Refined Multiscale Entropy Predicts Early Failure in Electrical Cardioversion of Atrial Fibrillation

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Abstract

Electrical cardioversion (ECV) is a well-established strategy for atrial fibrillation (AF) management. Despite its high initial effectiveness, a high relapsing rate is also found. Hence, identification of patients at high risk of early AF recurrence is crucial for a rationale therapeutic strategy. For that purpose, a set of indices characterizing fibrillatory (f-) waves have been proposed, but they have not considered nonlinear dynamics present at different time-scales within the cardiovascular system. This work thus explores whether a multiscale entropy (MSE) analysis of the f-waves can improve preoperative predictions of ECV outcome. Thus, two MSE approaches were considered, i.e., traditional MSE and a refined version (RMSE). Both algorithms were applied to the main f-waves component extracted from lead V1 and entropy values were computed for the first 20 time-scales. As a reference, dominant frequency (DF) and f-wave amplitude (FWA) were also computed. A total of 70 patients were analyzed, and all parameters but FWA showed statistically significant differences between those relapsing to AF and maintaining sinus rhythm during a follow-up of 4 weeks. RMSE reported the best results for the scale 19, improving predictive ability up to an 8% with respect to DAF and FWA. Consequently, investigation of nonlinear dynamics at large time-scales can provide useful insights able to improve predictions of ECV failure.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice, affecting 33 million individuals worldwide and presenting increasing incidence, as well as an age-dependent prevalence [1]. Also, this arrhythmia today remains being the major cause of cardiovascular morbidity and mortality [1]. When persistent AF arises, it lasts for more than 7 days and an external intervention is required for its termination [2, 3]. To this end, electrical cardioversion (ECV) is a well-established strategy. Although this procedure is able to initially revert almost every patient to sinus rhythm (SR) [3], its mid- and long-term success rates are notably limited. In fact, nearly 20% of the patients relapse to AF after 4 weeks and around 70% do it within a year [2]. Hence, being able to anticipate patients at high risk of AF recurrence after ECV is crucial for a rationale therapeutic strategy [4].

In this context, some parameters characterizing fibrillatory (f-) waves extracted from the electrocardiogram (ECG), such as the f-waves amplitude (FWA) and dominant frequency (DF) [5], have been proposed as predictors of early ECV failure. The well-known Sample Entropy (SampEn) has also been proposed for the same purpose, because it has been suggested by previous works that the presence of more disorganized atrial activity can be associated with higher probability of AF recurrence [6]. This index has obtained encouraging outcomes, thus reporting a better predictive ability of early ECV failure than FWA and DF [6]. However, SampEn is not able to precisely quantify dynamics generated at different spatiotemporal scales by some complex systems, such as the cardiovascular one [7]. To overcome this issue, multiscale entropy (MSE) was proposed by Costa et. al. [8]. This metric was introduced as a modification of SampEn to quantify the complexity of a time series over several time-scales, and simultaneously to reduce fast-temporal scales that may mask complex dynamics inherent to the system [9]. Hence, this work explores whether a MSE analysis applied to the f-waves can improved preoperative predictions about ECV outcome.

2. Methods

2.1. Study population

Seventy patients diagnosed with persistent AF indicated for ECV were considered. A standard 12-lead ECG was continuously recorded during the entire ECV procedure

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with a sampling rate of 1024 Hz and 16 bit resolution. After a 4 week follow-up, 39 patients relapsed to AF and the remaining 31 maintained SR.

2.2. Preprocessing of the ECG signal

The f-waves encountered in standard lead V1 for an interval of 90 second in length before ECV were extracted by means of an adaptive QRST cancellation algorithm [10]. Lead V1 was chosen due to its proximity to the left atria, as it typically exhibits the largest f-waves amplitude [5]. Briefly, the ECG signal was first preprocessed for removal of baseline wander, powerline interference and high frequency noise [11]. The R-peaks were then detected [12] and the QRS complexes were clustered into morphologies after an R-peak-based alignment. The QRS clustering was performed by a template matching procedure, where a cross correlation coefficient higher than 70% was always ensured. Finally, the QRST cancellation algorithm was applied in a recursive way, starting from the smaller cluster of QRS complexes and following an upward order. The QRST complex duration was set to the minimum value between 470 ms (typical value) and 90% of the median RR interval. The resulting f-waves were high-pass filtered at 3 Hz to remove ventricular residua.

2.3. Characterization of the f-waves

Considering $f(n)$ to be the N sample-length signal containing f-waves and n = 1:N, the index FWA was defined as [6]

$$FWA = \sqrt{\frac{1}{N}\sum_{n=1}^{N}|f(n)|^2}. \tag{1}$$

On the other hand, the DF was estimated as the frequency where the local maxima of the averaged (avg-) power spectral density (PSD) of the f-waves was located, within the 3–12 Hz band, i.e.,

$$DF = \arg\{\max_{f_k=3-12\ Hz}\{\text{avg-PSD}(f_k)\}\}. \tag{2}$$

The avg-PSD was estimated as the mean value of individual PSDs computed with a 2 second-length sliding protocol on signal segments of 6 seconds in length. PSDs were estimated using the Welch periodogram and those with a cross-correlation coefficient below 0.7 were discarded.

To compute the f-waves organization, SampEn was obtained from their main component [6, 13]. This signal, named $ff(n)$, was obtained by applying a band-pass filter to $f(n)$ centered on the DF with a 5 Hz bandwidth. SampEn is defined as the negative natural logarithmic likelihood ratio that two sequences of length m that remain similar within a distance r will remain similar for an incremental length of one unit [7]. From a mathematical point of view, this entropy can be obtained as follows: [7]:

1. Compute the subvectors of length m, $v_m(n)$, as:

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

2. Estimate the Chebyshev distance between every pair of subvectors, i.e.:

$$d_{jk}(m) = \max_{i}\{v_m(j) - v_m(k)\}. \tag{4}$$

3. Compute the number of matches of length m within a distance r, $\phi_k^m(r)$, and the probability of encountering a match, $\phi^m(r)$, according to:

$$\phi_k^m(r) = \frac{1}{N-m-1}\sum_{\substack{j=1\\ j\neq i}}^{N-m}(d_{jk}(m) < r), \text{and} \tag{5}$$

$$\phi^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m}\phi_k^m(r). \tag{6}$$

4. Increment m in one unit and compute $\phi_k^{m+1}(r)$ and $\phi^{m+1}(r)$ through equations (3)–(6).
5. Finally, SampEn is defined as

$$SampEn(x,m,r,N) = -\ln\frac{\phi^{m+1}(r)}{\phi^m(r)}. \tag{7}$$

As a modification of SampEn, MSE was originally proposed to account for the long-range correlations that are likely to be present in complex dynamical systems occurring at different spatiotemporal time-scales [8]. Hence, this index estimates SampEn over a coarse-grained version of $ff(n)$. According to [8], the coarse grained series at time-scale τ can be estimated as:

$$ff^\tau(j) = \frac{1}{\tau}\sum_{i=(j-1)\tau}^{j\tau} ff(i), \quad \text{for} \quad 1\leq j\leq\frac{N}{\tau}. \tag{8}$$

Despite that MSE has been used in a wide variety of ECG-based applications [9], an artificial decrease in the complexity associated to the coarse graining procedure is found. To counteract this limitation, a refined version of MSE (RMSE) was proposed by Valencia et. al. [14]. RMSE implies two modifications regarding MSE, i.e. (i) the coarse grained series, $ff^\tau(n)$, are estimated by low-pass filtering $ff(n)$ with a normalized cut-off frequency of 0.5/τ and subsequently downsampling it by τ, and (ii) the dissimilarity threshold r is set to a percentage of the standard deviation of the coarse-grained series.

In the present work, MSE and RMSE values for the first 20 time-scales were estimated. Moreover, the resulting curves obtained by plotting both indices as a function of the time-scales were also characterized by its area ($\mathcal{A}$) and slopes ($\mathcal{S}$) in short (SS, τ = 1:6) and long (LS, τ = 7:20) scales. Note that the slopes were computed by a linear fitting of the entropy values into a first grade polynomial. Finally, it should also be noted that SampEn, MSE and RMSE were computed using the widely recommended values of $m = 2$ and $r = 0.2$ times the standard deviation of $ff(n)$ or $ff^{\tau}(n)$ [7], as previously described.

2.4. Performance assessment

Normality in distributions obtained for the proposed indices was analyzed using a Kolmogorov-Smirnov hypothesis test. Then, statistical separability between groups of patients was evaluated using a two-sample t-test, if data were normally distributed, and a Wilcoxon rank sum test in other case. On the other hand, a receiver operating characteristic (ROC) curve was used to evaluate the discriminant ability of each index [15]. This plot displays the fraction of true positives out of positives (sensitivity) against the fraction of false positives out of the negatives (1− specificity) at different threshold settings.The optimum threshold was determined according to the Youden's criterion. Moreover, the area under the ROC curve (AROC) was also computed as an aggregate measure of performance for each metric.

3. Results

Fig. 1 shows MSE and RMSE curves as a function of τ. As can be seen, a very similar behavior and values are seen for both indices. Of note is that, for every τ, statistically significant higher median values and narrower interquartile ranges were observed for the patients who relapsed to AF than for those who maintained SR during the follow-up. However, discriminant abilities were found to be notably different among the time-scales, so only the entropy values computed for the time-scale exhibiting the highest AROC are given in Table 1.

As can be observed in this table, among the previously proposed predictors of ECV, only FWA was unable to provide statistical differences between groups of patients. Moreover, SampEn did not outperform the classification performance of DF, but that index provided a better trade-off between sensitivity and specificity. Both, DF and SampEn, obtained higher values for the patients relapsing to AF than for those maintaining SR. Similarly, MSE and RMSE indices also obtained higher values for the patients presenting AF recurrence, but they outperformed classification ability of SampEn at large time-scales, particularly for the time-scale 19.

Finally, it is also interesting to note that all RMSE-based parameters showed a better performance than MSE-based ones. Nonetheless, in both cases $\mathcal{S}$ presented a higher discriminant ability in the SS region, while $\mathcal{A}$ was better discerning between groups of patients in the LS region. Even though these aggregated complexity indices were unable to outperform the classification achieved by single entropy values for $\tau = 19$, they provided more balanced values of sensitivity and specificity. For instance, $\mathcal{S}_{SS}$ reported values around 75%.

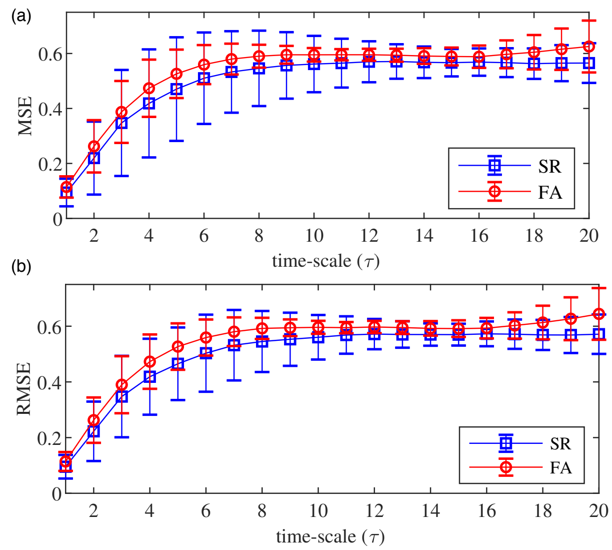

Figure 1. Median and interquartile ranges of (a) MSE (b) RMSE as a function of the time scale (τ) for patients relapsing to AF (red) and maintaining SR (blue).

4. Discussion and conclusions

According to the results obtained in this work, lower values of SampEn and DF for the patients maintaining SR than for those relapsing to AF have also been reported by some previous studies, thus suggesting that the presence of more disorganized f-waves increases the probability of AF recurrence after ECV [6, 13]. Contrarily, while previous findings point to higher values of FWA for the patients maintaining SR [6], an opposite trend was here found. However, it should be noted that the values for both groups of patients were very close and no statistically significant differences were noticed. These contradictory results could be due to the use of different ways to extract f-waves, as well as to compute FWA.

Anyway, the performance of these parameters was notably outperformed by the proposed MSE- or RMSE-based indices. Thus, these metrics achieved improvements in discriminant ability between 3 and 8%. These results agree with the idea introduced by Costa et. al. [8] that complex dynamical systems present long-range spatiotemporal correlations. In fact, the best results were provided by entropy values computed for the largest time-scales. Moreover, although the aggregated indices estimating complexity over

Table 1. Main results for the previously proposed predictors of ECV and the most predictive MSE- and RMSE-based parameters. Median values and interquartile ranges for patients relapsing to AF and maintaining SR, statistical significance (p-value), sensitivity (Se), specificity (Sp) and AROC are provided.

Parameter	**AF relapse**	**SR maintenance**	p**-value**	**Se (%)**	**Sp (%)**	**AROC (%)**
FWA	0.051 (0.039)	0.049 (0.080)	0.356	41.936	84.615	56.493
DF	5.615 (1.160)	4.883 (1.404)	0.003	69.231	61.290	70.678
SampEn	0.114 (0.039)	0.094 (0.050)	0.004	71.795	58.064	70.389
MSE ($\tau = 19$)	0.616 (0.075)	0.565 (0.066)	< 0.001	92.308	61.290	75.517
MSE $\mathcal{A}_{\text{LS}}$	8.291 (0.573)	7.901 (1.111)	< 0.001	79.487	67.742	74.938
MSE $\mathcal{S}_{\text{SS}}$	0.087 (0.005)	0.082 (0.021)	< 0.001	76.923	67.742	73.780
RMSE ($\tau = 19$)	0.627 (0.077)	0.568 (0.065)	< 0.001	94.871	58.064	78.164
RMSE $\mathcal{A}_{\text{LS}}$	8.362 (0.542)	7.922 (0.844)	< 0.001	84.615	64.516	76.427
RMSE $\mathcal{S}_{\text{SS}}$	0.088 (0.005)	0.081 (0.017)	< 0.001	76.923	74.194	75.021

several time scales, i.e., $\mathcal{A}$ and $\mathcal{S}$, were not able to outperform single-scale measures, they still performed better than FWA, DAF, and SampEn. Also, $\mathcal{A}$ provided the best accuracy in the LS area, while $\mathcal{S}$ did it in the SS region, thus suggesting that the real system complexity is better devised in the long-range, when most of the fast temporal variations have been removed [8].

To sum up, multiscale entropy analysis seems to be helpful in unveiling internal dynamics that rule the processes of SR rhythm maintenance in the mid- and long-term after ECV. Nonetheless, further analysis with broader databases are needed for corroborating this conclusion.

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