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Variation of P-wave indices in paroxysmal atrial fibrillation patients before and after catheter ablation

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Abstract

The effects of pulmonary vein isolation in the surface electrocardiogram of patients with paroxysmal atrial fibrillation are analyzed in this paper using non-invasive markers for early detection of the arrhythmia recurrences.

Several features have been extracted on P-waves of V1 lead for paroxysmal atrial fibrillation patients who underwent catheter ablation of pulmonary veins for restoring sinus rhythm permanently. Surface ECG was simultaneously recorded along with intracardiac recordings starting from the beginning of the intervention until half an hour after the catheter ablation successfully ended. Significant difference between the means before and after catheter ablation have been observed for the cross-correlation index, kurtosis and amplitude dispersion of P-waves.

A logistic regression applied to all the descriptors pointed to the amplitude dispersion index, as well as the minimum gradient joint with kurtosis of P-waves prior to catheter ablation as good predictors of recurrence of atrial fibrillation (78% accuracy). It is important to note how using a few descriptors good classification results are achieved. This study opens a door to early detection of atrial fibrillation recurrences using markers obtained by non-invasive methods.

Keywords: Electrocardiogram (ECG), atrial fibrillation, catheter ablation, pulmonary vein isolation

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice [1, 2] with a prevalence greater than 2% for general population and twice the last decade. It is becoming a relevant public health issue [3]. AF is characterized by the disorganized propagation of electrical signals through the atria such that there is desynchronization between atria and ventricles activity resulting in a fast and irregular heart rhythm.

Stratification of AF patients is based on the duration of the arrhythmia episodes. They usually start as paroxysmal AF, i.e. episodes which spontaneously terminate with or without external intervention. Often, the frequency and duration increase along time, thus sustaining the arrhythmia towards persistent and long-standing persistent AF.

Treatment of AF depends on the clinical stratification of the arrhythmia. It can include rhythm and/or heart rate control strategies, oral anti-coagulation (to prevent ischemic stroke) and catheter ablation for pulmonary vein isolation [4]. The treatment efficacy depends on the clinical stratification [5], showing lower rates of successful control of the arrhythmia for persistent AF [6].

Success rate of catheter ablation for paroxysmal AF (freedom from arrhythmia) is about 80% [7]. Indeed, paroxysmal AF patients had significantly lower rates of recurrence following an ablation procedure [8]. Thus, catheter ablation has become a popular strategy for rhythm control which also improves the outcome of anti-arrhythmic drugs [9]. However, medium and long-term AF recurrences are quite common after the procedure [10]. Patients with initially successful procedures present different recurrence rates depending on the energy source used in catheter ablation (differences between using radiofrequency or cryoablation have been reported [11], and also depending on sex and comorbidities [12]).

Many references have studied pulmonary vein isolation, and how the spontaneous reconnection after catheter ablation procedure is considered as the origin of AF recurrences [13]. It has been shown that AF late recurrences are associated to pulmonary vein reconnection after a single ablation procedure [14], and after redo procedures [10, 15].

Some researchers have studied which spectral features of ECG atrial activity could be used to select candidates for catheter ablation [16]. Other authors have found that abnormal P-waves or the presence of different morphology patterns can be used as indicators of AF development [17, 18].

Regardless, during the last years the main findings on ECG analysis to predict AF recurrences have been focused on the measurement of P-wave duration and dispersion. Long P-wave duration was found to be a significant predictor of AF recurrence after catheter ablation [19, 20, 21], and also able to evaluate the risk to develop the arrhythmia [22]. The dispersion of P-wave duration is lower in AF recurrence-free patients [23, 24]. Time to recurrence is also a major determinant of outcome: late recurrences are more likely to have paroxysmal episodes and better response to antiarrhythmic drugs [25].

Many more efforts have to be done in order to develop reliable tools for early recurrence detection [26, 27, 28]. Therefore, the identification of reliable non-invasive markers before the first symptoms is clinically relevant [29]. Unfortunately, nowadays there are not commmonly accepted predictors of AF recurrence [30, 31].

Our major aim is to determine personalized electrical markers based on the analysis of the ECG P-waves of patients with paroxysmal AF. The study compares the analyzed non-invasive markers before and after catheter ablation, for early detection of AF recurrence prior to suffering a new arrhythmia episode. In this manner, clinical assistance could be provided to electrophysiologists.

The data are described in Section 2. Signal preprocessing, feature extraction and the statistical analysis appear in Sections 3.1-3.3. Experimental results are given in Section 4. The discussion is contained in Section 4.2 and conclusions in Section 5.

2. Materials

Patients in our study suffered from paroxysmal atrial fibrillation and have undergone catheter ablation in order to reverse the arrhythmia. It is a sample of 45 consecutive patients without any previous selection criteria. Catheter ablation was performed in an arrhythmia clinic at Hospital Universitari i Politècnic La Fe of Valencia (Spain). Clinical follow-up for two years has been done. Table 1 describes the baseline characteristics of the patients.

The Labsystem Pro EP Recording System (Boston Scientific) was used for ECG signal acquisition. The standard 12-lead surface electrocardiograms were acquired at 1000Hz sampling frequency as long as the subject was in sinus rhythm. Recordings started before catheter ablation procedure began, and were continuously acquired until 30 minutes after catheter ablation was completed. Intracavitary recordings were acquired during all the ablation process to monitor the process of pulmonary vein isolation and assure a successful completion.

Table 1: Summary of baseline characteristics of the 45 patients included in the study (n, %). Hypertension was defined as systolic blood pressure above 140mmHg or diastolic blood pressure above 90mmHg. Diabetes mellitus was defined as serum fasting glucose $\geq$7.0 mmol/L or on medications. Hypercholesterolemia was defined as cholesterol $\geq$6.4 mmol/L or treatment with lipidlowering drugs. Structural heart disease is defined as left ventricular $>$ 15 mm, left ventricular ejection fraction $<$ 50%, moderate or greater degrees of valvulopathy, prior myocardial infarction, significant coronary artery disease or the presence of primary myocardial diseases.

Age (mean, range)	55 (26-72)
Male (n,%)	31, 68.9%
Hypertension (n,%)	23, 51.1%
Diabetes mellitus (n,%)	5, 11.1%
Hypercholesterolemia (n,%)	9, 20%
Structural heart disease (n,%)	3, 6.7%
Antiarrhythmic drugs (n,%)	43, 95.6%
Previous electrical cardioversion (n,%)	12, 26.7%

3. Methods

3.1. Signal processing

For each patient, two segments of 60 seconds-length were extracted from precordial lead V1 of surface ECG. The first recording corresponds to the initial period before catheter ablation. The second one was acquired once the four pulmonary veins were isolated and the catheter ablation was successfully completed.

Duration of segments (60 seconds-length) was chosen as a balance between the possibility to extract enough P-waves to be analysed in the acquired segments, and preventing that the patient fell in atrial fibrillation again (as patients included in the study have

paroxysmal atrial fibrillation, this length made easier to find segments in sinus rhythm with visible P-waves).

The V1 lead was chosen for this study because previous studies have pointed out that P-waves are most prominently seen in the V1 lead [32, 33, 34]. Additionally, the atrial enlargement is better observed in this lead [35]. V1 lead has also been previously studied to analyse the impact of catheter ablation on the ECG recordings [36, 37]. After removing power line interference (using a Notch filter at 50Hz) and baseline wander (using cubic splines [38]) P-waves on V1 were manually delineated and revised by an electrophysiologist specialized on atrial arrhythmias to make annotations of the onset and the end of each P-wave. Nevertheless, automatic delineation algorithms (such as the ones proposed in [39, 40, 41]) could be used instead to obtain annotations in order to save computation time.

3.2. Feature extraction

P-waves have been manually delineated, and different numerical descriptions calculated. The following descriptors are usual statistical numerical descriptors. Now we will consider a precise definition in our problem. A nice explanation of these quantities can be found in [42] (chapters 2 and 3) and [43] (chapter 3) among other references.

Let $\boldsymbol{X}_{ki} = [X_{ki}(j)]$ be the P-wave for the k-th subject where $X_{ki}(j)$ corresponds to the i-th P-wave observed at the j-th sampling time of the k-th subject. In fact, $X_{ki}(t_j) = X_{ki}(j)$ where t_j refers to the real time i.e. $X_{ki}(t)$ is the (continuous) function observed at the discrete times $\{t_1, \ldots, t_{n_{ki}}\}$. The observed duration of the i-th P-wave of the k-th subject would be n_{ki}.

The gradient vector $\nabla X_{ki} = \partial X_{ki}(t)/\partial t$ has been estimated at each observed time. Several morphological features were estimated.

Mean amplitude defined as $\sum_{i=1}^{m_k} A_{ki}/m_k$, where m_k is the number of P waves for the k-th patient, and $A_{ki} = \max\{[X_{ki}(t_j)]\} - \min\{[X_{ki}(t_j)]\}$ (i.e., the difference between the maximum and minimum voltage values for the i-th P wave).

Mean duration of P-waves defined as $\sum_{i=1}^{m_k}(t_{n_{kt}} - t_1)/m_k$.

Maximum gradient i.e. $\max_j\{\nabla X_{ki}(t_j)\}$.

Minimum gradient i.e. $\min_j\{\nabla X_{ki}(t_j)\}$.

Total area under the P-waves obtained by using numerical integration with the trapezoidal method,

$$\boldsymbol{areaP}_k = (t_{n_{kt}} - t_1)/(2 * n_{ki}) \sum_{j=1}^{n_{kt}-1} (X_{ki}(t_j) + X_{ki}(t_{j+1})) \tag{1}$$

Root mean square defined as the quadratic mean of the P wave can be used as an alternative measure of atrial activity

$$\boldsymbol{rms}_k = \sqrt{\frac{1}{n_{ki}} \sum_{j=1}^{n_{ki}} |X_{ki}(t_j)|^2}. \tag{2}$$

Kurtosis to measure how outlier-prone is a distribution.

$$\boldsymbol{kurtosis}_k = \frac{\frac{1}{n_{ki}} \sum_{j=1}^{n_{ki}} (X_{ki}(t_j) - \mu)^4}{\sigma^4}, \tag{3}$$

where $\mu = \sum_{j=1}^{n_{ki}} X_{ki}(t_j)/n_{ki}$, and σ is the standard deviation ($\sigma = [(1/n_{ki}) \sum_j (X_{ki}(t_j) - \mu)^2]^{1/2}$) of the P-wave values. Kurtosis values larger/smaller than 3 are due to more/less outlier-prone distributions than the standard normal distribution.

Skewness to measure the asymmetry around the mean defined as

$$\boldsymbol{skewness}_k = \frac{\frac{1}{n_{ki}} \sum_{j=1}^{n_{ki}} (X_{ki}(t_j) - \mu)^3}{\sigma^3}, \tag{4}$$

where μ and σ are respectively the mean and the standard deviation of the P-wave samples previously defined. Skewness measurements near to zero refer to nearly symmetric data around the mean of the P-wave, whereas positive or negative skewness values are due to data spread out more to the right/left of the mean, respectively.

Dispersion of duration defined as the difference of the maximum and minimum of the P-wave durations for the k-th subject

$$\boldsymbol{D}_k = \max_i (t_{n_{ki}} - t_1) - min_i (t_{n_{ki}} - t_1). \tag{5}$$

Amplitude dispersion or the mean difference of the maximum and minimum of the P-wave amplitudes for the k-th subject

$$\boldsymbol{AD}_k = (1/m_k) \sum_{j=1}^{m_k} (\max_i X_{ki}(t_j) - \min_i X_{ki}(t_j)). \tag{6}$$

Cross-correlation index is the coefficient of correlation between the i-th P-wave for the k-th subject (X_{ki})) and a template for that subject (X_{kt}) calculated as the mean of the set of P-waves of the k-th subject,

$$\boldsymbol{\rho}_{ki} = \frac{cov(X_{ki}, X_{kt})}{\sigma_{X_{ki}} \sigma_{X_{kt}}}, \tag{7}$$

where cov is the covariance and $\sigma_{X\,ki}$ and $\sigma_{X_{kt}}$ are the standard deviations of X_{ki} and X_{kt}.

Amplitude dispersion index is a measure of the P-wave amplitude variations along the signal, defined as the maximum amplitude dispersion for the k-th subject normalized by the maximum measurement of all P-waves.

$$\boldsymbol{ADI}_k = \frac{\max_k \{AD_k\}}{\max\{X_{ki}\}} \tag{8}$$

3.3. Statistical analysis

The previous features have been calculated for each patient and all P-waves of the V1 lead of ECGs in sinus rhythm before and after the catheter ablation procedure. We have a paired experimental design.

The medians of each feature before and after pulmonary vein isolation have been compared using the Wilcoxon test. It provides an evaluation of each feature and its possible association with the treatment. Then, an analysis of the differences between the different features has been done, obtaining the most significant parameters by combination of different groups.

We have many features describing P-waves. Our major aim is the ablation outcome classification, using these features, into two possible classes: patients with recurrent and non-recurrent AF. A well established approach to do this is the logistic regression (see [44] for a basic introduction and [45] for a deeper study), for which the predictors are the considered features and the response is the class (recurrence or no-recurrence). Thus, a logistic regression analysis has been used to study a preliminary classification of those patients who presented AF recurrences during the two years of follow-up after catheter ablation. The estimated probabilities of recurrence have also been obtained. We pretend to have a simple model with a few variables but a good performance in the classification task. We will apply a forward variable selection starting with different sets of features and using the Akaike Information Criterium (AIC) to evaluate the quality of the model ([45]). The final models obtained will be evaluated using the leaving-one-out procedure (i.e. each patient is left out and the model is constructed by training on all other patients).

4. Results

All one-minute length segments of ECG recordings were in sinus rhythm both before and after catheter ablation. Table 2 displays the sample medians and the intervals from the lower to the higher quartile of the parameters studied before and after the ablation. The last column shows the p-values of the Wilcoxon test. Figure 1 displays the boxplots for the same features.

According to the presented results, the most significant parameter which shows differences before and after catheter ablation is the maximum value of P-waves, followed by the cross-correlation index (ρ) and kurtosis. Nonetheless, maximum value of P-waves is not a feature characterized by repeatability, since positions of the leads can vary and the patient can gain or lose weight, thus making more difficult the comparative method. Thus, further studies will be based on mean amplitude of P-wave.

The cross-correlation index between P-waves seems to show the greatest differences when studying the pulmonary vein isolation after catheter ablation. Figure 2 displays an example of lesser amplitude variability among P-waves after pulmonary vein isolation. This is directly related to the cross-correlation parameter, whose increment is due to a more regular cardiac rhythm after the catheter ablation procedure.

Different groups of features have been compared using the Hotelling T^2 test (with null distribution obtained using permutations). No significant p-values were obtained for groups of more than 2 features. Significant results (randomization p-values smaller than

0.05) were obtained for the the following sets: Maximum amplitude and root mean square; maximum amplitude and amplitude dispersion; kurtosis and ADI.

Table 2: Median, interquartile ranges and p-values (Wilcoxon test) on P-waves features before and after catheter ablation (CA) of paroxysmal atrial fibrillation subjects. Significant differences are bolded.

Features	Before CA	After CA	p-value
Maximum amplitude (μV)	223.97 (43.88, 397.71)	354.59 (170.75, 543.01)	**<0.0001**
mean amplitude (μV)	610.11 (492.70, 850.84)	674.43 (494.63, 883.71)	0.0689
mean duration (ms)	124 (106, 140)	129 (105, 145)	0.5913
$\nabla_{max} X_k$	13.526 (11.425, 17.994)	13.348 (11.227, 18.071)	0.5683
$\nabla_{min} X_k$	-22.278 (-28.548, -16.981)	-21.285 (-33.319, -15.566)	0.7713
areaP	30775 (23362, 41779)	28972 (24063, 42008)	0.7289
rms	291.95 (213.86, 406.97)	314.05 (222.47, 399.34)	0.5091
kurtosis	1.723 (1.634, 1.773)	1.646 (1.550, 1.745)	**0.0049**
skewness	0.090 (-0.065, 0.300)	0.077 (-0.097, 0.248)	0.3523
Dispersion of duration D (ms)	44 (32, 52)	42 (32, 53)	0.6991
Amplitude dispersion AD (μV)	439.45 (344.99, 526.29)	432.58 (323.25, 592.07)	0.7122
ρ	0.911 (0.871, 0.942)	0.943 (0.911, 0.958)	**0.0124**
ADI	1.496 (1.106, 2.546)	1.413 (1.052, 1.809)	**0.0402**

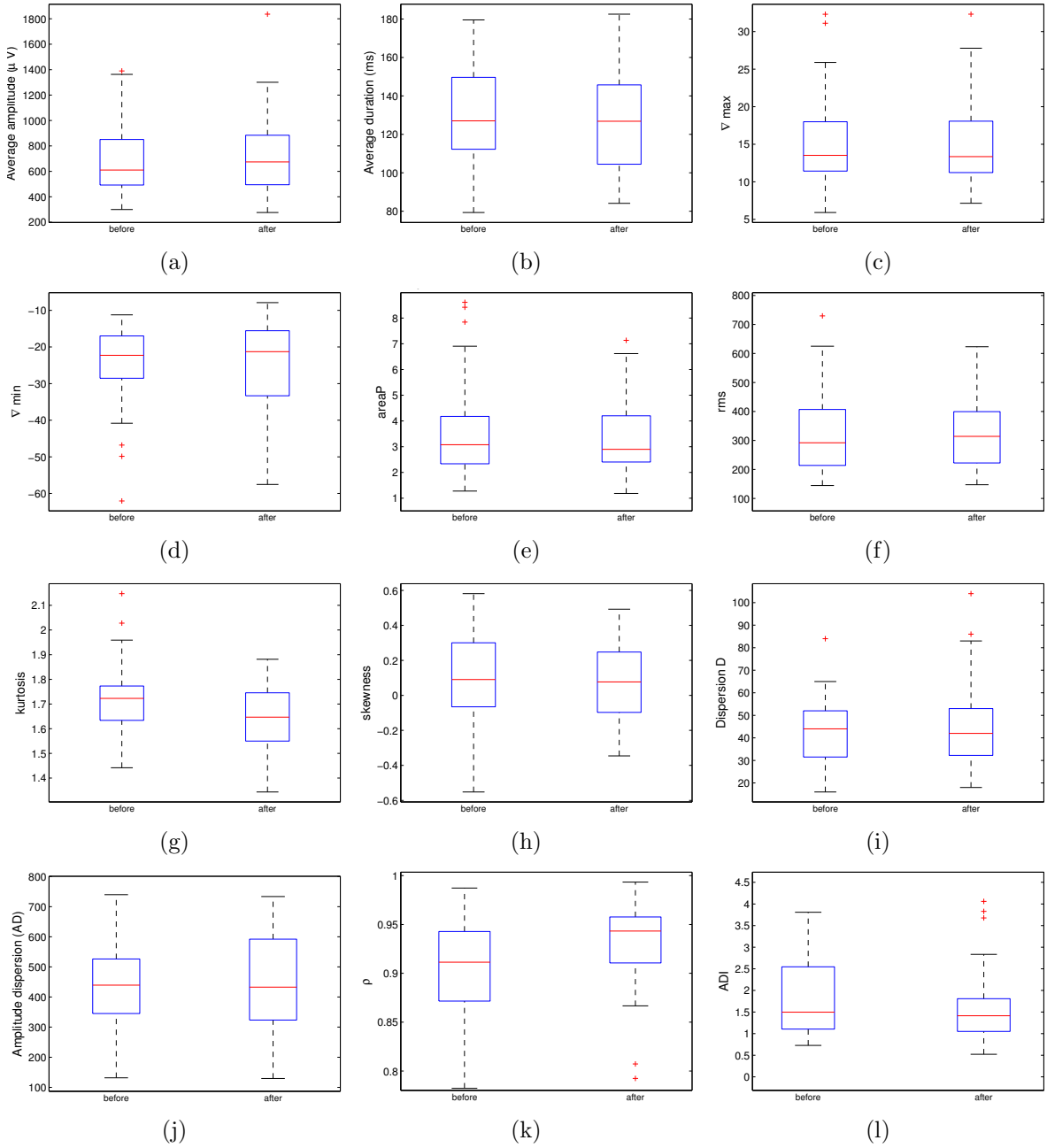


Figure 1: Boxplots for the different parameters under study before and after catheter ablation. (a) Mean amplitude; (b) Mean duration; (c) Maximum gradient; (d) Minimum gradient; (e) Area under P wave; (f) Root mean square; (g) Kurtosis; (h) Skewness; (i) Dispersion of duration; (j) Amplitude dispersion; (k) Cross-correlation index; (l) Amplitude Dispersion Index.

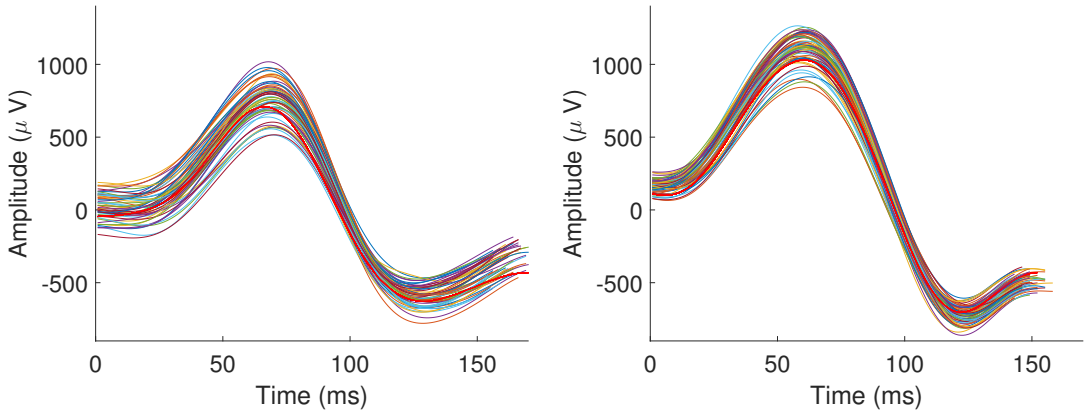


Figure 2: Example of superimposed and time-aligned P waves of a patient (a) before, and (b) after catheter ablation.

4.1. Logistic regression

We are interested in the relationship between the AF recurrence and the proposed predictors. The response is binary (AF recurrence yes or not). A generalized linear model will be used, in particular, a logistic regression model with 26 predictors (13 features before and 13 features after catheter ablation) and 45 observations (45 patients, 9 of which had AF recurrence).

Three different models have been evaluated corresponding with three different sets of predictors: pre-ablation, post-ablation and all features. The first analysis has used pre-ablation features. It has been applied a **forward** variable selection. The model with the remaining variables will be called `model1`. The second analysis has used the post-ablation features: the corresponding selected model is `model2`. Finally, `model3` has started from all features pre- and post- ablation i.e. all predictors are used. A detailed description of the models and the code used can be found in the file `SupplementaryMaterial.pdf` in the Supplementary Material. The same analysis is reproduced for each set of predictors.

For each initial set of variables a logistic regression model has been fitted. Then, a forward variable selection has been applied starting with the null model, i.e. the model just with the intercept and no other predictor. Tables 3, 4 and 5 display a summary for the final `models` 1, 2 and 3, respectively. Each table displays the coefficients estimated (column named "Coef"), the p-value for testing a null coefficient ("p"), the confidence intervals for the coefficients ("LCI" and "UCI"), and the estimated natural logarithm of the coefficients (i.e. the log odds-ratio) named "exp(coef)" with the corresponding confidence interval for this log-coefficient.

It seems important for each set of predictors to compare the model with the selected variables and the null model with just the intercept. It is a global evaluation. Tests to evaluate the difference of deviances assuming an approximate chi-square distribution have been performed. We have three p-values corresponding to the three models. The observed p-values are 0.032 (`model1`), 0.154 (`model2`) and 0.023 (`model3`). Note that using only the pre-ablation features results are better (more different models) that using only post-ablation features. We have a significant difference between the null model (only

intercept) and `model1`, and `model3`.

The fitted models 1, 2 and 3 are illustrated in Figures 3, 4 and 5 by plotting the estimated probabilities of recurrence for the corresponding predictors, with the confidence interval using a confidence level of 0.95. Analogous figures with the corresponding code can be found in `SupplementaryMaterial.pdf`.

Cross validation has been applied using the leaving-one-out method. The observed accuracies (proportion of correctly classified observations) have been 0.78, 0.8 and 0.76 for the models 1, 2 and 3, respectively. They have been obtained using the package published in [46]. Note that from this point of view there is no clear difference between the three models.

Table 3: Selected model using pre-ablation features: model 1. From left to right: estimated coefficients (Coef.), p-value of a null coefficient (p), lower and upper extremes of the confidence interval (LCI, UCI), the exponential of the coefficients (exp(coef)), lower and upper extremes of the confidence interval for the exponential of the parameters.

	Coef.	p	LCI	UCI	exp(coef)	LCI	UCI
(Intercept)	4.93	0.39	-5.82	16.99	138.18	0.00	23857985.95
pre-ADI	0.25	0.04	0.02	0.51	1.28	1.02	1.66
pre-$\nabla_{min} X_k$	-0.07	0.08	-0.17	0.00	0.93	0.84	1.00
pre-kurtosis	-5.31	0.14	-13.16	1.14	0.01	0.00	3.12

Table 4: Selected model using post-ablation features: model 2. From left to right: estimated coefficients (Coef.), p-value of a null coefficient (p), lower and upper extremes of the confidence interval (LCI, UCI), the exponential of the coefficients (exp(coef)), lower and upper extremes of the confidence interval for the exponential of the parameters.

	Coef.	p	LCI	UCI	exp(coef)	LCI	UCI
(Intercept)	-0.03	0.98	-2.04	2.18	0.97	0.13	8.82
post-D	-0.03	0.20	-0.09	0.01	0.97	0.91	1.01

Table 5: Selected model using pre- and post- ablation features: model 3. From left to right: estimated coefficients (Coef.), p-value of a null coefficient (p), lower and upper extremes of the confidence interval (LCI, UCI), the exponential of the coefficients (exp(coef)), lower and upper extremes of the confidence interval for the exponential of the parameters.

	Coef.	p	LCI	UCI	exp(coef)	LCI	UCI
(Intercept)	-2.86	0.06	-6.25	-0.10	0.06	0.00	0.90
pre-ADI	0.32	0.03	0.05	0.64	1.37	1.05	1.90
post-$\nabla_{min} X_k$	-0.10	0.03	-0.21	-0.02	0.90	0.81	0.98
post-AD	-0.01	0.15	-0.01	0.00	0.99	0.99	1.00

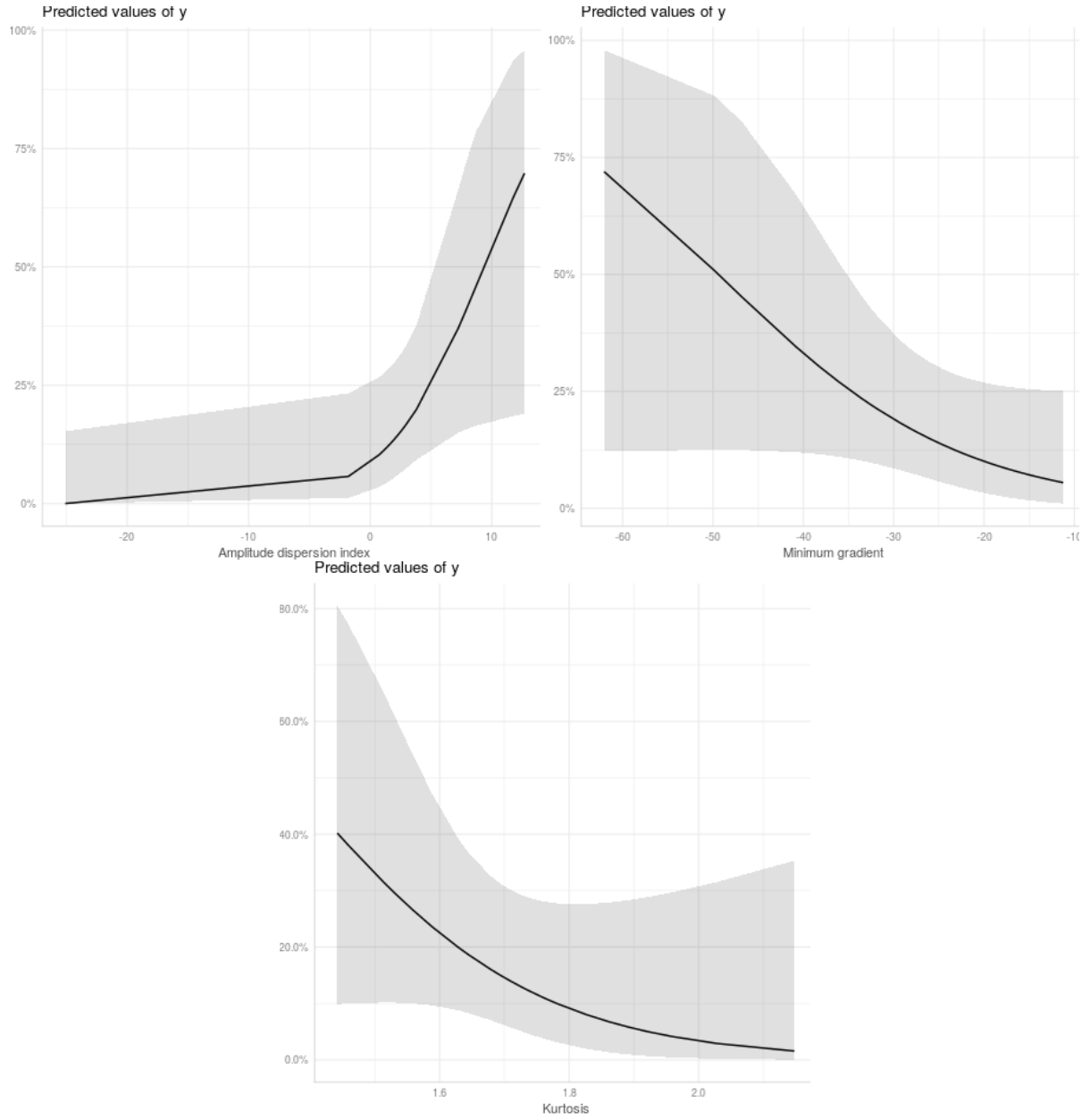


Figure 3: Estimated probabilities for different pre-ADI values (top-left), pre-minimum gradient (top-right) and pre-kurtosis values (bottom). For each plot, the other predictors are set to their observed means.

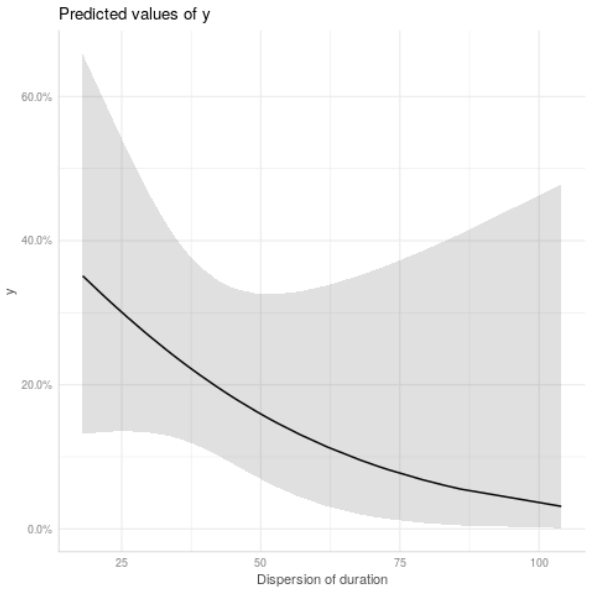


Figure 4: Estimated probabilities for post-dispersion of duration. The other predictors are set to their observed means.

For each plot, one predictor is chosen and the other two predictors are set to its observed mean. No great (deviance, Pearson or standardized) residual has been observed for any model. See Supplementary Material for details.

Figure 6 displays the ROC curves in order to evaluate the global performance of the classification method using the estimated recurrence probabilities. It is clear that the best performance is obtained for the `model3` using previous and posterior procedure information. The second best model is the `model1` using only previous information and finally the worst model is the `model2` that uses only posterior information.

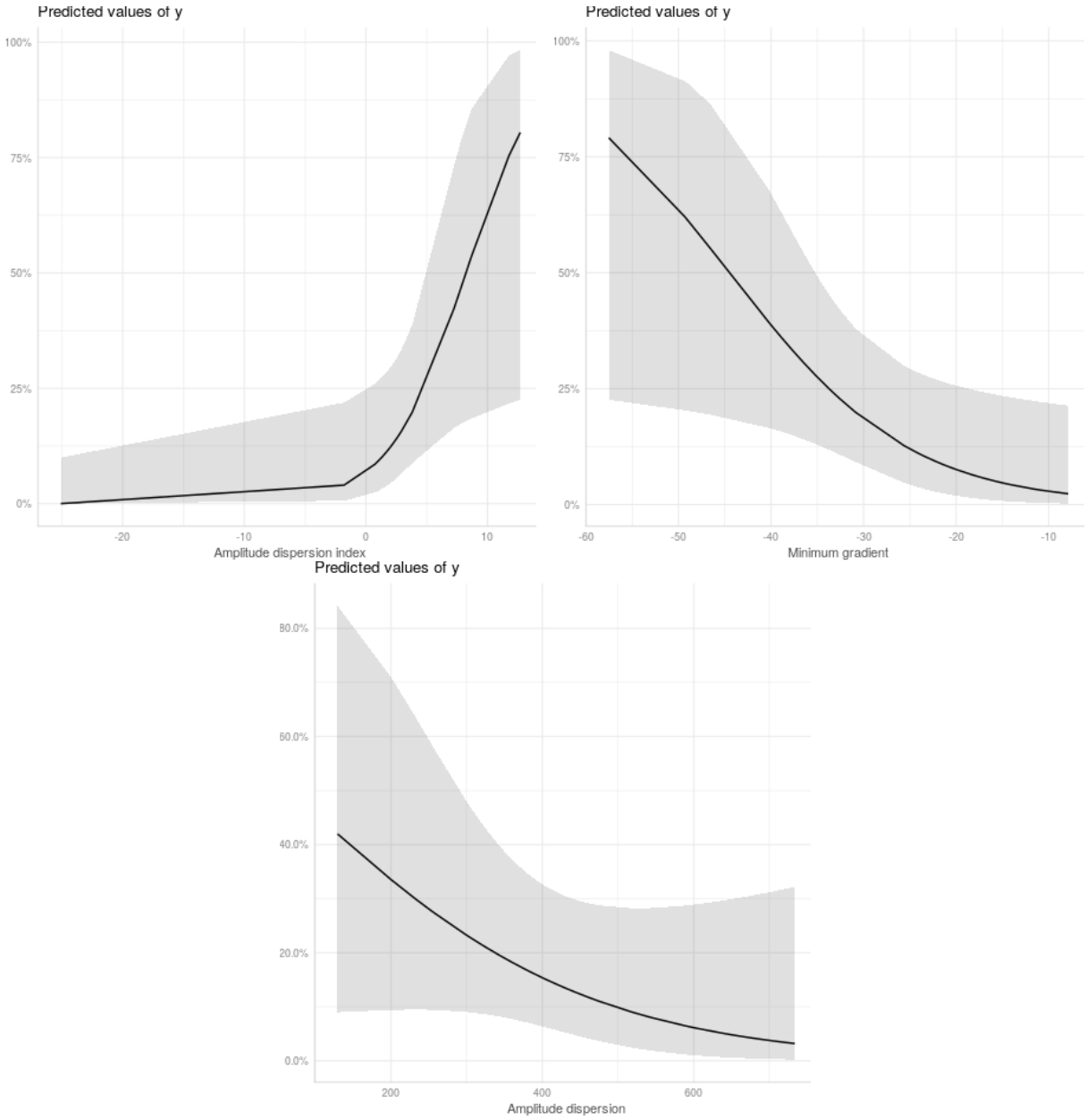
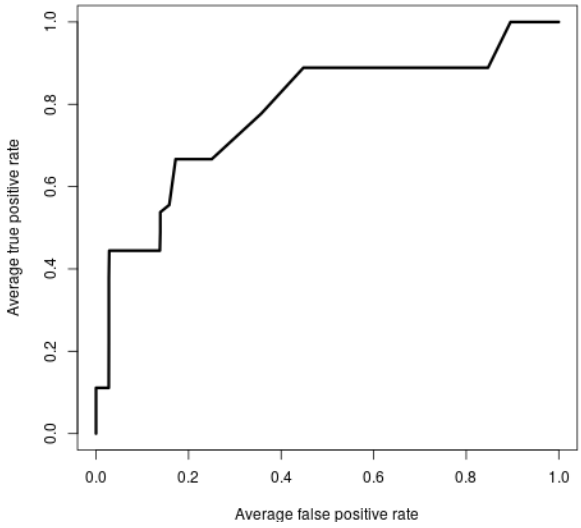
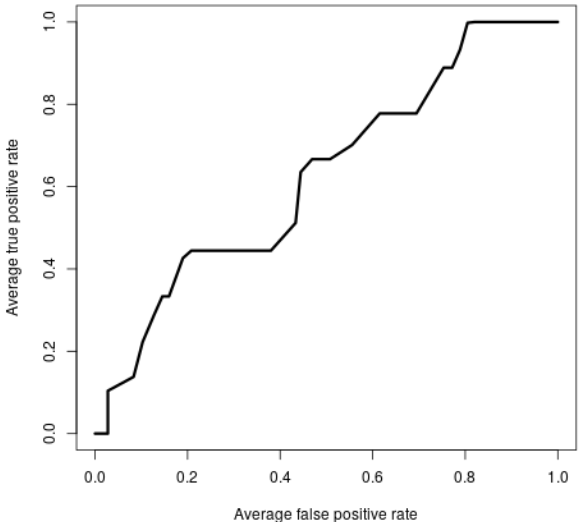


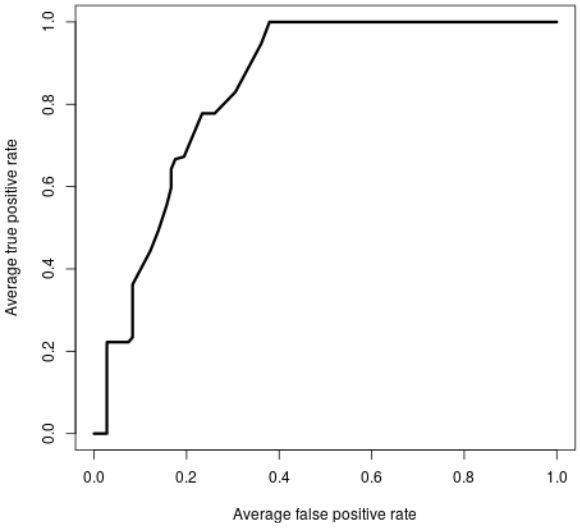
Figure 5: Estimated probabilities for different pre-ADI values (top-left), post-minimum gradient (top-right) and post-amplitude dispersion values (bottom). For each plot, the other predictors are set to their observed means.



(a) Model1



(b) Model2



(c) Model3

Figure 6: Receiver Operating Characteristic curves for the three fitted models.

4.2. Discussion

Multiple non-invasive electric markers based on the surface ECG have been analyzed in order to study their correspondence with the pulmonary vein isolation performed during AF catheter ablation.

Recent studies have found that there exists an increment of the variability of P-wave morphology in subjects who are more prone to develop AF [47, 48], as well as controls have less variability over time due to less amount of fragmentation and variability with respect to AF patients [49]. In our results, when assessing extracted features individually, cross correlation index of P-waves has shown to be significantly higher after catheter ablation for the 80% of the patients enrolled in the study. This result is connected to the decrease of P-waves variability after catheter ablation shown by previous studies.

Maximum P-wave amplitudes were also higher for 84% of subjects after catheter ablation, whereas the mean amplitudes behave in the same way for about 70% of patients. This behaviour goes in line with previous references which have shown an increment of P-wave areas after pulmonary vein isolation [50].

On the other hand, in our data set P-wave mean duration did not significantly differ, despite the fact that it was mostly shorter once the pulmonary veins were completely isolated when individually comparing the paired data of each subject. Nevertheless, for a smaller cohort of the patients involved in this study [51], we can observe that P wave duration was significantly shorter after pulmonary vein isolation was completed. This result agrees with previous studies which have found that patients who are likely to develop AF have longer P-waves [21, 26, 28]. Thus, the observed duration shortening goes in line with previous findings in recent references [30, 34], which showed that P-wave duration longer than 140ms could be used as a time feature to predict AF onset or AF recurrences, with sensitivity of 69% and specificity of 53%. Despite the reasons for P-wave changes in the duration are still not fully understood, these authors hypothesized that atrial conduction delays are related with prolongation of P-waves [52]. This would reflect structural abnormalities, such as left atrial enlargement, which implies an structural remodelling involved in the maintenance of the arrhythmia.

In addition, some recent references have also found an increment of the dispersion of P-waves duration when subjects are prone to AF [19, 22, 23]. In our study, if we calculate dispersion differences as the standard deviation of P-waves duration before and after catheter ablation, they vary from 9.19±4.45 ms to 9.16±4.68 ms, respectively. Although not statistically significant, probably due to the small data set under analysis and the mean on the different patients, these results are expected to be maintained after the blanking period. In addition, these results agree on the reduction of dispersion and the associated AF risk once pulmonary veins have been successfully isolated, specially in patients with apparent heart disease or another cardiac comorbidities [53].

Not only P-waves dispersion of duration appeared to be reduced after the procedure, but also the amplitude dispersion, which is reflected in parameters AD and ADI. This decrease presented in our preliminary study [51] is also related with the significant increment of cross-correlation (measured as ρ) between P-waves, which can be explained by less amount of fragmentation and variability associated with the absence of atrial arrhythmias substrate [49].

Kurtosis and cross-correlation parameters also presented statistically significant differences between the pre- and post-ablation states, being more likely to be reduced and incremented after the procedure, respectively.

On the other hand, even without statistically significant values, rms of P-waves showed to be incremented after catheter ablation, which can be associated with the increment in maximum and mean P-wave amplitudes. This result goes in line with the computer simulations performed by Saha et al. in [54], which revealed that, after pulmonary vein isolation, biatrial activation time was prolonged and P-wave area decreased in V6 and increased in V1 (which is the lead under analysis in this study).

Furthermore, it can be observed that the proposed logistic regression `model3` (the one which includes pre- and post- ablation features) obtains the most significant results. We are aware that one limitation of the presented study is that post-ablation recordings included in the analysis are obtained just half an hour after the pulmonary vein isolation completion, so the atrial tissue is with inflammation and not completely healed from the procedure. However, if we respect the blanking period after the intervention, we would lack of information about the real condition of spontaneous reconnection of pulmonary veins, since the only way to be aware whether the pulmonary veins are still isolated is to perform a catheterisation. This invasive procedure would be ethically problematic. Very few studies have performed an invasive procedure to observe whether pulmonary veins are still isolated after some follow-up period [55], which have observed that a quite high percentage of patients had some pulmonary vein reconnected, even not all of them presented AF recurrences yet. In order to overcome this issue, we have proposed to assess three different models in the logistic regression analysis: one which only used pre-ablation features (`model1`, p-value 0.032), a second one for only immediately post-ablation features (`model2`, p-value 0.154), and a third one which combines both pre- and post- features (`model3`, p-value 0.023). The use of these models would allow to early predict those patients for whom the procedure will be successful at long-term.

Finally, global classification performance pointed to `model2` as the one which obtained the best results, followed by `model1` (i.e. the one obtained when the patient is at baseline, prior the procedure, with 78% accuracy) when estimating AF recurrences. Therefore, presented results may open a door for personalized electric markers able to early detect recurrence of AF in patients who have undergone catheter ablation. Nowadays these recurrences are not detected until the patient feels the first symptoms. So, the proposed features would be highly clinically significant, since the use of non-invasive electric markers could allow clinicians to apply beforehand the most suitable antiarrhythmic treatments and early try to stop the arrhythmia progression. The potential clinical value of the presented surface ECG features (individually or grouped) will be further analysed in prospective studies.

5. Conclusions

In this paper we have presented a study whose objective is to analyze which features can be extracted from the surface ECG and reveal significant differences after catheter ablation of pulmonary veins for patients with paroxysmal AF, in order to early detect future recurrences of the arrhythmia by non-invasive techniques.

It has been shown that amplitude dispersion, kurtosis, and cross correlation index of P-waves exhibit significant differences before and after catheter ablation. In addition, the model obtained by means of logistic regression has also revealed that amplitude dispersion index, the minimum gradient and the amplitude dispersion of P-waves can be used as recurrence predictors of atrial fibrillation. We have proposed three different logistic regression models to predict AF recurrences, with best performance when combining information extracted from pre- and post- ablation recordings (80% accuracy). Nevertheless, 78% of accuracy is obtained when selecting only features extracted from ECG recordings prior to the procedure, avoiding this way the influence of tissue inflammation present during the blanking period.

Proposed ECG parameters can be used as non-invasive markers to early detect those patients with paroxysmal AF who are prone to have recurrences of the arrhythmia after the pulmonary vein isolation, and use this information to help clinicians to decide which patients will require additional ablation procedures or treatments to definitely control the arrhythmia.

Thus, the analyzed ECG indices may benefit electrophysiologists, since they could use these non-invasive markers to early detect atrial fibrillation recurrences and subsequent episodes. Future work will focus on thoroughly analyse these parameters on larger cohorts of patients and further prospective studies, including a multi-lead approach.

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Competing interests

None declared.

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