Dynamic Risk Assessment of the Onset of Paroxysmal Atrial Fibrillation

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Abstract

We propose a computational methodology for evaluating the temporal evolution of the risk of onset of Paroxysmal Atrial Fibrillation (PAF) episodes. Firstly, we obtained 75 records of hour long ambulatory electrocardiograms (Holter monitoring) from healthy volunteers. From these we constructed a catalog of normal heart rate behavior patterns. For each record, patterns were defined as the standardized sequences of 5 consecutive values of RR intervals and the catalog was made up of all possible patterns contained in the 75 records. Secondly, 25 records of RR intervals corresponding to one hour long electrocardiograms ending with a PAF episode (group 1) and 25 additional records from healthy volunteers (group 2) were compiled. We then implemented a numerical procedure to compare the patterns belonging to these two groups with those of the catalog: using mobile windows of 6 consecutive minutes, we tested the null hypothesis that the patterns contained in windows of data taken from groups 1 and 2 were statistically indistinguishable from different subsets of patterns within the catalog. Our results demonstrated that the power at which this hypothesis is rejected indicates increased fluctuations in the patterns as we approach arrhythmia. This enabled us to propose an early warning system for the onset of PAF episodes with a specificity of 74% and sensitivity of 88%.

1. Introduction

Atrial Fibrillation (AF) is a public health problem which, due to its high morbidity and mortality, high costs of adequate treatment, the fact that it is the most common cardiac arrhythmia and that its prevalence increases with age, has attracted the attention of epidemiologists, physicians and scientists in the search for a solution. In this regard, in addition to the stratification of the risk of the onset of clinical and subclinical AF using traditional methods, there has been a breakthrough in the development of protocols for predicting AF episodes, in order to carry out timely prophylactic controls [1]-[4]. Most of these methods are based on the early detection of the physiological changes that usually accompany the transition of normal sinus rhythm to AF, such as for example, imbalances in the autonomic nervous system and/or the presence of atypical ectopic beats. However, accurate prediction of Paroxysmal Atrial Fibrillation (PAF) episodes (intermittent, recurrent and usually self-terminating, with durations of 2 min to 7 days), based on electrocardiographic signals (which have the advantage of being obtained in a non-invasive, low-cost way and from which information of interest using protocols that do not require a high computational cost can be generated) remains technically challenging [5].

As a contribution to this field of study, we asked whether it is possible to define an index whose evolution allows the dynamic assessment of the risk of occurrence of a paroxysmal AF episode. We modified a methodology previously used for the characterization of Heart Rate Variability (HRV) records prior to episodes of paroxysmal ventricular arrhythmias [6] and examined whether PAF episodes are preceded by the appearance of atypical patterns in HRV obtained from ambulatory electrocardiograms (24-hour Holter).

In the next section we define the patterns of interest and in section 3 we examine how we can characterize these in order to estimate statistically significant differences between patterns representative of normal sinus rhythm behavior in healthy volunteers and patterns from records taken prior to PAF episodes. Conclusions and final considerations are given in section 4.

2. Standardized heart rate patterns

Records were obtained using a magnetic recorder (3-channels, Rozinn Electronics, Holter Recorder Model 151), at the Experimental Cardiology Department at the Institute of Tropical Medicine, Universidad Central de Venezuela. Digitalization was performed at 500 samples per second with an 8 bit A/D converter and a standard al-

gorithm for detecting the R peaks was employed [7], [8].

The generated database consisted of:

- 25 one hour records of the *RR* intervals ending with self-terminating episodes of PAF (all records have a low noise level and began at least 1h after previous events, if any), from 37 patients (20 males, mean age 62).
- 100 randomly selected, one hour records of the *RR* intervals from 27 healthy subjects. None of them had clinical symptoms nor cardiac disease after they were evaluated according to the following protocol:

1. Clinical Evaluation
2. Chest X-Ray
3. Echocardiogram
4. Signal Averaged ECG
5. Stress Test
6. Standard ECG (12 derivations)
7. Holter's Dynamical Electrocardiogram (24h)

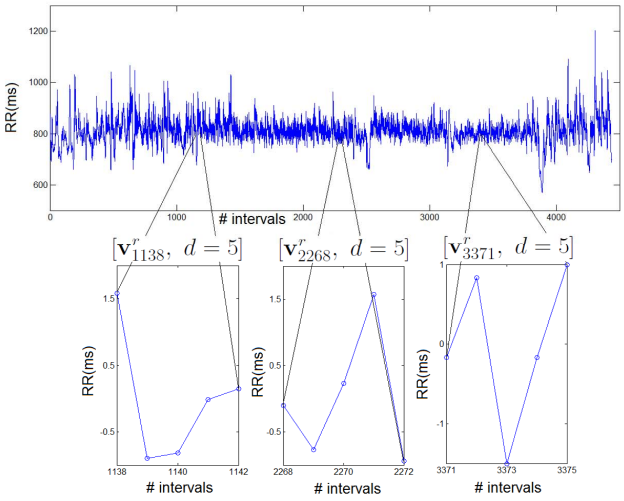

Figure 1. Constructing patterns from records of healthy subjects. From the long series on the top, different 5-dimensional patterns are shown at the bottom. Standardization enabled us to compare each past pattern with the current pattern independent of scale.

From this database, we constructed all the sequences of d consecutive RR intervals for each of the records:

$$\begin{aligned} \mathbf{v^r_1} &= (RR^r_1, RR^r_2, \ldots, RR^r_d) \\ \mathbf{v^r_2} &= (RR^r_2, RR^r_3, \ldots, RR^r_{d+1}) \\ &\vdots \\ \mathbf{v^r_{N^r-d+1}} &= (RR^r_{N^r-d+1}, \ldots, RR^r_{N^r-1}, RR^r_{N^r}) \end{aligned}$$

where N^r is the number of RR intervals from the r-th record. The patterns we analyzed are the standardizations of these sequences:

$$\mathbf{zv^r_\tau} = (zRR^r_\tau, zRR^r_{\tau+1}, \ldots, zRR^r_{\tau+d-1});$$

$$1 \le \tau \le N^r - d + 1$$

$$zRR^r_s = \frac{RR^r_s - \overline{RR}^r_\tau}{\sigma_{RR^r_\tau}};\ \tau \le s \le \tau + d - 1$$

$$\overline{RR}^r_\tau = \frac{1}{d}\sum_{s=\tau}^{\tau+d-1} RR^r_s;$$

$$\sigma_{RR^r_\tau} = \sqrt{\frac{1}{d-1}\sum_{s=\tau}^{\tau+d-1}(RR^r_s - \overline{RR}^r_\tau)^2}$$

such that even when the scales of the RR intervals may differ widely between sequences, the patterns are scale-free (see Figure 1).

To compare the behavior of patterns observed before PAF episodes with that of healthy volunteers, we began by constructing a catalog consisting of 75 of the 100 hours of records from this latter group: $\{\mathbf{zv^r_n};\ 1 \le n \le N^r - d + 1;\ 1 \le r \le 75\}$, and quantifying the degree of variability among these patterns by calculating the minimum distances:

$$\epsilon_n = Min\{\|\mathbf{zv^r_n} - \mathbf{zv^s_m}\|; r \ne s\}$$

of each of the $\mathbf{zv^r_n}$, to the rest of the catalog (excluding those of the record itself). Figure 2 shows the distribution of these minimum distances, which together constitute the yardstick by which we assessed the risk of a PAF episode.

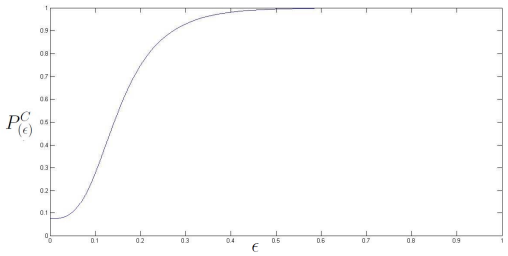

Figure 2. Figure shows the cumulative distribution $CD^C = P^C(\epsilon) < \epsilon$, for the example of d = 5, which represents the proportion of the catalog patterns that are separated from their nearest neighbor by less than ϵ.

3. Dynamic risk assessment of PAF using a hypothesis test

The 25 healthy volunteers not included in the catalog records were used as the comparison (H) group. Each of these records, $h_1, h_2, \ldots, h_{25}$, as well as the records from the PAF patients, $paf_1, paf_2, \ldots paf_{25}$, were divided into 10 consecutive 6-minute windows and the minimum distances between the patterns found in these windows with those observed from the catalog were calculated. This

data was then used to generate the distribution of these distances, $P_{h_i}^{w_t}(\epsilon)$ and $P_{paf_i}^{w_t}(\epsilon)$ ($i = 1, 2, \ldots, 25$), corresponding to the t-th window ($t = 1, 2, \ldots, 10$).

We then carried out a hypothesis test, using the null hypothesis that the patterns observed from the windows represented a typical sample of the catalog patterns. In other words, that the distributions of the distances, $P_{h_i}^{w_t}(\epsilon)$ and $P_{paf_i}^{w_t}(\epsilon)$ ($i = 1, 2, \ldots, 25$; $t = 1, 2, \ldots, 10$), were statistically indistinguishable from those of the catalog, $P^C(\epsilon)$. The test used was the tail-weighted Kolmogorov-Smirnov (wKS):

$$wKS_{paf_i}^{w_t} = max_\epsilon \frac{|P_{paf_i}^{w_t} - P^C(\epsilon)|}{\sqrt{P^C(\epsilon)[1-P_{paf_i}^{w_t}]}};$$
$$wKS_{h_i}^{w_t} = max_\epsilon \frac{|P_{h_i}^{w_t} - P^C(\epsilon)|}{\sqrt{P^C(\epsilon)[1-P_{h_i}^{w_t}]}}$$

Very small values ($wKS < 0,3$) indicate a strong similarity between the distributions [9].

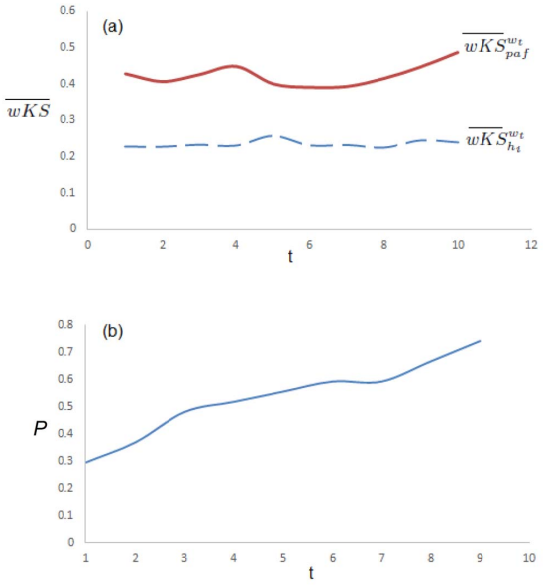

Figure 3. (a) The solid line represents the 25 mean values of the test statistic from each of the windows analyzed from the PAF group, while the dashed line represents the 25 mean values of the records from Group H. (b) The line indicates the proportion of the records from the PAF group in which the alarm is activated as the number of windows increases.

Figure 3 (a) shows the average values of the test statistic for each window for both the H group and the PAF group. It can be observed that these are considerably higher in the PAF group and, as t increases, (i.e. as the start of the arrhythmia episode approaches), form a wave that diminishes spontaneously and then increases monotonically until the onset of the episode. When we analyzed each of the records from the PAF group separately, we found that most of the statistical values showed more than one oscillation. This suggests that it is important to establish thresholds as a criterion for alert. For example, for the 25 records in the H Group, if we take as an early warning criterion the point at which the value of the test statistic exceeds the 0.95 percentile of the distribution of the minimum distances (= 0.4527) in 2 or more windows, this will activate an alert for more than 74% of the records of PAF patients (and 12% of records in the H group).

4. Final considerations

In general, we observed fluctuations in the number of atypical patterns of the HRV before the onset of PAF episodes. Although this imbalance is spontaneously controlled (at least in terms of the average behavior), a number of atypical patterns is subsequently observed which increases until the onset of a PAF. When we analyzed the records from the PAF group individually, we observed that these oscillations (associated with increases in the number of atypical patterns) occurred several times in most of the records examined. In other words, the emergence of atypical patterns is mitigated by a regulatory mechanism that varies from one patient to another. If we establish as an alarm signal the second time that the statistic exceeds the threshold 0.4527, a sensitivity of 74% and a specificity of 88% is attained. As shown in Figure 3 (b), this can occur at any time prior to the onset of the critical episode: starting with a 29% which is activated during the first 12 minutes of observation (i.e. more than 48 minutes before the start of the episode), and increases progressively up to 74%.

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