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The Effect of Medication on P-wave Beat-to-Beat Variability in Atrial Fibrillation during Sinus Rhythm

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Abstract— **Atrial Fibrillation (AF) is the most common cardiac arrhythmia, and its progressive nature is associated with gradual atrial remodeling. The P-wave in the surface Electrocardiogram (ECG) reflects the atrial activation, while the modification of the atrial pathophysiological properties leads to P-wave morphology (PWM) alternations. In paroxysmal AF (pAF), the modifications of the PWM may have a spontaneous rather than permanent presence in the ECG signal. The analysis of the P-waves, during sinus rhythm, on a beat-to-beat basis, has revealed the existence of at least two PWM. In addition, the wavelet characteristics of the P-wave matching the main morphology can accurately distinguish the patients with pAF from healthy volunteers. In this work, we examine the hypothesis that there is an effect of the anti-arrhythmic medication on beat-to-beat PWM alternations of pAF patients. ECG signals of high frequency (1000Hz), in the three orthogonal leads, were collected for 81 pAF patients of minimal and mild AF burden, 47 of which receiving antiarrhythmic medication treatment, and from 56 healthy volunteers. Kruskal-Wallis test was performed, and the preliminary results denote the existence of statistically significant differences between the groups. A 3-class Random Forest classifier was trained, using the forward wrapper approach, resulting in a high overall classification performance (AUC = 85.75%). This analysis is a step towards improving understanding of medication effect on the variability of P-wave.**

Clinical Relevance— **The methodology presented in this paper can be used to perform a non-invasive characterization of low burden pAF patients using the ECG recording.**

I. Introduction

Atrial Fibrillation (AF) is recognized as the most common cardiac arrhythmia while its prevalence is projected to increase in the coming decades [1]. Even though AF is not a life-threatening arrhythmia, it is associated with several clinical implications, including increased risk of stroke [2], heart failure [3] or dementia [4]. AF leads to a progressive atrial remodeling and thus an AF-prone substrate. The early detection of AF can improve patient’s management using pharmacological or interventional treatment [5].

AF diagnosis is established by irregularly irregular rhythm and P-wave absence in an electrocardiographic recording (ECG). P-wave reflects atrial depolarization, and its analysis has been used to evaluate underlying atrial remodeling. Several indices, including P-wave duration, P-wave area or P-wave terminal force in lead V1 ($PTFV_1$) has shown their predictive value for AF detection [6].

Antiarrhythmic medication is widely used to manage AF patients. This approach is based on specific intacellular ion currents modification, using agents such as potassium or sodium channel blockers, which affect the action potential duration (APD) and other ionic current characteristics, and thus prevent AF episodes. Different classes (I-V) of medication target different ionic channels.

The transient nature of AF episodes allows beat-to-beat analysis of the P-wave characteristics during sinus rhythm (SR). The existence of several P-wave morphologies has been documented, while according to [7], the percentage of beats, during SR, matching the main morphology is higher in healthy subjects compared to patients with history of paroxysmal AF (pAF), while the percentage of P-waves matching specific types of morphology can be a predictor of AF recurrence after circumferential pulmonary vein isolation [8]. We envision using this characteristic as a marker of pAF presence, deterioration, or post-treatment recurrence. In this scope, to ensure the precision and accuracy of such a marker, we need to understand the factors that may affect its performance beyond the targeted condition, including the conditions under which the ECG measurement takes place. The presence of antiarrhythmic medication is a potential factor.

In this paper we use the methodology proposed by [7] to investigate whether the use of antiarrhythmic medication is associated with alternations of P-wave characteristics in pAF patients. A three-class model is developed to separate the normal patients from those with and without medication and minimal/mild AF burden.

II. Methodology

A. Dataset

Patients with pAF were included in the study, while healthy age- and gender-matched volunteers formed the control group. Exclusion criteria were the presence of comorbidities, such as previous cardiovascular surgery, previous cardiac ablation, heart failure NYHA class III-IV, severe valvular heart disease, prosthetic valves, reduced life expectancy, age > 75 years, atrioventricular block, presence of implanted pacemaker or cardiac defibrillator, moderate/severe renal or hepatic impairment. All participants gave written informed consent, and the study complied with the Declaration of Helsinki and was approved by the Medical Ethics Committee of our Institution.

The patients were categorized in two groups based on whether they were receiving any antiarrhythmic drug (AAD) with the pAF patients without receiving any AAD to been included in the first groups (D^-) while the patients receiving at

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least one AAD were included in the second one (D+). Regarding the allocation of the AAD, 3 patients were receiving sotalol, 14 propafenone, 11 amiodarone and 19 flecainide. The AF symptoms severity and burden were classified according to [9] in four scales. The classification is based on a questionnaire which is designed to assess objective measures of disease and health-care utilization such as the duration of episodes during a specific period of time, their frequency and the number of electrical cardioversions provided. For the purposes of this study, only patients allocated to the first two classes were considered (minimal and mild), while patients with moderate to severe score (>6) were excluded. Table I provides more details on the dataset.

TABLE I. SUBJECTS' CHARACTERISTICS

	PAF D- **(n=34)**	**PAF D+** **(n=47)**	**Healthy** **(n=56)**
AF burden minimal (%)	16 (47)	11(23)	n/a
Age	55.7±13.3	57.4±10.2	55.2±5.7
Male sex (%)	38 (68)	31 (66)	24 (73)
Body mass index (kg/m2)	28.7±6.7	29.9±6.2	26.3±5.9
CHA_2DS_2-VASc score	1.32±1.22	1.26±1.24	0.7±0.8

B. P-wave analysis and morphologies

Orthogonal 1000Hz ECG signals of 10 minutes duration were collected using a Galix GBI-3S Holter monitor. All the participants were in a supine position in resting condition. Butterworth filters followed by a wavelet filter were used to remove noise and artifacts from the signals. The QRS complexes were detected, and two cardiologists applied a manual investigation of the signals to identify beats that were considered to be atrial or ventricular ectopies). In case of a disagreement, a consensus was reached. Those beats were excluded from the analysis.

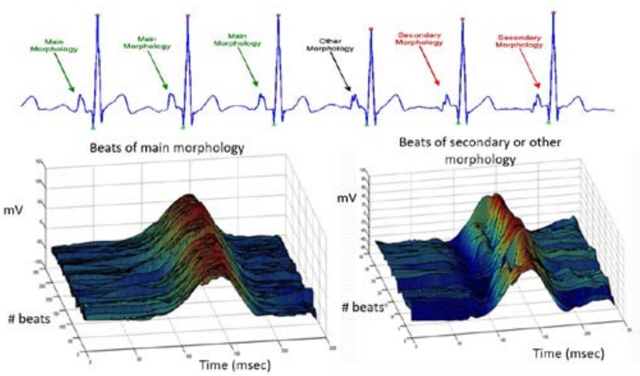

Figure 1. An example of ECG in lead Z, where P-waves of main, secondary/other morphology are depicted (upper). In the bottom, each type is depicted separately.

The beat-to-beat analysis of the P-waves was based on a methodology proposed by [7]. In brief, a segment, before the QRS complex was considered and following a semi-automated process involving k-means clustering and correlation techniques, specific morphologies are defined. The P-waves matching each morphology were detected and the respective percentages of the P-waves were computed. The most frequently observed morphology of the P-waves in each lead is defined as the main P-wave morphology of the ECG signal. Afterwards, continuous wavelet analysis of the P-waves belonging to the main morphology was applied, using morlet mother wavelet. Several time-domain features, such as the distance between ECG fiducial points, and wavelet characteristics, such as wavelet energy and its association with P-wave signal, were computed for each beat matching the main P-wave morphology, as described in [6]. The wavelet characteristics were calculated in three non-overlapping frequency bands (L: 30-70Hz, M: 70-160Hz, H: 160-200Hz). The mean value and the coefficient of variation (cv) for each of the features were computed [7].

B. Feature Selection and Classification

For the development of the multiclass model, a feature selection step was foreseen, and a two-step approach was followed in this work, taking into account the high number of features initially calculated. First, the statistically insignificant features were excluded from further analysis, while for the remaining, a ranking of their importance was performed, to end up with the most important ones.

Regarding the first step, the Kruskal-Wallis test was used to investigate whether the features originate from the same distribution [10]. If a feature was found to differ significantly for at least one of the remaining 2 classes, it was considered for further analysis. In addition, pairwise comparisons using Dunn's were used to identify the features that differentiate each group [11]. Furthermore, the correlation between the features was estimated, and those which presented a correlation greater than 95% were excluded.

Following, the methodology proposed by [12] for the multiclass feature selection was applied. According to this approach, a multiclass problem can be considered as a set of binary ones, the most usual ones to be "One-vs-One" (OVO) and "One-vs-All" (OVA). For classification problems of c classes the number of binary problems is $M = c(c-1)/2$ and $M = c$ for OVO and OVA, respectively. Most works propose the estimation of feature importance as the average of its importance in each binary classification problem, which can lead to sub-optimal selections. However, in [12] additional measures are presenting. In our work the Average-SD feature ranking was used. According to this approach, the relative position of the j-class problem for the feature i is the mean value of $r_{i,j}$, where:

$$r_{i,j} = \frac{f - pos_{i,j}}{f} \tag{1}$$

, where f is the total number of features and $pos_{i,j}$ is the position of the i^{th} feature in the j^{th} binary problem. In our work only the features that present a $p < 0.05$ in the Kruskal-Wallis were considered.

The ranking of each binary problem was based on a model that estimated each variable's contribution to the model. A Random Forest (RF) model was used for this purpose.

For the final classifier, a RF model was used. A forward wrapper feature selection approach was adopted, and a 10-fold cross-validation technique was used to improve the reliability of the results. According to this approach, one feature is added in the classifier based on its importance. The performance of the classifier is extracted, and in case the newly added feature leads to an improvement, it is added in the final feature set, while in the other case it is excluded from the analysis. In the current work, the Area Under the Curve (AUC) was selected as the metric to evaluate the performance of the classifier.

III. Results

The analysis of the P-waves for each patient resulted in the extraction of 11 features reflecting the morphology, 54 features from the time analysis, and 198 features from the wavelet domain.

A. *Statistical analysis*

The Kruskal-Wallis test revealed the existence of statistically significant differences in 108 out of the 263 features. Table II provides more details on the number of features that differ significantly for at least one of the classes. As observed the differences between healthy volunteers and pAF patients receiving medication are higher, while the comparison of healthy people with patients without medication reveals less statistically significant features. Those findings in association with the existence of differences between pAF groups reveal the importance of medication on P-wave characteristics, even if the patients are of minimal or mild AF burden.

TABLE II. Number of statistically signifficant features between the classes using Dunn test. In parethesis the respective number after applying Bonferroni correction.

	Healthy	**D^-**	**D^+**
Healthy		20 (12)	132 (99)
D^-	20 (12)		56 (26)
D^+	132 (99)	56 (26)	

Figure 2 provides a visual representation of the percentage of beats matching the main morphology in each axis. As depicted, a distinct P-waves morphology, in leads X, Y and Z exists in all the groups and the comparison of them is statistically significant in most of the cases.

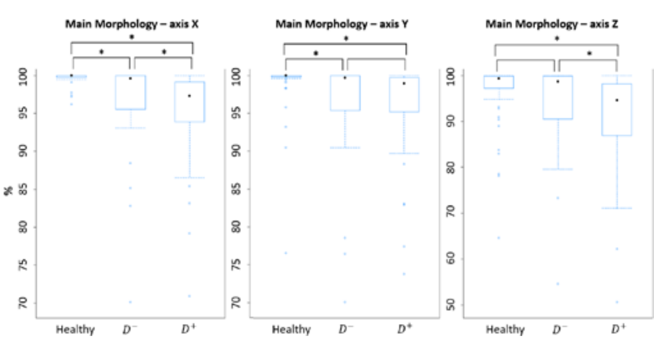

Figure 2 Boxplot for the percentage of beats matching the main morphology in axis X, Y and Z for the three classes. The asterisk denotes the existence of statistically significant differences, using Dunn test, between the classes, after applying Bonferroni correction.

B. *Feature Selection*

Based on OVO approach, the importance of the features was extracted based on the RF model, and the Average-SD feature ranking was estimated for the 3 classes. Table III includes the ten most important features for each binary classification and their position in each of the binary classifiers.

TABLE III. List of top 10 Ranked Features of the Multiclass Problem based on the Average-SD Feature Ranking and the Respective Position in Each Binary Problem

3-class	**Binary problem**		
	C-D^-	***C-D^+***	***D^--D^+***
% of beats of main morphology in lead X	3	15	1
cv of Maximum energy in H band in lead Y	4	12	4
% of beats of main morphology in all leads at the same time	8	10	8
cv of median energy in H band in lead Y	26	8	5
cv of P-wave peak position to the position of maximum wavelet energy in L band in lead X	14	16	11
cv of maximum energy in M band in lead Y	33	6	3
% of beats of main morphology in lead Y	28	9	6
cv of P-wave start to R distance in lead X	25	14	10
cv of P-wave start to R distance in lead Y	29	5	16
cv of P-wave maximum position to R distance in lead X	43	2	7

C for healthy, D^- and D^+ for the classes without receiving and receiving medication respectively

As observed, features form all types of analysis were included in the final list (Table III) highlighting the importance of the P-wave beat-to-beat analysis in different domains.

C. *Classification*

The forward wrapper feature selection approach resulted on the inclusion of 10 features in the final classification model. The AUC of the final 3 class model was found to be 85.75%.

The final features are the following:

(1) percentage of beats of main morphology in lead X
(2) cv of Maximum energy in H band in lead Y
(3) percentage of beats of main morphology in all leads at the same time
(4) cv of the distance between P-wave peak and maximum wavelet energy location in L band in lead X
(5) percentage of beats of main morphology in lead Y
(6) cv of the distance between P-wave onset and R-wave in lead X
(7) cv of Maximum energy in H band in lead X
(8) cv of the distance between P-wave peak to Q-wave in lead X
(9) cv of the distance between P-wave peak and Q-wave in H band in lead X
(10) cv of P-wave peak position to P-wave duration in lead X

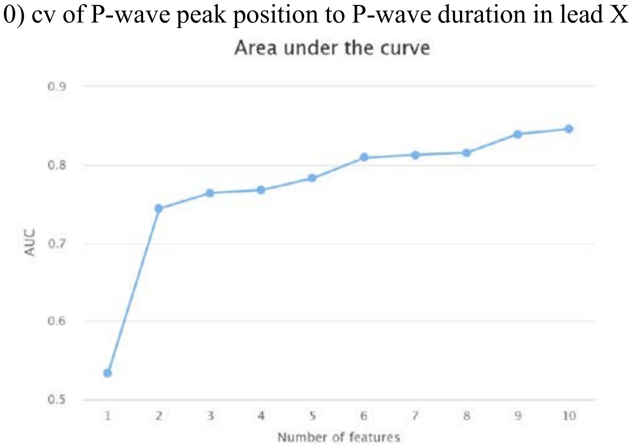

Figure 3 The AUC of the classifier when additional features are included.

As observed, most of the features listed in Table III are also used in the final set of features for the classifier. This finding highlights the importance of Average-SD approach for feature ranking. In addition, it must be underlined that, features from all analysis domains are used for the classification, with the characteristic observed in lead X and Y to be more important.

IV. Conclusion

The effect of clinical and biological factors on the P-wave duration have been examined in [13], however, no direct association between antiarrhythmic medication and P-wave characteristics was documented.

In [14], data from more than 7,000 subject were analyzed in order to investigate the association of P-wave morphological characteristics with the risk of hospitalization, in patients with AF. In that study, patients with diverse types of medication were included, and it was reported that the type of medication can affect the type of P-wave morphology. As reported in that study, antihypertensive medication or β-blockers alter the observed types of P-waves in a statistically significant way, while the respective difference in the cases of Digitalis medication is not statistically significant. The outcome of that study was that the P-wave morphology is associated with the risk of hospitalization in patients with AF.

All these works highlight the effect of medication of P-wave characteristics; however, their analysis in diverse domains, such as morphology, time and wavelet analysis can improve the classification results.

This work aims to evaluate the effect of the medication on the P-wave characteristics as measured on the surface ECG signal in patients with pAF. In addition, the analysis aims to investigate the importance of those characteristics on the classification of signals. Data from a total of 137 ECG recordings, derived from healthy volunteers and two groups of low-burden PAF history patients, one with and one without usage of antiarrhythmic medication, were used in the analysis.

Based on the statistical analysis, even when applying Bonferroni correction, we observe that these features can be used to allocate ECG signals to three different groups. The existence of more statistically significant differences between healthy subjects and pAF patients with medication while, on the other hand, the differences between healthy subjects and pAF patients without medication are moderate, reveals the importance of medication on ECG analysis, and in P-wave in particular. While the AF burden is minimal or mild, suggesting a limited remodeling in the atria, medication can significantly alter the electrical propagation in the heart.

The existence of distinct P-wave morphologies is also revealed in this study. In particular, the percentage of beats matching the main morphology in all leads is high in healthy subjects (~100%), while medication leads to a significant decrease of this percentage in all leads.

Furthermore, the inclusion of features from different domains of analysis highlights the fact that the P-wave has information that is not always revealed using the standard P-wave indices. However, more data must be collected to achieve a consolidation of results and a safe extraction of novel biomarkers that can be used in medical practice.

While this work constitutes of an initial attempt to evaluate medication effect on P-wave characteristics using novel features, several limitations must be highlighted. Initially, the sample size was limited and thus, the analysis of the P-wave based on specific types of antiarrhythmic medication could not be feasible. In addition, in this study, an internal validation of the classifier was applied, via10-fold cross-validation. However, no external testing dataset was available to evaluate the final model performance. Finally, in this work only patients with the minimal and mild AF burden were considered while the two groups were merged. It would be also interesting to investigate P-wave alterations observed on each one of the four AF burden categories and how AAD affects P-wave beat-to-beat variability.

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