Noninvasive Predictors of Atrial Fibrillation Early Recurrence After Electrical Cardioversion and their Link to Atrial Remodeling

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Abstract. Several clinical factors have been studied to predict atrial fibrillation (AF) recurrence after electrical cardioversion (ECV) with limited predictive value. In this work, several time-frequency parameters from the fibrillatory (*f*) waves characterization were studied to improve ECV outcome prediction at mid follow-up. By analyzing ECV outcome one month after the procedure of 63 persistent AF patients, *f* waves power (fWP) presented the highest predictive accuracy of 82.5%, whereas *f* waves organization, computed by sample entropy (SampEn), provided a 79.4%. Other analyzed features revealed accuracies lower than 70%. A stepwise discriminant analysis provided a model based on fWP and SampEn with 90.5% of accuracy. Moreover, a thorough analysis of the results allowed the outline of possible associations between these two features and the concomitant status of atrial remodeling. As a consequence, the information provided by advanced signal processing methodologies could be more effective in the prediction of long-standing AF early recurrences than previously analyzed clinical parameters.

Keywords: Long-standing atrial fibrillation, atrial remodeling, cardioversion, fibrillatory wave power, sample entropy

1. Introduction

Atrial fibrillation (AF) is the most common sustained supraventricular arrhythmia, especially in older people, and it is an important cause of morbidity and hospitalizations [Rich, 2009]. An important goal of clinicians is to restore normal sinus rhythm (NSR), using drugs or electrical cardioversion (ECV), in order to avoid remodeling of the atria, to preserve cardiac performance, and to prevent the potential risk of chronic anticoagulation therapy [Fuster et al., 2006].

ECV is more successful than chemical-induced cardioversion, especially if the arrhythmia has been present for more than 24 hours [Gall and Murgatroyd, 2007]. However, although the ECV success rate is high [Raitt et al., 2006], AF recurrence is common, especially during the first 2 weeks following the procedure [Tieleman et al., 1998], even when the patients are under pharmacological anti-arrhythmic therapy [Lundström and Rydén, 1988]. Thus, approximately 40-60% of cardioverted patients revert back to AF within three months following ECV and around 60-80% within one year [Lundström and Rydén, 1988]. Several clinical factors have been identified to predict the risk of AF recurrence including prolonged duration of AF, increased left atrial size, underlying heart disease [Alt et al., 1997], increased heart rate variability [Vikman et al., 2003], etc. However, the predictive value of these factors is limited and they are only used to advise against the procedure in patients with a high risk of AF recurrence [Alt et al., 1997].

Within this context, the definition of new parameters able to provide an improved selection of patients and avoid ineffective ECV procedures is of great clinical interest. To this respect, although ineffective ECVs present very low mortality rates, they imply several medical risks, disturbance for the patient and extra clinical costs [Gall and Murgatroyd, 2007]. Therefore, the knowledge of factors able to predict early recurrence of AF after ECV may allow tailoring of therapy for some AF patients.

The goal of the present work is to define a robust method able to predict early AF recurrences based on analyzing the atrial activity (AA) signal, which is extracted from surface electrocardiographic (ECG) recordings. The AA will be characterized through the use of parameters related to the time course of the *f* waves morphology and to the AA spectral features, as will be described next.

2. Material and Methods

2.1. Study population

Sixty-three patients with persistent AF lasting more than 30 days, undergoing ECV were followed during four weeks. After ECV, 22 patients (34.93%) maintained NSR during the first month. In 31 patients (49.20%), NSR duration was below one month and the remaining 10 (15.87%), relapsed to AF immediately after ECV. These 41 patients constituted the group of AF recurrence. All the patients were under drug treatment with amiodarone.

2.2. Data preprocessing and time-frequency *f* waves characterization

A standard 12-lead ECG was acquired for each patient during the whole procedure with a sampling rate of 1024 Hz and 16-bit resolution. This recording was first pre-processed to remove the baseline wander, high frequency noise and powerline interference. A 30-second length ECG segment preceding the procedure from lead V1 was analyzed for each patient. This signal was normalized to its maximum R peak amplitude in order to get comparable values when relative variations of the proposed parameters were pursued. Finally, to facilitate the time-frequency characterization of the fibrillatory (*f*) waves morphology, AA was obtained from the chosen V1 segments. To this respect, a ventricular activity cancellation method was used [Alcaraz and Rieta, 2008].

After extracting the AA signal, the *f* waves power (fWP) was estimated. This power represents the energy carried by the *f* waves within the time interval under analysis and, thus, it can be considered as a robust indicator of the signal amplitude [Alcaraz and Rieta, 2009]. On the other hand, AA organization was estimated by means of a nonlinear regularity index, such as sample entropy (SampEn) [Richman and Moorman, 2000]. This tool quantifies the predictability of fluctuations in the values of a time-series and assigns a non-negative number to the sequence, with larger values corresponding to more irregularity in the data (Richman & Moorman 2000). The mathematical definition of SampEn together with a specific method to evaluate AA organization through this index have been described in detail in previous works [Alcaraz and Rieta, 2010].

As the atrial component is typically an oscillation with a main frequency in the 3–9 Hz range [Holm et al., 1998], spectral analysis applied to the AA signal is an appropriate approach to its characterization. The AA power spectral density (PSD) was obtained using the Welch Periodogram. A Hamming window of 4096 points in length, a 50% overlapping between adjacent windowed sections and a 8192-points Fast Fourier Transform were used as computational parameters. The frequency with the highest amplitude was selected as the dominant atrial frequency (DAF), whose inverse is directly related to atrial refractoriness [Capucci et al., 1995] and, hence, to atrial cycle length [Holm et al., 1998]. Finally, the frequency corresponding to the first harmonic of the DAF was obtained and the PSD value in these frequencies were also considered in the study, as suggested in previous works [Alcaraz and Rieta, 2009].

2.3. Statistical analysis

Student's *t*-test was used to determine whether there was any significant difference between the groups. A two-tailed value of $p<0.05$ was considered statistically significant. The value of each parameter that provided maximum discrimination between patients who relapsed to AF and resulted in NSR, that is, the optimum threshold, was obtained by means of the receiver operating characteristic (ROC) curves. The ROC is a graphical representation of the trade-offs between sensitivity and specificity. Sensitivity was the proportion of ECVs relapsing to AF correctly identified, whereas specificity represented the percentage of ECVs resulting in NSR precisely classified. Other related parameter is accuracy, which quantifies the total number of ECVs properly predicted.

A stepwise discriminant analysis (SDA) with a leave-one-out cross-validation scheme was performed to investigate group classification. Variable selection was performed by a forward stepwise approach including, at each step, the feature which led to maximization of the Lawley-Hotelling trace (Rao's V), as used by previous works [Alcaraz and Rieta, 2009].

3. Results

All the analyzed features were significant predictors of the NSR maintenance after ECV, as Table 1 shows. Nonetheless, fWP presented the highest predictive ability, classifying properly 82.5% of the analyzed patients with optimal thresholds of 0.053 squared normalized units (n.u.). SampEn also

provided a considerably high diagnostic accuracy of 79.4% with an optimal threshold of 0.078, although it misclassifies a considerable number of patients who maintain NSR after ECV. In contrast, the remaining features, including clinical factors, provided a more limited discriminatory power with accuracy values lower than 70%.

Table 1. *Mean and standard deviation of the single parameters computed for each group of patients, statistical significance (p), sensitivity (Se), specificity (Sp) and accuracy (Ac) of the classification approach. Results for the model discriminant based on fWA and SampEn are also presented.*

Parameters	AF Recurrence	NSR Maintenance	p	Se (%)	Sp (%)	Ac (%)
fWP (n.u.)	0.036 ± 0.019	0.081 ± 0.029	<0.001	781	909	825
SampEn	0.107 ± 0.022	0.086 ± 0.033	<0.001	902	591	794
DAF (Hz)	6.0 ± 1.0	5.3 ± 0.8	<0.001	610	727	651
PSD value for DAF (n.u.)	0.280 ± 0.187	0.411 ± 0.312	<0.01	634	636	635
First harmonic frequency (Hz)	12.0 ± 2.0	10.5 ± 1.5	<0.001	659	636	651
PSD value for the first harmonic (n.u.)	0.028 ± 0.013	0.041 ± 0.035	<0.01	731	455	635
SDA: fWA and SampEn	—	—	<0.001	927	864	905

For the discriminant analysis, a model of two variables provided the highest discrimination power associated to the entire 7-parameter set. The first variable to enter the discriminant model was fWP, which is coherent, since it provided the best single classification. Next, SampEn was added to the model because it provided a discriminatory ability greater than the remaining parameters when used in conjunction with fWP. In addition, this feature was highly correlated with the DAF (Pearson correlation of 0.81). Finally, in the last step, the remaining parameters were left out of the analysis because no additional information was provided. It is noteworthy that this discriminant model based on fWP and SampEn outperformed the discriminatory ability of each single parameter. In this sense, 90.5% of the analyzed patients were correctly classified, being 93.7% of cross-validated grouped cases properly discerned. This fact implies an increase of 7.9% of diagnostic ability with respect to the result achieved by using only fWP. In addition, as can be appreciated from Fig. 1, this combination of fWP and SampEn was able to classify, with an accuracy of 90%, the patients who immediately relapsed to AF after ECV.

4. Discussion and conclusions

Nowadays, mechanisms leading to the termination and maintenance of AF after ECV are not completely understood. Nonetheless, electrophysiological and structural atrial remodeling during the arrhythmia have shown to influence the procedure outcome [Anter et al., 2009]. Hence, given that *f* waves are modified by both electrophysiological and structural remodeling [Xi et al., 2004], in the present work, time–frequency AA characterization has been analyzed to improve the prediction of ECV outcome at mid follow-up. In this line, the *f* waves amplitude has proved to be the most significant single predictor among all the analyzed time-frequency features, with an accuracy higher than 82%. The parameter can be combined with SampEn to build up a discriminant model able to predict ECV outcome with an accuracy beyond 90%. As a consequence, the information provided by advanced signal processing methodologies has proved to be more effective in the prediction of long-standing AF early recurrences than previously analyzed clinical parameters [Alt et al., 2003].
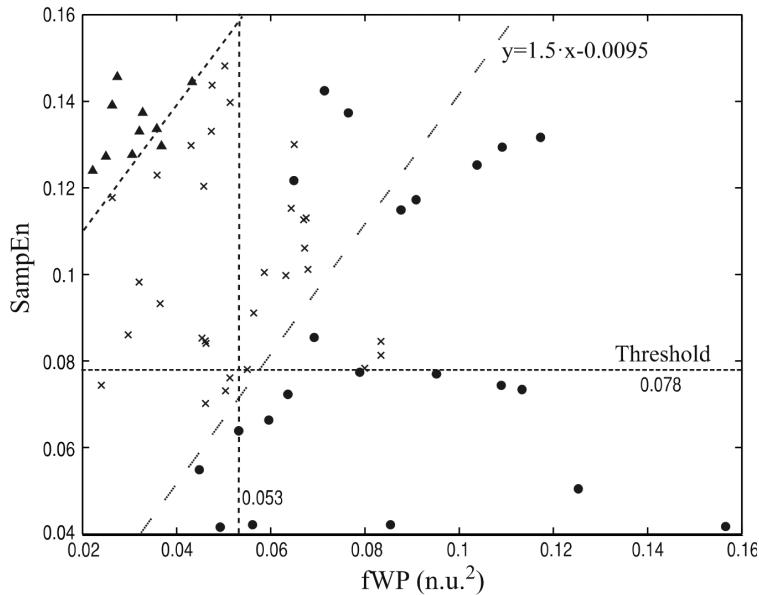
Figure 1. *Classification into ECVs relapsing to AF and resulting in NSR (•) with the discriminant model based on fWP and SampEn. Remark that patients who relapsed to AF immediately (▲) and during the first month (×) after ECV were separately displayed.*

On the other hand, an interesting association of fWP and SampEn to atrial remodeling could be evidenced from the results. To this respect, given that structural remodeling is a progressive but slow process [Morillo et al., 1995], which provokes decreasing amplitude in the *f* waves [Nault et al., 2009], the fWP could be a concomitant indicator of structural remodeling regardless of the number of active reentries; hence, the low values of fWP could indicate advanced structural remodeling. In this respect, it has been proved that the root mean square amplitude of atrial electrograms in paroxysmal AF may be an alternative metric for voltage mapping to characterize the myocardial atrial substrate [Chang et al., 2010]. On the other hand, SampEn can be considered as an AF organization estimator [Alcaraz and Rieta, 2010], thus outlining the number of simultaneous reentries wandering the atria and, as a consequence, giving an idea about electrical remodeling independently of the *f* waves amplitude. Hence, the high values of SampEn could indicate a notable degree of electrical remodeling.

The fact that fWP and SampEn are able to classify very precisely the patients who immediately relapse to AF, could suggest a notable degree of electrical and structural remodeling. On the contrary, the patients who maintain NSR after ECV, misclassified by SampEn, show high entropy values, indicating a high AA disorganization and a remarkable electrical remodeling, but all of them present a relative high fWP, associated with low structural remodeling, which is coherent with NSR maintenance after ECV in patients with a low evolved but disorganized AF [Gall and Murgatroyd, 2007]. Moreover, several studies have demonstrated a substantial interindividual variability in the fibrillatory rate and exponential decay, which is not only present in long-lasting permanent AF, but is also already present in the first detected AF episode and, therefore, less dependent on the evolution time of the arrhythmia [Xi et al., 2006]. In fact, electrical remodeling starts very quickly after the arrhythmia onset with a time course from days [Wijffels et al., 1997]. This fact has been also recently assessed in paroxysmal AF, showing that AF disorganization presents a gradual increase along the first 3 minutes from the onset before reaching a plateau. In the same manner, it decreases from the plateau within the last minute prior to the arrhythmia termination [Alcaraz and Rieta, 2010]. The same concept is indirectly reflected in the work presented by Holmqvist et al., in which the mean atrial fibrillatory rate provided high sensitivity and specificity values in patients with AF duration lower than 30 days. This corresponds well to the timeframe in which electrical remodeling is likely to have the largest impact on relapse probability [Holmqvist et al., 2006].

Acknowledgements

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