wave time course before the onset of PAF has started to be studied very recently through a new alternative able to assess time diversity of the P-wave features from single-lead ECG recordings [25]. The method has demonstrated that the P-wave features presented an increasing variability as PAF onset approximates, thus suggesting intermittently disturbed conduction in the atrial tissue. Indeed, it is able to assess the risk of arrhythmia one hour before its onset, thus being a significant advance in the early prediction of the risk of PAF with clinical usefulness [25].

The method can be decomposed in various steps. Firstly, because no standard definition of the P-wave fiducial points can be found in the literature, the P-wave onset and offset were determined by an automatic delineator [37]. It is important to note that the delineator had the ability to deal also with ectopic beats in the same way as with normal beats [37]. Therefore, P-wave fiducial points that originated from APCs were automatically detected without any additional requirement.

After its delineation, several P-wave time features were defined as potential indicators that might be of interest for PAF onset prognosis in a beat-to-beat way, as shown in Fig. 3. To this respect, the P-wave duration was defined as the distance between its offset and onset, i.e.,

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$$P_{dur} = P_{off} - P_{on}. \tag{1}$$

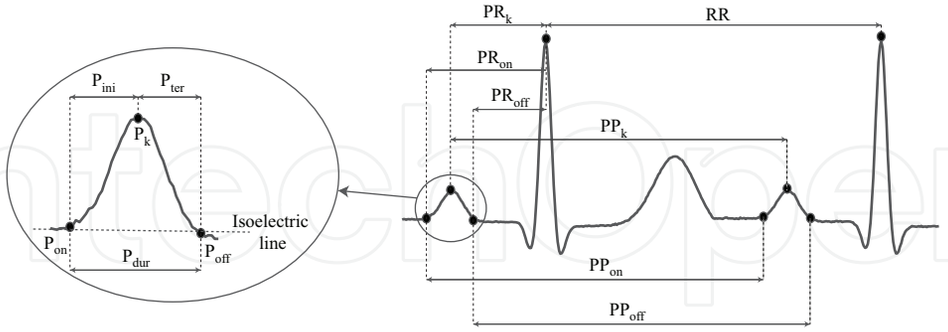


Figure 3. Visual description of the chosen parameters to characterize P-wave time features and assess its time course variation.

Previous works have demonstrated that increased P-wave duration can be considered as an indicator of increased risk of AF [11, 38, 39, 40]. In a similar way, the P-wave morphology measured from lead V1 has also shown ability to stratify the AF risk [41]. Hence, the duration of the P-wave initial and terminal portions was considered as the distances between its peak and the P-wave onset (P_{ini}) and offset (P_{ter}), respectively. Therefore, these features were defined as

$$P_{ini} = P_k - P_{on}, \tag{2}$$

and

$$P_{ter} = P_{off} - P_k. \tag{3}$$

Moreover, the P-wave asymmetry was estimated by computing the ratio between the duration of its initial and terminal portions [42], i.e.,

$$P_{asy} = \frac{P_{ter}}{P_{ini}}. \tag{4}$$

On the other hand, conduction time from the sinus node to the ventricles defines the PR interval. Thus, this interval contains information about different specific places of the atria [43]. In fact, prolongation of the PR interval has been associated with increased risk of AF in the Framingham Heart Study [43, 44]. This fact motivated the measurement of this interval from three different ways, considering the time from the onset, the peak, and the offset of the P-wave up to the R peak. This can be mathematically defined as

$$PR_{on} = R - P_{on}, \tag{5}$$

$$PR_{k} = R - P_{k}, \tag{6}$$

$$PR_{off} = R - P_{off}. \tag{7}$$

Finally, differences between successive P-waves were considered to estimate the P-wave location variability. In this case, three data series were also calculated. Thus, the distances among onset, peak, and offset from the i th and $i+1$ th waves were computed as

$$PP_{on} = P_{on}^{(i+1)} - P_{on}^{(i)}, \tag{8}$$

$$PP_{k} = P_{k}^{(i+1)} - P_{k}^{(i)}, \tag{9}$$

$$PP_{off} = P_{off}^{(i+1)} - P_{off}^{(i)}. \tag{10}$$

Once all the P-wave time features were defined, they were applied on a database of 24 patients with 24-h Holter ECG recordings. The 120 minutes preceding the onset of PAF from the longest sinus rhythm interval of every patient were extracted and divided into two 60-minute-length intervals. Moreover, a third set of 28 healthy individuals without statistically significant differences in terms of age and gender compared to the PAF patients was also analyzed. Subjects in this control group did not present any previous history of AF or structural heart disease. From each individual, a one-hour-length segment was randomly chosen.

Given the relatively low amplitude of the P-wave in the ECG, to minimize the impulsive noise in results, 10 sample-length blocks from data series for each P-wave metric were considered [25]. In each block, the variability was obtained as the difference between the 90- and 10-quantiles. On the other hand, the electrophysiological alterations occurring in the atria prior to the onset of PAF [39] provoke a great deal of scatter in the variability of the aforementioned P-wave features. To this respect, P_{dur} variability over time for a healthy subject and intervals far from PAF and close to PAF from a diseased patient are shown in Fig. 4. Then, to reduce the effect of this variability, the expected P-wave feature trend was estimated by means of a linear fitting also shown in Fig. 4. Obviously, the slope α of this fitting line provides information about the P-wave variability over time. Whereas positive α values indicate an increasing variability, a lower dispersion in the data can be indicative of negative values. Finally, α values near zero could be indicative of very reduced variability in the P-wave over time.

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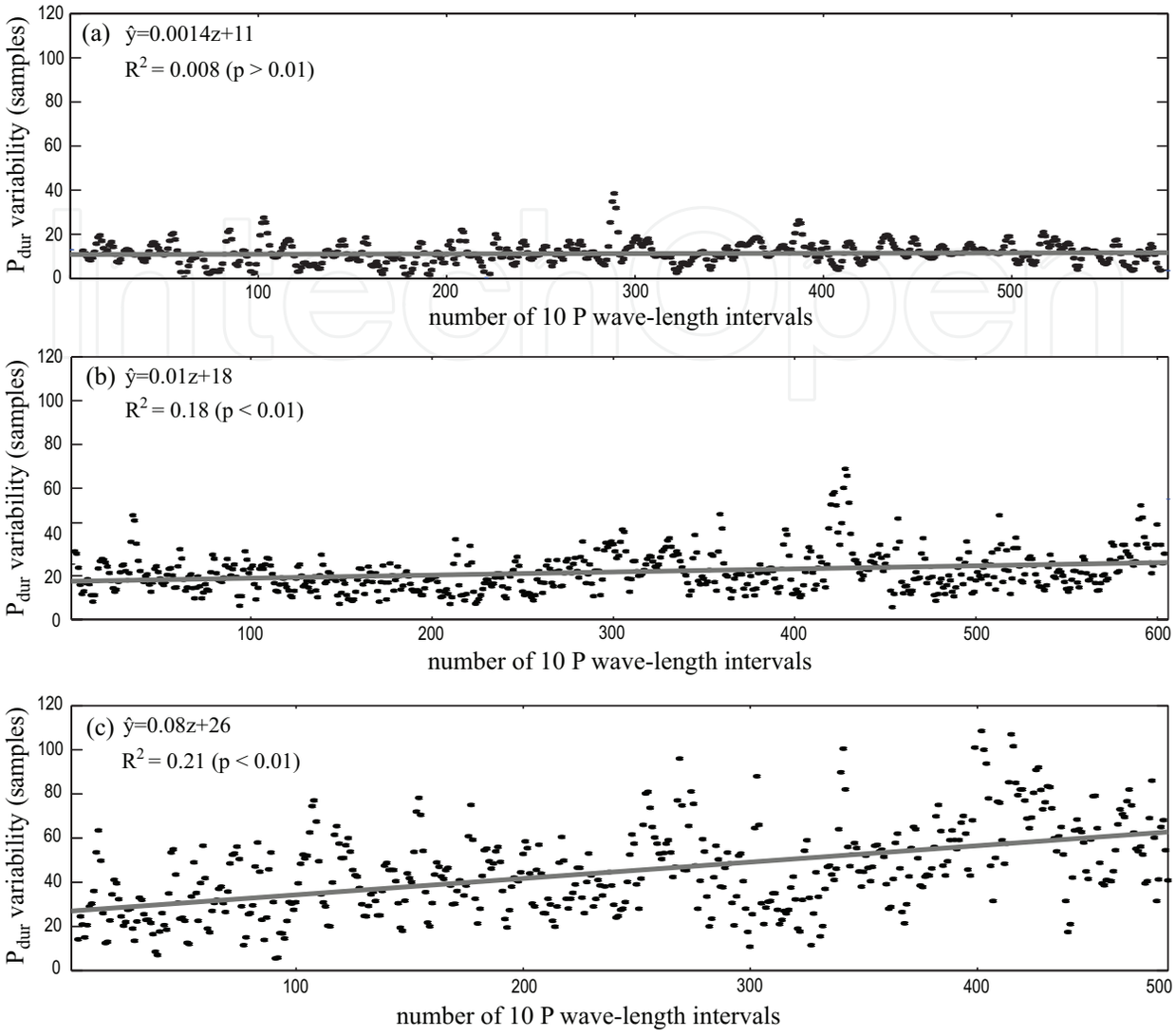


Figure 4. Typical P-wave duration variability over time from (a) a healthy individual and from ECG intervals (b) close to PAF and (c) far from PAF for a diseased patient.

Receiver operating characteristic (ROC) curves were used to obtain discriminative thresholds between the patient groups. For each P-wave feature, optimal thresholds were selected as those values of α minimizing the classification error. In the end, a stepwise discriminant analysis (SDA) was performed with the objective of improving the patient group classification.

Interestingly, for all the studied metrics, significant differences among sets were noticed, although the features measuring P-wave duration showed the most remarkable trends. Regarding the classification performance, apart from P_{ter}, metrics associated with the P-wave duration reported a higher predictive ability than the other single parameters (see Table 1). Indeed, 84.21% of all the analyzed patients were correctly identified by P_{dur}, providing among healthy subjects and PAF patients and among ECG intervals far from PAF and close to PAF accuracy values of 90.79% and 83.33%, respectively (see Fig. 5). The metric estimating the PP rhythm constituted a second set of predictive power. A global accuracy around 70% was

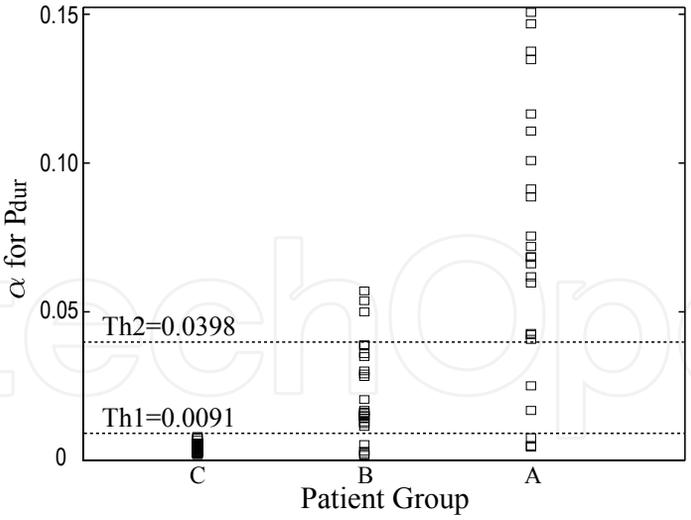


Figure 5. Classification into healthy subjects (group C), patients far from PAF (group B), and patients close to PAF (group A) making use of the P-wave duration time course.

provided by all of them, with more than 65% of the cross-validated grouped cases appropriately classified. Moreover, the RR series variability showed a classification performance very similar to PP_k and also it provided almost identical statistical differences among patients. In fact, for the three studied groups, correlation between these metrics was 0.98, 0.92, and 0.84, respectively. Finally, the most reduced ability to identify patient groups was provided by the metrics associated with the PR interval. Nevertheless, PR_{on} provided an accuracy close to the metrics computed from the PP series.

Feature	Healthy Subjects	ECGs far from PAF	ECGs close to PAF	GAcc	CV
P_{dur}	100.0% (28/28)	70.83% (17/24)	79.17% (19/24)	84.21% (64/76)	82.89% (63/76)
P_{ini}	67.86% (19/28)	70.83% (17/24)	79.17% (19/24)	72.37% (55/76)	72.37% (55/76)
P_{ter}	89.29% (25/28)	16.67% (4/24)	83.33% (20/24)	64.47% (49/76)	61.84% (47/76)
P_{asy}	96.43% (27/28)	66.67% (16/24)	75.00% (18/24)	80.26% (61/76)	78.94% (60/76)
PR_k	89.29% (25/28)	45.83% (11/24)	50.00% (12/24)	63.16% (48/76)	60.53% (46/76)
PR_{on}	85.71% (24/28)	58.33% (14/24)	62.50% (15/24)	69.74% (53/76)	68.42% (52/76)
PR_{off}	78.57% (22/28)	37.50% (9/24)	58.33% (14/24)	59.21% (45/76)	60.53% (46/76)
PP_k	82.14% (23/28)	58.33% (14/24)	70.83% (17/24)	71.05% (54/76)	69.74% (53/76)
PP_{on}	82.14% (23/28)	45.83% (11/24)	75.00% (18/24)	68.42% (52/76)	67.11% (51/76)
PP_{off}	89.29% (25/28)	33.33% (8/24)	87.50% (21/24)	71.05% (54/76)	69.74% (53/76)
RR	82.14% (23/28)	45.83% (11/24)	70.83% (17/24)	67.11% (51/76)	65.79% (50/76)
SDA (P_{dur}, PP_k)	100.0% (28/28)	83.33% (20/24)	91.67% (22/24)	92.10% (70/76)	90.79% (69/76)

Table 1. Percentage of ECG segments correctly classified for each group from the slope α obtained for each studied time P-wave feature. The table also shows the global accuracy (GAcc) and cross-validation (CV) results.

On the other hand, the SDA revealed an improved classification among patients from a discriminant model constructed by the combination of P_{dur} and PP_k. To this respect, as can be seen in Table 1 and Fig. 6, 92.10% of the analyzed patients were properly classified, 90.79% of cross-validated grouped cases being correctly discerned. Therefore, an increase of around 8% in the accuracy was reached in comparison with P_{dur}. Moreover, this model was also able to discern 96.05% of healthy subjects from patients suffering from PAF with a false-positive rate lower than 4%, such as can be observed in Fig. 6.

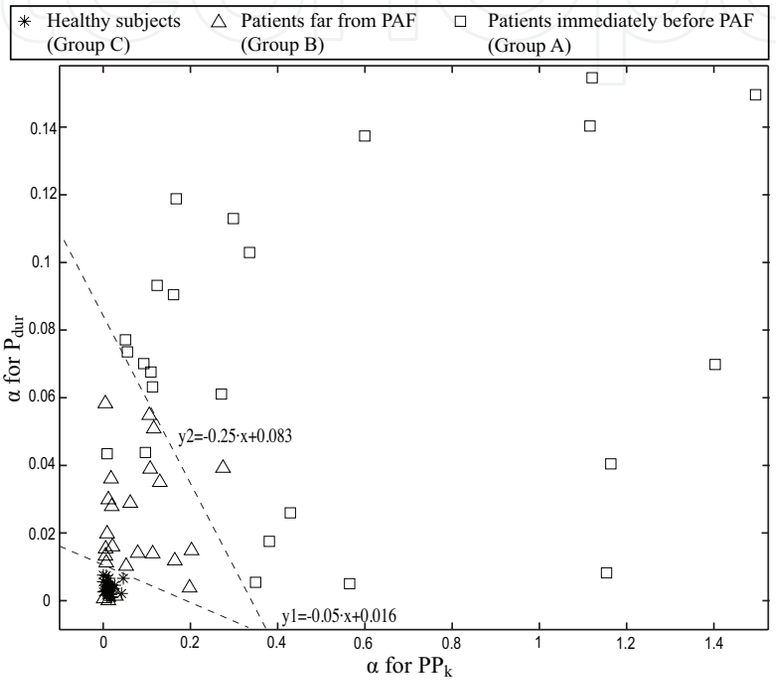


Figure 6. Classification into healthy subjects, patients far from PAF, and patients close to PAF making use of the discriminant model based on the parameters P_{dur} and PP_k. Each dotted line represents optimal discrimination thresholds between groups.

These outcomes agree with previous findings showing that prolongation of the P-wave duration is associated with history of AF [15, 38, 45, 46, 47]. Moreover, it is also worth noting that a relevant correlation between P-wave duration variability and the longest duration of the right atrial activation registered on electrograms has been previously documented [48]. Nonetheless, both for discerning among healthy subjects and PAF patients [49] and among ECG segments far from PAF and close to PAF, the beat-to-beat P-wave variability analysis over time has revealed higher discriminant ability than previous works.

The P-wave duration reflected on the ECG can be considered as the overlapped result of two effects [42]: (i) its prolongation due to the decrease in atrial conduction velocity and (ii) its shortening due to overlapping between atrial depolarization and possible premature atrial repolarization, as a result of decreased refractory period. Given that the patients prone to AF manifest a heterogeneous combination of both effects [42, 2], the observed higher P-wave duration variability preceding the onset of PAF can be considered as a natural consequence

feasible to be expected. A similar behavior could also be expected for the PR interval variability over time, because that variability could reflect alterations in atrial depolarization and delays in atrioventricular node conduction. Anyway, although both parameters showed the same behavior, it has to be remarked that the P-wave duration variability was a better predictive marker. Moreover, any of the three estimates of the PR interval reported a classification higher than 70%. Nonetheless, statistically significant differences among groups were revealed by the three metrics, thus agreeing with previous works which have addressed the susceptibility to spontaneous AF [50] and post-coronary bypass surgery AF [51].

On the other hand, the notable correlation between the series of RR and PP merits special attention. This result suggests that similar information is provided by both series. However, in comparison with healthy subjects, the correlation for PAF patients was lower, thus suggesting that some information differences are revealed in this case. These differences between PP and RR series may be related to the P-wave variability before the onset of PAF, such as the aforementioned. As a consequence, the assessment of the PP series instead of the RR series is recommended to estimate the risk of PAF onset.

In recent years, a wide variety of previous works have analyzed the RR series preceding the onset of PAF to predict this event [52, 32, 53, 54, 55, 56, 57]. Whereas typical time and frequency measurements on the RR time series provided not to be relevant markers of the onset of PAF, the identification of a decreased heart rate complexity has proven ability to identify that event [52, 53, 54]. Entropy metrics such as approximate entropy and sample entropy have been mainly used to analyze RR complexity. However, the result provided by these metrics is in contrast with the previously presented increasing trend in the PP series variability. This contradictory outcomes could be justified by an incorrect use of the entropy metrics. In previous works, a notable effect of spikes on entropy metrics has been reported [58], and the increasing presence of APCs before the onset of PAF is a notable source of spikes in RR series [53]. Anyway, additional studies are required to validate this hypothesis.

On the other hand, although many studies quantifying RR complexity have presented a higher ability to predict the onset of PAF than the metrics based on PP series, they had to combine a wide variety of different indices by using very complex classifiers. To this respect, artificial neural networks, self-organization maps, support vector machines, or linear discriminant classifiers have been introduced in different studies [32, 55, 56, 57]. Obviously this kind of metrics combination hinders the direct and clinical interpretation of the results, thus obstructing the possibility to be used in daily clinical routine. On the contrary, the beat-to-beat P-wave variability analysis has revealed a simple discriminant model based on the combination of two clearly interpretable metrics such as P_{dur} and PP_k [25]. Indeed, the discriminant model suggests that the presence of a high P-wave duration and rhythm variability over time is indicative of a high risk of the onset of PAF.

3.2. Morphological characterization of the P-wave

Factors such as right and left atrial depolarization as well as the shape and size of atrial chambers determine the P-wave morphology [9]. Therefore, alterations in the P-wave mor-

phology can be indicative of a disrupting atrial conduction [11]. Within this context, recent works have focused on quantifying the P-wave morphological variability during the two hours preceding the onset of PAF [26]. In this case, a wider database composed of 48 Holter recordings from PAF patients and 53 healthy individuals, age and gender matched, has been considered [26]. As in [25], the longest sinus rhythm interval in the recording from each patient was selected and the two-hour segment preceding the onset of PAF was analyzed. The interval under study was divided into two one-hour-length segments. Additionally, an ECG segment of one hour in length was randomly chosen from the Holter recording of each healthy subject.

In order to define the morphological features able to characterize the P-waves, it has to be considered that previous works have suggested that inhomogeneous intra-atrial and interatrial electrical conduction predisposes to the development of AF [42, 16]; therefore, maximum and minimum conduction velocities during the atrial depolarization were estimated as [42]

$$v_{\max} = \max_{n=2,3,\ldots,L} \left(\tilde{w}[n] - \tilde{w}[n-1] \right) \qquad \text{and} \tag{11}$$

$$v_{\min} = \min_{n=2,3,\ldots,L} \left(\tilde{w}[n] - \tilde{w}[n-1] \right), \tag{12}$$

respectively, $\tilde{w}[n]$ being each individual sample of the P-wave. Moreover, the dispersion in the propagation velocity during the depolarization process was also obtained as

$$v_{\text{disp}} = v_{\max} - v_{\min}. \tag{13}$$

On the other hand, altered and fractionated atrial activity seems to be reflected as the appearance of bumps in the P-wave normal gaussian shape [15], which could provoke even phase changes in lead V1 [41]. This morphology change was computed by means of the arc length of each P-wave (P_{al}), i.e.,

$$P_{al} = \sum_{n=2}^{L} \sqrt{1 + \left(\tilde{w}[n] - \tilde{w}[n-1] \right)^2}. \tag{14}$$

This metric is able to discern between two waves with the same duration but different morphologies (see Fig. 7), because it computes the rectified P-wave length. In fact, in this figure, a notably longer arc length can be observed for the wave with abnormal morphology than for those with a normal waveform.

On the other hand, the P-wave amplitude has been widely analyzed in previous works. Indeed, various authors have suggested a relationship between this metric and the electrical mass depolarized in each atrial beat, thus showing a significant decrease after pulmonary vein ablation [59] and external electrical cardioversion [14]. Overall, several metrics to quantify this

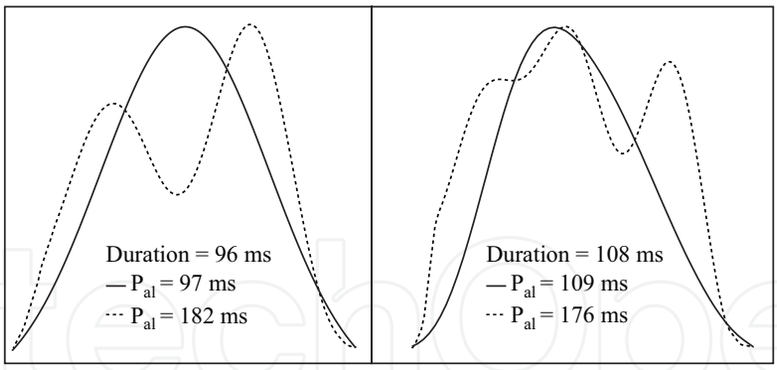


Figure 7. Representative P-waves showing different morphologies but similar lengths. As can be observed, the P-wave arc length is able to discern between the two different morphologies.

amplitude have been proposed in the literature [26]. To this respect, two robust parameters are based on computing the normalized root mean square value and the area of the P-wave as

$$P_{nrms} = \sqrt{\frac{1}{L}\sum_{n=1}^{L}\tilde{w}\left[n\right]^2} \quad \text{and} \tag{15}$$

$$P_{area} = \sum_{n=1}^{L}\left|\tilde{w}\left[n\right]\right|, \tag{16}$$

respectively. Finally, to avoid the effect of the P-wave duration on its amplitude, both parameters have been also normalized as follows:

$$P_{nenergy} = \frac{P_{nrms}^{\ 2}}{P_{al}}, \quad P_{narea} = \frac{P_{area}}{P_{al}} \tag{17}$$

The variability of these parameters over the one-hour-length recordings was estimated in the same way as in the previous subsection. However, the performance of each single-parameter variability to discriminate between ECG segments far from and close to PAF and healthy subjects was evaluated by means of a stratified 2-fold cross-validation. The results are summarized in Table 2. In this case, more than 82% of the healthy subjects were identified by all the metrics. Additionally, P_{al} and P_{area} discerned between ECG intervals far from PAF and close to PAF with a accuracy greater than 60% and 70%, respectively. Thus, the greatest global accuracy around 80% was reached by the P-wave arc length, also presenting accuracy values of 94.48% and 86.96% among healthy individuals and PAF patients and among ECG intervals far from PAF and close to PAF, respectively. The second highest discriminant ability was presented by the P-wave area, which reported a global accuracy slightly higher than 75% in the test sets.

Feature	Healthy subjects		Far from PAF		Close to PAF		Global Accuracy	
	training	test	training	test	training	test	training	test
v_{max}	90.01%	86.95%	55.22%	42.17%	57.83%	52.61%	68.76%	61.86%
v_{min}	90.58%	87.96%	45.00%	35.87%	63.48%	56.52%	67.52%	61.46%
v_{disp}	90.60%	88.60%	40.22%	35.87%	73.91%	71.74%	69.30%	66.55%
P_{al}	96.62%	89.98%	79.57%	68.75%	84.78%	79.79%	87.45%	80.02%
P_{nrms}	86.82%	83.82%	58.26%	52.39%	69.35%	65.87%	72.22%	68.15%
P_{area}	90.72%	87.76%	70.22%	60.91%	75.22%	70.87%	79.31%	75.24%
$P_{nenergy}$	86.42%	82.94%	51.52%	40.65%	73.04%	62.83%	71.10%	63.16%
P_{narea}	89.05%	86.58%	55.43%	46.09%	72.83%	67.17%	73.23%	67.58%

Table 2. Percentage of ECG segments correctly classified for each group from the slope α obtained for each studied morphological P-wave feature.

Moreover, a decision tree was assembled to investigate non-monotonic relationships among single parameters, thus improving group classification. This tree showed that the optimal combination of parameters was also achieved by the P-wave arc length and area. Figure 8 shows the obtained decision tree. As can be observed, low P-wave area variability identified healthy individuals. On the contrary, increasing variability in P-wave area and arc length over time was observed when the onset of PAF approximated. Thus, a classification improvement around 6% and 10% was reached by this classifier, respectively. In fact, the three considered patient groups were classified with accuracies of 95.42%, 79.29%, and 83.98%, respectively, the global accuracy being around 86%. Additionally, healthy subjects and PAF patients were discerned with an accuracy of 95.42% and false-positive rate around 5%.

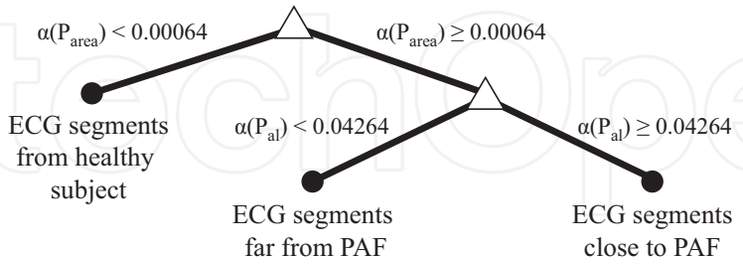


Figure 8. Decision tree generated from the learning sets to classify ECG segments from healthy subjects, far from PAF and close to PAF.

By considering these results, the analysis of the P-wave morphological variability over time could be considered as a useful tool to anticipate PAF. More concretely, 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 morpho-

logical features. As for the time P-wave features, higher morphological variability was observed when the onset of PAF approximated. This finding is in line with the atrial alterations preceding the onset of PAF, which eventually will provoke an intermittently disrupted electrical conduction [39].

Other authors have also suggested a greater P-wave morphology alteration when AF onset approximates. Thus, by using a P-wave modeling based on the addition of gaussian functions, more fragmented atrial depolarizations have been observed in patients with greater risk of AF development [15]. Similarly, the P-wave modeling based on singular value decomposition [60] or wavelet analysis [61] has also reported a higher P-wave complexity in patients developing AF after coronary artery bypass grafting compared to those who maintained normal sinus rhythm. Finally, making use of the P-wave spectral turbulence analysis, Barbosa et al. [62] have found a direct relationship between the probability of AF recurrence after electrical cardioversion and the P-wave fragmentation. However, it has to be remarked that such a kind of analysis was not proposed to study the beat-to-beat P-wave morphological alterations.

Regarding the P-wave energy, other works have reported higher energy values for PAF patients than for healthy subjects in the signal-averaged P-wave [17]. Similarly, within PAF patients, higher energy values have been observed in those patients with an increased number of episodes [16]. Moreover, a P-wave energy reduction after pharmacological treatment with antiarrhythmic drugs has also been corroborated by several authors [14]. Because these drugs can enlarge the refractory period without altering conduction velocity, this metric has been proposed as a noninvasive marker of atrial refractoriness [14]. According to this finding, parameters such as P_{area}, P_{nrms}, $P_{nenergy}$, and P_{narea} reported high variability over time. However, it is noteworthy that the P-wave energy has been computed in frequency [17] or wavelet [16] domains in the aforementioned previous work.

On the other hand, it is interesting to note that only the number of gaussian functions to appropriately fit this model to the signal-averaged P-wave was studied in [15]. Moreover, only spatial diversity between the acquired 32 leads was considered by comparing the obtained results from each other. Nonetheless, a similar P-wave modeling in a wave-to-wave fashion with a single gaussian function has also been proposed to analyze P-wave variability over time [27]. In order to quantify their morphology, each P-wave was modeled by a gaussian function defined as

$$\hat{w}[n] = A \cdot e^{-\left(\frac{n-C}{W}\right)^2}, \tag{18}$$

where the constants A, C, and W represent its amplitude, time position, and width, respectively. To compute these parameters, the gaussian function $\hat{w}[n]$ was fitted to every single P-wave by a nonlinear least squares approach [27].

On the other hand, previous works have proved that a normal P-wave resembles a gaussian shape [63]. However, altered and fractionated atrial electrical activity seems to be reflected in the appearance of bumps in the P-wave [15]. Therefore, higher differences between the real P-

wave and its gaussian model could be expected when PAF onset approximates. This P-wave alteration can be assessed by the normalized root mean square error (ε) between the real and the gaussian modeled P-wave [27]. As an example, Fig. 9 shows typical cases of P-waves coming from healthy and diseased PAF patients together with their corresponding gaussian modeling. Observe how ε is able to represent quite robustly the differences between real and modeled P-waves.

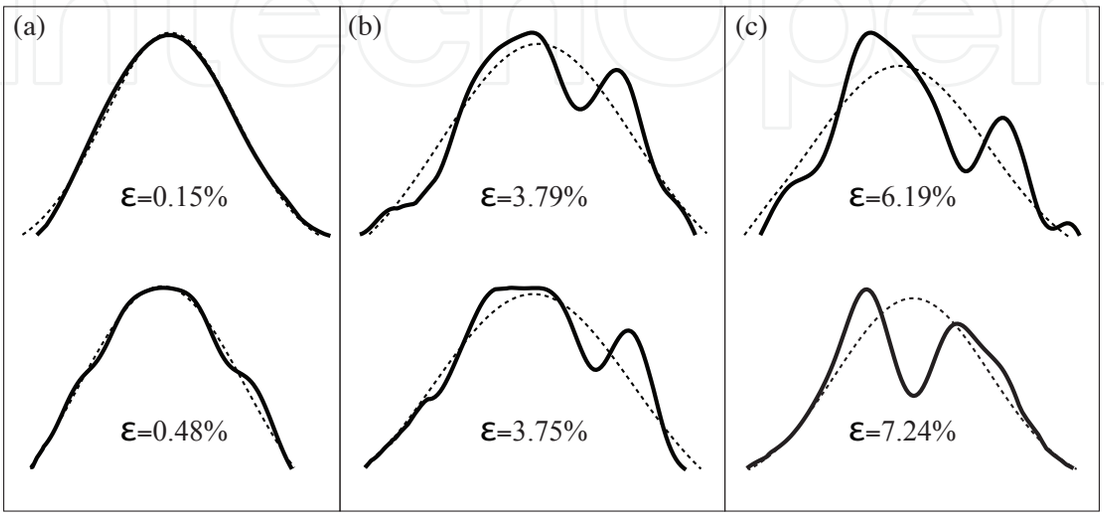


Figure 9. Comparison between the obtained gaussian models (dotted line) and representative P-waves (solid line) from typical (a) healthy subjects, (b) patients far from PAF, and (c) patients close to PAF. It has to be remarked that as PAF onset approximates, the root mean square error ε increases.

The variability of A, C, W, and ε over the one-hour-length recordings was estimated in the same way as before by fitting a linear model to the data in which the fitting slope (α) indicated the corresponding variability. The results obtained are summarized in Fig. 10. As was expected, an increased P-wave variability was shown by these parameters when the onset of PAF approximated. To this respect, the time course variability of W for typical ECG intervals from the studied groups is displayed in Fig. 11.

From a numerical point of view, the classification results are summarized in Table 3. As can be observed, parameters derived from the P-wave gaussian modeling did not improve the P_{dur} discriminant ability. However, the metric W only presented an accuracy slightly lower (around 3.5%) than the time course variability of the P-wave duration. In addition, a greater global accuracy than the feature PP_k was reached by the remaining morphological P-wave features. Thus, improvements around 3.5, 9, and 6% in the global accuracy were obtained from the metrics A, C, and ε, respectively, compared with the PP_k. Moreover, it is also interesting to note that a stepwise discriminant analysis provided a global accuracy increase of around 6 and 9% compared with the features P_{dur} and W, respectively. As expected, given that these metrics provided the highest single accuracy, they were combined to produce the optimal discriminant model.

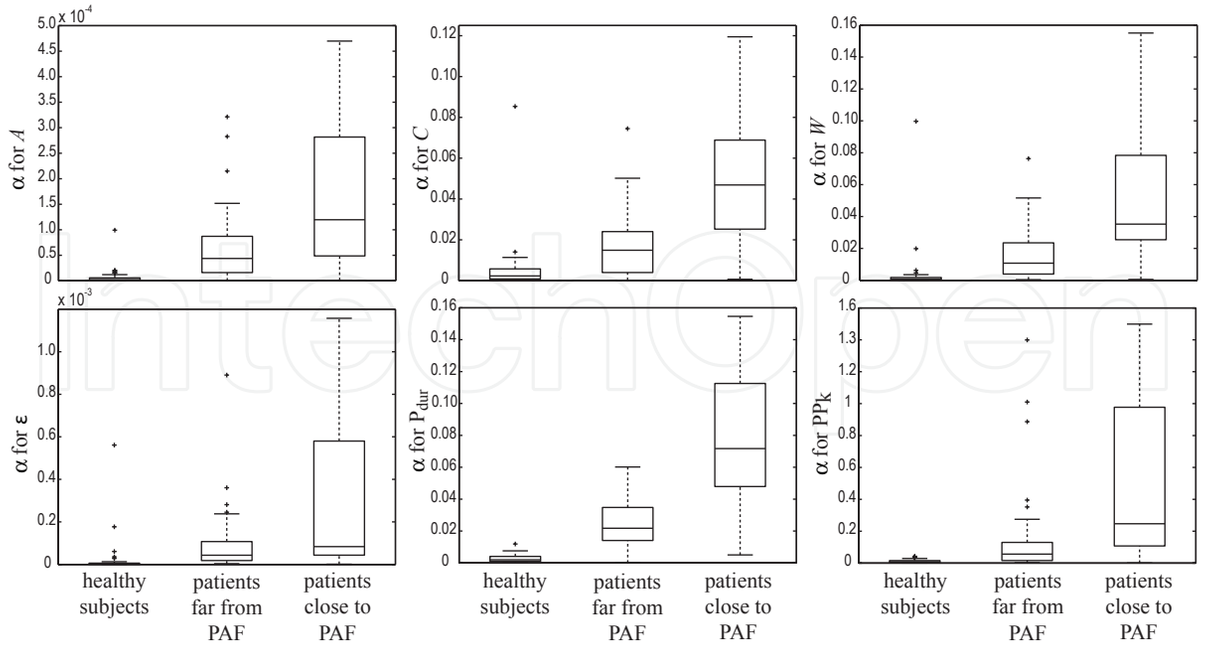


Figure 10. Boxplots showing the distribution of the fitting line slope associated to each analyzed parameter from the gaussian modeling of the P-wave for healthy subjects, patients far from PAF, and patients close to PAF.

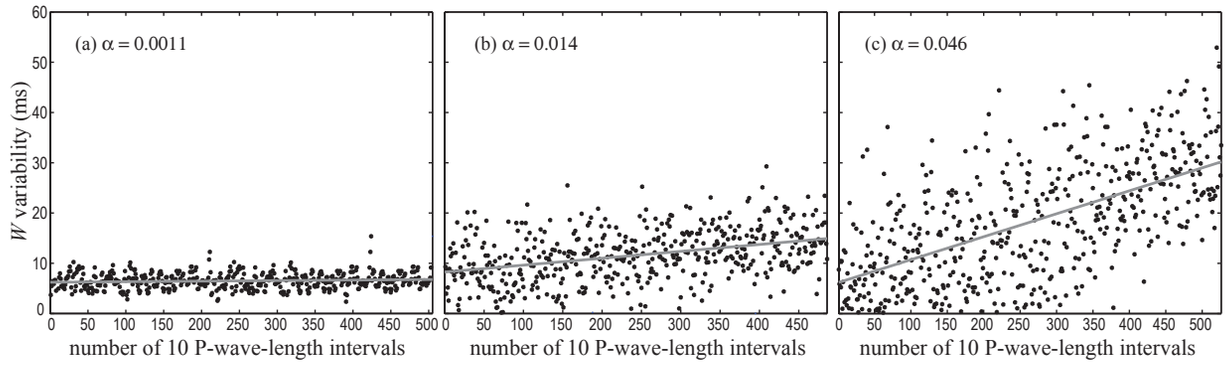


Figure 11. Typical P-wave width W variability over time from representative ECG intervals from (a) a healthy subject, (b) patients far from PAF, and (c) patients close to PAF.

Finally, it has to be remarked that other attempts to quantify the P-wave morphology can also be found in the literature. To this respect, a classification rate higher than 90% among P-waves with different morphologies has been reached by means of systems identification in [64]. On the other hand, the AF risk after post-coronary artery bypass grafting has been successfully quantified by analyzing the singular value decomposition of the P-wave morphology [60]. Similarly, Clavier et al. [24] have presented an automatic method based on a hidden Markov model and wavelet transform to detect and delineate the P-wave. Moreover, they also proposed a polynomial characterization of this wave, thus noticing the need of higher orders to represent slight morphological details of the P-wave. Finally, the P-wave energy has also been analyzed by several authors from wavelet and frequency domains [16, 17], providing P-waves with higher energy when the risk of AF development was increased.

Feature	Healthy subjects		Far from PAF		Close to PAF		Global Accuracy	
	training	test	training	test	training	test	training	test
A	85.79%	82.16%	59.78%	47.83%	67.39%	59.78%	71.74%	66.16%
C	86.78%	81.84%	60.65%	53.91%	78.70%	74.78%	75.92%	71.75%
W	89.64%	86.91%	75.87%	64.13%	82.43%	78.30%	83.19%	77.36%
ε	84.92%	77.12%	58.91%	49.13%	71.96%	67.83%	72.55%	68.30%
P_{dur}	93.88%	91.47%	80.61%	69.58%	85.17%	80.42%	88.90%	81.02%
PP_k	85.24%	78.17%	48.04%	37.39%	73.70%	69.78%	69.78%	62.54%

Table 3. Percentage of ECG segments correctly classified for each group from the slope α obtained for each studied P-wave feature from its gaussian modeling.

4. Spatial analysis of the P-wave

The P-wave duration has also been widely characterized from the standard 12-lead ECG recording. Thus, the P-wave duration has been normally measured in at least ten of the 12 surface leads, with the maximum being the longest P-wave duration in any lead and the minimum being the shortest P-wave duration in any lead [38]. Moreover, the P-wave dispersion has been defined as the difference between the maximum and the minimum P-wave duration [39]. Whereas the minimum P-wave duration has only provided recently significant clinical information to identify an increased risk of lone AF [65], the maximum one and its dispersion have shown to be widely useful in the prediction of PAF. To this respect, Dilaveris et al. [38] found a high correlation between the maximum P-wave duration and the risk of idiopathic PAF. Moreover, the P-wave dispersion complemented this metric for a clearer separation between patients with PAF and normal controls. These findings were validated two years later by Aytemir et al. [47], who analyzed a slightly wider database. Additionally, De Bacquer et al. [66] showed that the maximum P-wave duration was a very important risk indicator for the development of AF over 10 years. In agreement with these works, Andrikopoulos et al. [67] showed that the maximum P-wave duration and its dispersion were significantly higher in patients with PAF than in control subjects. However, these authors also reported that the variance of the P-wave duration in the 12-lead ECG was a stronger predictor of the onset of idiopathic PAF than the previous metrics. The same result was also obtained by Perez et al. [40], who measured the standard deviation of the P-wave in the ECG. However, in this case, more than 40,000 patients who were followed for the development of AF for at least 5 years were analyzed. In view of this outcome, the authors suggested that the P-wave variance may account for the differences in atrial conduction across different areas, thus reflecting more accurately the heterogeneity of the diseased atria.

In addition to these works, others have also corroborated the usefulness of the P-wave dispersion to predict the onset of PAF. Thus, Dilaveris et al. [68] showed the ability of this metric to predict frequent symptomatic AF paroxysms. In the same study, a significant positive

correlation was observed between the P-wave dispersion and its maximum duration. Similarly, a relevant negative correlation was noticed between the P-wave dispersion and its minimum duration. In another publication, the P-wave dispersion also showed to be a sensitive and specific ECG predictor of paroxysmal lone AF. Furthermore, it also provided a significant correlation with the maximum P-wave duration and a weak, although significant, association with age [47]. On the other hand, Dilaveris et al. [69] and Ciaroni et al. [70] revealed the P-wave dispersion as an independent predictor of the onset of PAF in the hypertensive population. Indeed, this metric was found to be significantly higher in hypertensives with a history of PAF than those without history of arrhythmia. Finally, it is interesting to mention that Koide et al. [71] concluded that the P-wave dispersion was a clinically useful predictor of progression from paroxysmal to persistent AF. In this study, more than 200 patients with a diagnosis of PAF were followed for more than 60 months.

5. Discussion

Recent works have shown that the beat-to-beat analysis of the P-wave can reveal clinically relevant information about the altered atrial conduction preceding the onset of PAF as any signal-averaging approach. Furthermore, the main advantage of the individualized single P-wave analysis is the possibility of being easily used in a routine clinical environment, because it can be developed from daily recordings such as short surface ECGs or long-term Holter signals. Hence, this kind of P-wave analysis could be considered as the most practical way to perform exploratory investigations about the onset of PAF.

It is highly relevant to highlight that in recent years, the analysis of PAC has been improved to reach a clinically significant result. Thus, it has been able to identify the imminent onset of PAF with an accuracy very near to 100%. However, it has also been noticed that the frequency of these ectopics is considerably decreased as the distance to the episode onset increases [53, 52]. Therefore, it could be elucidated that this approach is only feasible just before the arrhythmia starts [31], which is too late for the application of an efficient prophylactic therapy [72, 73]. In contrast, the analysis of the P-wave variability over time has proven to be able to operate with notably more anticipation in the prediction of PAF onset. Indeed, the time evolution of all the studied P-wave features has revealed an interesting ability to predict successfully the onset of PAF with, at least, one hour in advance.

Moreover, it is worth noting that all the analyzed P-wave features show a time course variation as a function of how far is the onset of PAF. Indeed, all the analyzed features provided an increased variability trend as the PAF onset approximates. This outcome is in strong agreement with the atrial electrophysiological alterations noticed in clinical studies before the onset of spontaneous or induced AF. To this respect, a common atrial alteration in patients prone to PAF is the presence of decreased and different cell refractory periods in various atrial regions. Sometimes, these site-specific conduction delays can be increased by intracellular or intercellular factors, such as connections, ion channels, or regulatory proteins [9, 74]. This heterogeneity may provoke irregular atrial conduction which could result in overlapped atrial

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depolarizations or even premature atrial repolarizations [42, 2]. Thus, the way through which the sinus beat travels across the atria may be notably altered by the presence of these delays as well as structural abnormalities in atrial walls (e.g., fibrosis) [9]. Hence, the highly variable and fragmented atrial activation morphology over time could be a result from this site-dependent inhomogeneous and intermittent atrial conduction [39]. Overall, the beat-to-beat analysis to quantify P-wave progression over time seems to be a promising new way to identify the onset of PAF. Furthermore, the study about how this method's performance is maintained in more anticipated predictions has to be validated in future prospective studies. In this way, earlier predictions of the onset of PAF could be reached and patients could benefit from preventive therapies.

Finally, although the single P-wave analysis from short ECGs cannot provide information about the time progression of the atrial electrophysiological alterations preceding the onset of PAF, it can reveal interesting information about the regional differences in atrial activation and conduction [39]. To this respect, previous works have shown that the electrical activity in the surface ECG closely correlates with the conduction in specific parts of the atria [75]. Hence, inhomogeneous atrial conduction can be identified by variations in the P-wave duration between differently oriented surface ECG leads [39]. This information has proven to be widely useful to discern between PAF patients and healthy subjects from the sinus rhythm ECG. This is also an interesting clinical challenge [32] because PAF can sometimes be asymptomatic and not only a single episode may appear during long-time Holter monitoring. Thus, this information could allow the identification of patients with PAF without the need of long-term recordings and they may be early treated, thus minimizing the atrial remodeling and reducing the probability of arrhythmia perpetuation.

6. Conclusions

This study aimed to review the most recent advances in the beat-to-beat P-wave analysis to stratify the risk of suffering PAF and how long in advance its onset can be predicted. In recent years, considerable progress has been reached in both purposes, this kind of analysis being able to provide, in an easy and noninvasive way, clinically useful information related to the time progression and regional differences of the atrial conduction alterations preceding the onset of PAF. The use of this information may be helpful in routine clinical practice to improve the diagnostic and therapeutic management of atrial fibrillation.

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