Multidimensional Characterization of the Atrial Activity to Predict Electrical Cardioversion Outcome of Persistent Atrial Fibrillation

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Abstract

European Society of Cardiology guidelines recommend electrical cardioversion (ECV) as a rhythm control strategy in persistent atrial fibrillation (AF). Although ECV initially restores sinus rhythm (SR) in almost every patient, mid- and long-term AF recurrence rates are high, so that additional research is needed to anticipate ECV outcome and rationalize the management of AF patients. Although indices characterizing fibrillatory (f-) waves from surface lead V1, such as dominant frequency (DF), amplitude (FWA), and entropy, have reported good results, they discard the spatial information from the remaining leads. Hence, this work explores whether a multidimensional characterization approach of these parameters can improve ECV outcome prediction. The obtained results have shown that multidimensional FWA reported more balanced values of sensitivity and specificity, although the discriminant ability was similar in both cases. For DF, a similar outcome was also obtained. In contrast, multivariate entropy overcome discriminant ability of its univariate version by 5%, rightly anticipating result in more than 80% of ECV cases. Therefore, multidimensional entropy analysis seems to be able to quantify novel dynamics in the f-waves, which lead to a better ECV outcome prediction.

1. Introduction

Atrial fibrillation (AF) is today one of the most relevant causes of cardiovascular mortality and morbidity in the world [1]. Moreover, this arrhythmia is also associated with high rates of hospitalization, as well as to deteriorated quality of life [2, 3]. With the aim of reducing symptomatology and preserve cardiac function in patients suffering from persistent AF, the European Society of Cardiology guidelines recommend to pursue rhythm control strategies for sinus rhythm (SR) restoration [2]. Among the different rhythm control strategies, common pharmacological cardioversion is able to restore SR in about 50% of the patients [2]. However, electrical cardioversion (ECV) is a more effective and quicker technique for SR restoration, presenting a 90% of initial effectiveness and a reduced hospitalization rate [2, 3]. Unfortunately, despite of its high initial success, AF recurrence rates in the mid- and long-term remain high. Thus, nearly 30% of the patients relapse to AF one month after ECV, around 60% within the six first months, and about 80% before the first year [4]. Consequently, anticipation of patients with high risk of early AF recurrence is a relevant clinical challenge, which could be helpful in rationalizing clinical therapeutic strategy for every patient [5]. This way, ECV could be avoided in patients with low chance of SR maintenance, then saving healthcare costs and preventing associated risks, such as post-shock bradycardia or arterial thromboembolism [6].

In the last years several predictors of ECV have been proposed, most of them being based on characterizing fibrillatory (f-) waves reflected on the ECG signal. Some of the metrics that have reported promising results are amplitude of the f-waves (FWA), their dominant frequency (DF), and their regularity, estimated via sample entropy (SampEn) [7, 8]. However, they have been mostly computed over lead V1, as it presents the largest f-waves compared to the ventricular activity [9], and therefore spatial information about cardiac dynamics found in the remaining leads are discarded. Thus, the present work explores if a multidimensional extension of the parameters FWA, DF and SampEn can improve prediction of ECV result.

2. Methods

2.1. Study population

Fifty-eight patients diagnosed with persistent AF, under antiarrhythmic drug treatment, and indicated for ECV

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Table 1. Clinical characteristics of the patients enrolled in the study. Information is separately presented for the patients who maintained SR and relapsed to AF.

Parameters	SR maintenance	AF relapse
Patients	27	31
Men / Women	15 / 12	18 / 12
Underlying heart disease	9	10
Left atrial diameter (mm)	47.32± 4.76	44.72 ± 7.32

were enrolled in the present study. The ECV protocol consisted of the application of a maximum of four synchronized electrical shocks on the patient's thorax with an increasing sequence of 200, 300, 360 and 360 J. One paddle was placed in the second intercostal space on the right side parasternally and the other one was placed in a left-sided lateral position along the midaxillary line. All subjects recovered sinus rhythm (SR) during the procedure, but only 27 of them maintained SR after a follow-up of 4-weeks. More clinical information about these subjects can be found in Table 1.

2.2. Preprocessing of the ECG signal

Before the ECV procedure, a 12-lead ECG was continuously recorded with a sampling rate of 1024 Hz and 16 bit resolution. All recordings had a duration of 90 seconds and were initially preprocessed to remove baseline wander, powerline interference and high frequency noise. Next, the QRS complexes were detected using a previously published algorithm [10], and then clustered according their morphology [11]. Finally, an adaptive QRST cancellation algorithm [12] was recursively used to remove all beats from the same cluster. This approach started with the cluster containing the lowest number of beats and continued progressively up to finish with the dominant one. The QRST segment duration was set to the minimum length between 470 ms (typical value) and 90% of the median RR interval. The resulting signal contained the f-waves and was high passed filtered at 3 Hz for removing all ventricular residua.

2.3. Characterization of the f-waves

As a reference, unidimensional characterization of the f-waves was obtained by computing FWA, DF and SampEn from lead V1. Contrarily, multivariate extension of these indices was achieved by jointly considering the 12 leads of the ECG recordings.

Mathematically speaking, if $f(n)$ is considered as a N sample-length signal containing the f-waves and n=1:N, unidimensional FWA was computed from the difference of its local minima and maxima envelopes, $e_{MIN}(n)$ and $e_{MAX}(n)$ [8], i.e.

$$FWA = \frac{1}{N}\sum_{n=1}^{N}|e_{MAX}(n) - e_{MIN}(n)|. \qquad (1)$$

For computation of multivariate extension of FWA, referred to as MFWA, a first-order rank principal component analysis (PCA) was applied to the 12 leads of the ECG. Then, MFWA was obtained by applying equation (1) to each lead and taking the median value. This way, MFWA is able to summarize information about f-waves in the whole ECG recording on a single index [8].

On the other hand, the univariate DF was estimated from the average (avg-) power spectral density (PSD) of the f-waves as the frequency with the largest amplitude within the 3–12 Hz band [11], i.e.

$$DF = \arg\{\max_{f_k=3-12\text{ Hz}}\{avgPSD(f_k)\}\}. \qquad (2)$$

The avg-PSD was estimated over the 90 second-length signal containing the f-waves on a 2 second-length sliding window protocol with windows of 6 seconds in length. Individual PSD for each window was estimated using a Welch periodogram. Note that only segments whose PSD presented a cross-correlation coefficient higher than 0.7 were considered for computation of the avg-PSD. Also, applying equation (2) to the spectral envelope obtained from the 12 leads, the multivariate extension of DF (MDF) was estimated. Briefly, the spectral envelope summarizes PSD of the f-waves found in the 12 leads through PCA, such as thoroughly described in [13].

Finally, the organization of the f-waves was assessed by computing SampEn over the main component of the f-waves, $ff(n)$. This signal was obtained by filtering the f-waves with a band-pass structure with a 5 Hz bandwidth centered on the DF [7]. SampEn is an entropy-based metric belonging to a family of statistics designed to account for the inherent regularity in a nonlinear time-series [14]. More precisely, it is defined as the logarithmic likelihood ratio that two sequences that match for m points within a distance r will do it for an incremental length of one unit. The index associates higher values to more irregular and less predictable time-series [14], and its mathematical computation follows the next steps [14]:

1. Obtain the epochs $v_m(n)$ of length m as

$$v_m(n) = \{ff(n+i) : 0{\leq}i{\leq}m-1\}. \qquad (3)$$

2. Estimate the probability that two epochs of length m will match within a distance r, $B^m(r)$, following the Chebyshev distance, i.e,

$$B^m(r) = \frac{1}{N-m}\sum_{k=1}^{N-m}B_k^m(r), \qquad (4)$$

where

$$B_k^m(r) = \frac{1}{N-m-1} \sum_{\substack{j=1 \\ j \neq k}}^{N-m} (d_{jk}(m) < r), \qquad (5)$$

and

$$d_{jk}(m) = \max \{|v_m(j) - v_m(k)|\}. \qquad (6)$$

3. Increase the sequence length in one unit, $m + 1$, and repeat the steps (3)–(6). Then, SampEn is defined as

$$\text{SampEn}(ff, m, r, N) = -\ln \frac{B^{m+1}(r)}{B^m(r)}. \qquad (7)$$

The multivariate extension of SampEn (MSampEn) complies with the described approach, but some considerations have to be taken [15]: (i) simultaneous signals must be scaled to the same amplitude range; (ii) the embedding epochs can evolve in as many ways as simultaneous signals; and (iii) the threshold r should be set to the total variation of the covariance matrix for all simultaneous signals. A full description of MSampEn can be found in [15]. As previously recommended [14, 15], values of m = 2, r = 0.2 and N = 30 seconds were here used to compute both SampEn and MSampEn.

2.4. Statistical analysis

Data normality was assessed via a Kolmogorov-Smirnov test, and statistical differences between groups of patients were then determined based on the resulting information. Thus, if data were normally distributed, a Student t-test was considered, otherwise a Wilcoxon rank sum test was preferred. On the other hand, the discriminant ability of all the analyzed univariate and multivariate metrics was evaluated by means of a receiver operating characteristic (ROC) curve [16]. The area under this curve (AROC) was computed as an aggregate measure of performance across all possible classification thresholds. Moreover, values of sensitivity (Se) and specificity (Sp) were also computed for the threshold obtained according to the Youden's criteria.

3. Results

The values of sensitivity, specificity and AROC obtained by the analyzed univariate and multivariate metrics are displayed in Table 2. Despite that FWA and DF obtained similar values of AROC to their multivariate extensions, these later parameters showed more balanced values of sensitivity and specificity. Moreover, the discriminant ability of SampEn was notably overcomed by its multivariate extension, which achieved an AROC of 80.5% with values of sensitivity and specificity about 75%.

On the other hand, Figure 1 presents boxplot distributions for all univariate and multivariate parameters. As can be observed, FWA and MFWA showed completely overlapped values for the patients who maintained SR and relapsed to AF. In fact, no statistically significant differences between both groups of patients were noticed for the two cases. Contrarily, DF and MDF reported higher median values for the patients relapsing to AF, the unidimensional approach exhibiting a wider interquartile range. In a similar line, both SampEn and MSampEn also displayed lower median values for the patients who maintained SR. In this case, a wider interquartile range was also noticed for the univariate measure. Of note is the fact that MSampEn showed notably lower values than SampEn for both groups of patients.

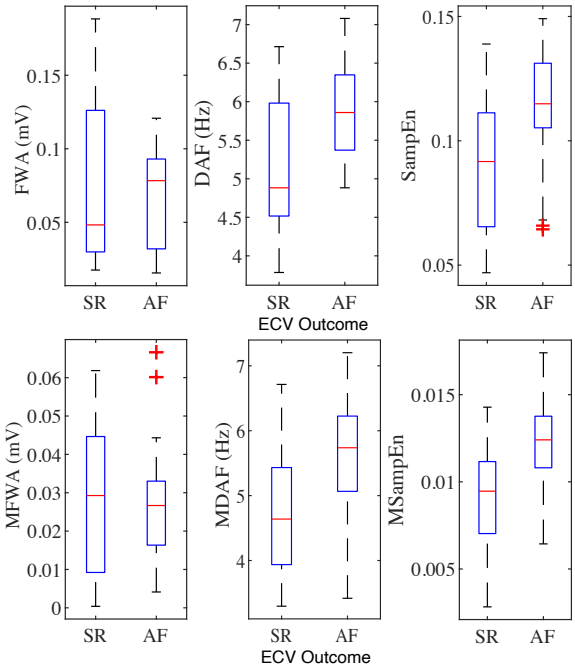

Figure 1. Boxplot distribution for all the analyzed indices.

Table 2. Statistical significance (p) and performance for the proposed indices.

Version	Parameter	p	Se	Sp	AROC
Univariate	FWA	0.607	40.7%	77.4%	54.2%
	DF	0.001	80.6%	59.3%	75.7%
	SampEn	0.001	80.6%	63.0%	74.7%
Multivariate	FWA	0.629	48.4%	66.7%	54.6%
	DF	0.001	71.0%	74.1%	72.1%
	SampEn	0.001	74.2%	81.5%	80.3%

4. Discussion and conclusions

In contrast to previous works, where amplitude of the f-waves has revealed to be a promising predictor of the

outcome of both, ECV [7] and catheter ablation [8, 17], in the present study FWA and MFWA have not reported statistically significant differences between the patients who relapsed to AF and maintained SR during the follow-up. These controversy results could be due to the different approaches used in each study to compute the amplitude of the f-waves. For instance, whereas FWA was manually computed in [17], it was estimated as the root mean square value of the signal containing the f-waves in [7].

On the other hand, according to previous works [7], univariate and multivariate versions of DF provided higher median values for the patients who relapsed to AF than for those who maintained SR. However, it should be noted that MDF presented a notably lower variability than DF, particularly for the patients who maintained SR during all the follow-up. This result could be due to the fact that the spectral envelope used for the computation of MDAF can be considered as a smoothed version of the maxima envelope of the 12 leads individually estimated PSDs [13]. This aspect could also explain that MDF yielded more balanced values of sensitivity and specificity than DF.

Concerning the entropy analysis, it must be noted that MSampEn outperformed SampEn more than 5% in terms of AROC, and also exhibited a better trade-off between values of sensitivity and specificity. Moreover, MSampEn also provided smaller and more balanced interquartile ranges for both groups of patients. The fact that the values of MSampEn were around 10 times lower than those of SampEn is not relevant and could be simply associated with the higher probability of founding similar vectors in MSampEn [15]. Anyway, it could be concluded that, while multivariate extension of FWA and DF have not reported new predictive information, multidimensional entropy analysis has been able to estimate novel AA dynamics, which have resulted to be very useful in improving anticipation of ECV outcome.

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