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Additional Information

Non-invasive Electrophysiological Mapping Entropy Predicts Atrial Fibrillation Ablation Efficacy Better than Clinical Characteristics

AS de la Nava^{1,2}, MC Fabregat¹, M Rodrigo², I Hernandez^{1,3}, A Liberos^{1,2}, F Fernández-Avilés¹, MS Guillem², F Atienza¹, AM Climent¹

¹Hospital GU Gregorio Marañón, IiSGM, CIBERCV, Madrid, Spain

²ITACA, Universitat Politècnica de València, Spain

³Department of Signal Theory and Communications, Universidad Rey Juan Carlos, Madrid, Spain

Abstract

Success rate of atrial fibrillation (AF) ablation remains far from satisfactory. In this study, a 6 months AF freedom predictive model based on Fuzzy Entropy of non-invasive body surface potential maps is compared with clinical predictors.

The study included 29 patients referred for pulmonary vein isolated catheter ablation procedure. Non-invasive electrocardiographic mapping with 54 ECG electrodes was recorded for all patients during the ablation procedure. Six months follow up was used to evaluate the efficacy of the ablation procedure.

Predictions based on non-invasive electrocardiographic mappings during adenosine infusion (accuracy: 90%, AUC: 0.93) showed a clear improvement over standard-of-care clinical parameter models (accuracy: 62.1%, AUC: 0.54).

Our results indicate that measurements of electrophysiological complexity of AF signals could improve the clinical practice by predicting the efficacy of AF ablation procedures.

1. Introduction

Atrial Fibrillation (AF) is the most common arrhythmia with an index of occurrence of 2% worldwide [1]. Among the different alternatives to treat AF, ablation procedure is used to recover normal rhythm. However, this procedure is expensive and is not always effective.

Different studies have tried to predict the efficacy of ablation therapies by means of different clinical or electrophysiological characteristics ([2], [3]).

This study evaluated the potential usefulness of Fuzzy Entropy of Non-invasive Electrophysiological mapping to identify AF patients in which ablation treatment was not effective. The accuracy of this novel methodology is compared with standard of care clinical characteristics.

2. Data Set Description

A total of 29 patients were included in the study, 55.14% (N=16) were diagnosed with paroxysmal AF and 44.82% (N=13) with persistent AF. All were referred for pulmonary vein isolation ablation procedure.

During the ablation procedure a Body Surface Potential Mapping (BSPM) consisting of 54 electrodes homogeneously distributed over the torso. AF was induced in those patients that arrive to the procedure in sinus rhythm. For all patients, BSPM signals were recorded under AF after the administration of adenosine (12-18mg) before ablation to block atrioventricular during few seconds and avoid the need of QRST cancellation on BSPM signals. A total of 80 records of at least 4 seconds were obtained. In those signals with no adenosine, QRST complexes were cancelled in order to only account for atrial activity.

After the procedure, follow up of each patient were registered 6 months after ablation. Patients are labeled as AF freedom or AF presence according to that 6 months follow-up. Clinical biomarkers were collected before ablation and 6 months after ablation and are summarized on Table 1.

All subjects gave written informed consent to participate in the study, and the institutional review committees approved the study protocols.

3. Methods

The ability of 4 matching learning models to predict which patients would be in sinus rhythm and which would remain in AF six months after ablation was tested.

The 4 predictive models were (1) differences in clinical characteristics, (2) classical paroxysmal vs. persistent classification, (3) a predictive model based on Fuzzy Entropy of Non-invasive Electrocardiographic mapping

	All patients	6 months outcome		p-value
		AF Freedom	AF	
Anthropometrics	29 patients	18 patients	11 patients	
Age, yrs	61 ± 14	56 ± 15	69 ± 7	0.001
Female	22 (75%)	11 (61.1%)	11 (100%)	0.002
Height (cm)	161.61 ± 8.52	163.76 ± 9.71	158.27 ± 5.00	0.02
Weight (kg)	69.83 ± 12.44	73.19 ± 13.65	64.38 ± 10.86	0.01
HR (bpm)	78 ± 21	77.33 ± 20.52	80 ± 23	0.39
Blood samples				
Potassium	4.02 ± 0.33	4.05 ± 0.34	3.98 ± 0.34	0.37
Creatinine	0.88 ± 0.21	0.91 ± 0.19	0.83 ± 0.23	0.14
Hemoglobin	13.36 ± 1.70	13.23 ± 1.92	13.57 ± 1.30	0.21
Leucocytes	7.25 ± 2.38	7.40 ± 2.52	6.46 ± 2.79	0.28
Platelets	204 ± 46	200 ± 51	211 ± 38	0.18
INR	1.22 ± 0.52	1.16 ± 0.42	1.33 ± 0.66	0.25
LVEF	56.56 ± 6.36	58.17 ± 5.78	53.2 ± 6.033	0.03
Atria Size (cm ²)	32.66 ± 6.96	32.50 ± 7.35	32.71 ± 6.10	0.32
Previous diagnostics				
Mitral insufficiency	14 (48.3%)	7 (38.9%)	8 (72.7%)	0.05
Tricuspid Insufficiency	13 (44.83%)	8 (44.4%)	7 (63.6%)	0.13
Mitral Stenosis	9 (31,03%)	5 (27.8%)	4 (36.4%)	0.36
Medical Therapy				
Beta-blockers	21 (72.4%)	12 (72.2%)	10 (90.9%)	0.09
Flecainide	8 (27.6%)	5 (27.7%)	2 (18.2%)	0.25
Amiodarone	5 (17.2%)	3 (16.7%)	2 (18.2%)	0.49

Table 1. Clinical characteristics of the patients in the study, including statistical significance (p-value).

during AF recordings under the administration of adenosine.

The three predictive models were compared in terms of accuracy and area under the receiver operating characteristic curve (ROC curve).

3.1. Predictive models based on Non-invasive Electrocardiographic mapping

Fuzzy Entropy expresses the degree of similarity of a variable to a set, therefore, similar measurements with similar characteristics will result in similar Fuzzy Entropy [4].

Fuzzy Entropy was calculated for the 54 electrodes in each of the episode following the methodology described in [2]. Fuzzy entropy parameters were $m=2$, $r=0.25$ times the standard deviation of the time series as suggested by Pincus [5] and n is fixed to 2.

After the calculation of the Fuzzy Entropy for each

electrocardiographic segment, a model of ensembles based on subspace K-nearest neighbor (KNN) Discriminant was built.

In Machine Learning applications, an ensemble is a method that aims to obtain better predictive performances, constructing a more flexible structure to exist as a solution for the classification problem [6]. In this specific experiment, the number of ensembles was fixed to 30.

A Subspace KNN Discriminant is a model that prevents the algorithm from overfitting by diminishing the number of features included in the algorithm, thus increasing stability of the method [7]. Specifically, the algorithm reduces the number of features not to be greater than the number of samples that the data set has.

Once the predictive model of ensembles was built, the accuracy and Area Under the Curve (AUC) were measured. AF presence and AF freedom 6 months after ablation was used as label. Furthermore, summary maps showing the areas of the torso with higher difference on entropy between AF Freedom patients and AF patients

after six months of ablation were calculated.

3.2. Predictive models based on Standard of Care clinical data

The ability to predict the efficacy of ablation therapy based on standard of care parameters was compared with the predictions of Fuzzy Entropy on Non-invasive Electrocardiographic mapping.

Specifically, two prediction models were constructed. One based on the 19 clinical parameters included in table 1 and obtained from the clinical history of each of the 29 parameters. A second model based only on the standard classification of AF as paroxysmal or persistent was also created. In both cases a Subspace KNN Discriminant analysis was performed using labelling after 6 months for prediction.

4. Results

4.1 Accuracy and ROC comparison

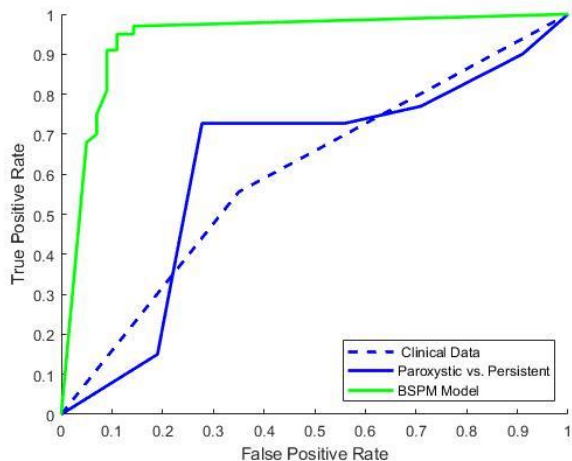


Figure 1. ROC curves of the four evaluation methods

After six months of the procedure, 18 patients (62%) were labelled as AF freedom and 11 patients (38%) were label with permanence of AF.

Figure 1 shows the ROC curve for the three ablation therapy prediction models. Accuracy and Area Under the Curve (AUC) for the three different models proposed for clinical outcome is presented in Table 2.

Despite the fact that six clinical parameters presented statistically significant differences between both groups (i.e. Table 1: age, gender, height, weight, LVEF and previous mitral insufficiency. $p < 0.05$), the model including only the clinical data presented the lowest accuracy (62.1%) and AUC (0.54) out of the three models.

Classification based on Paroxysmal vs. Persistent clinical classification improved clinical data results by

increasing both accuracy (72.4%) and AUC (0.60).

Predictions based on non-invasive electrocardiographic mappings with adenosine showed a clear improvement over standard-of-care clinical parameter models. This model obtained the best performance best with accuracy of 90% and AUC of 0.93.

Model	Accuracy	AUC
Clinical Data	62.1%	0.54
Paroxysmal vs. Persistent	72.4%	0.60
AF BSPM signals during adenosine	90%	0.93

Table 2. Accuracy and Area Under the Curve (AUC) of the four evaluation methods proposed

4.2 Spatial characteristics of BSPM Fuzzy Entropy

Spatial variability of Fuzzy Entropy over the torso of patients was analyzed after the administration of adenosine.

Interestingly, the Fuzzy Entropy was higher in those patients in which the ablation was not efficient suggesting that higher levels of complexity are associated with worse outcomes.

Figure 2 shows the difference between the mean Fuzzy Entropy of BSPM during adenosine administration maps from the patients that remain in AF and the patients free from AF. Notice that the inferior area between the left-anterior and posterior of the torso showed the ECG electrodes with more variations between groups.

5. Discussion

This study shows that Fuzzy Entropy of non-invasive electrocardiographic signals can predict the success of AF ablation therapies better than standard-of-care clinical characteristics.

Our results indicate that high level of variability of atrial signals (i.e. high entropy), specially on left posterior bottom BSPM electrodes, is associated with lowest efficacy of pulmonary vein isolation. Those areas of the torso have been associated with activity from the left-atrium [8] and are not recorded in standard 12 leads ECG.

Interestingly, BSPM signals during adenosine segments resulted as good predictors of AF ablation efficacy, suggesting that the activation of inward rectifier potassium channels can emphasize the differences between AF ablation responders and not responders. The mechanisms for this phenomenon could be related with the acceleration

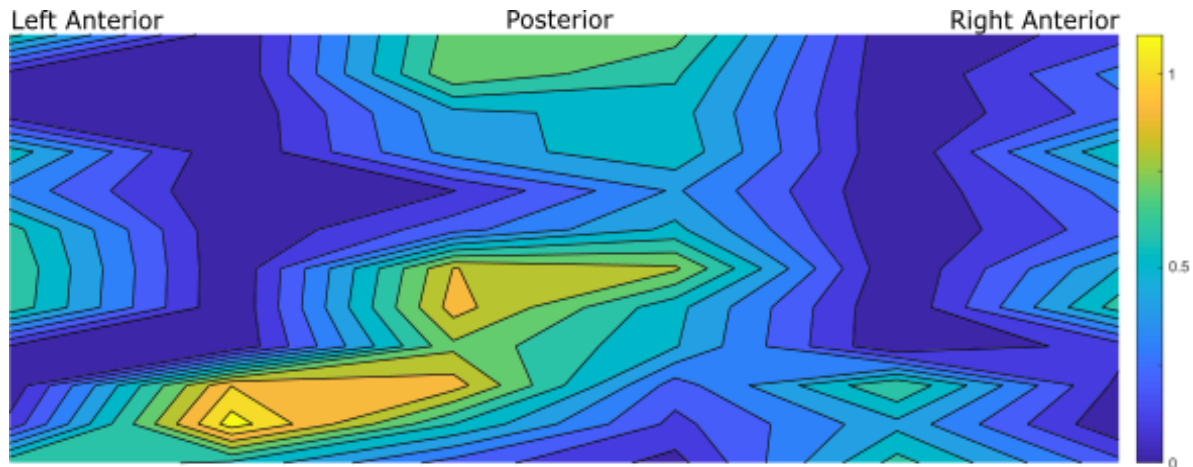


Figure 2. Torso surface with superimposed summary map showing the areas with higher difference on entropy between AF Freedom patients and AF patients after six months of ablation

of AF drivers of adenosine [9].

Further studies including more patients and longer term follow up of the patients should be developed in order to obtain a combination of electrophysiological and clinical parameters that optimize diagnosis and personalized treatment of the patients.

6. Conclusions

Complexity of non-invasive electrocardiographic maps signals appears as a potential tool to predict the efficacy of AF ablation therapies. Combined with clinical data, the use of this information can help diagnose and adjustment of the treatments for personalized medicine.

Acknowledgments

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References

- [1] S. S. Chugh *et al.*, “Worldwide Epidemiology of Atrial Fibrillation,” *Circulation*, vol. 129, no. 8, pp. 837–847, 2013.
- [2] T. Lankveld *et al.*, “Atrial Fibrillation Complexity Parameters Derived From Surface ECGs Predict Procedural Outcome and Long-Term Follow-Up of Stepwise Catheter Ablation for Atrial Fibrillation,” *Circ. Arrhythmia Electrophysiol.*, vol. 9, no. 2, p. e003354, Feb. 2016.
- [3] R. Alcaraz, F. Hornero, and J. J. Rieta, “Electrocardiographic Spectral Features for Long-Term Outcome Prognosis of Atrial Fibrillation Catheter Ablation,” *Ann. Biomed. Eng.*, vol. 44, no. 11, pp. 3307–3318, Nov. 2016.
- [4] L. . Zadeh, “Fuzzy Set Theory,” in *Information and Control*, vol. 8, 1965, pp. 338–353.
- [5] S. M. PINCUS, “Assessing Serial Irregularity and Its Implications for Health,” *Ann. N. Y. Acad. Sci.*, vol. 954, no. 1, pp. 245–267, Jan. 2006.
- [6] D. Opitz and R. Maclin, “Popular Ensemble Methods: An Empirical Study,” *J. Artif. Intell. Res.*, vol. 11, pp. 169–198, Aug. 1999.
- [7] S. Li, E. J. Harner, and D. A. Adjeroh, “Random KNN feature selection - a fast and stable alternative to Random Forests,” *BMC Bioinformatics*, vol. 12, no. 1, 2011.
- [8] O. B. M.S. Guillem, A.M. Climent, J.Millet, A.Arenal, F.F.Avilés, J.Jalife ,F. Atienza, “Noninvasive Localization of Maximal Frequency Sites of Atrial Fibrillation by Body Surface Potential Mapping,” *Changes*, vol. 29, no. 6, pp. 997–1003, 2013.
- [9] F. Atienza *et al.*, “Activation of inward rectifier potassium channels accelerates atrial fibrillation in humans: Evidence for a reentrant mechanism,” *Circulation*, vol. 114, no. 23, pp. 2434–2442, 2006.

Address for correspondence:
 Andreu M Climent
 Instituto de Investigación Sanitaria Gregorio Marañón,
 CIBERCV
 c\ O'Donnell 48,
 28009, Madrid, Spain
 acliment@cibercv.es