Seven-day Analysis of Atrial Fibrillation and Circadian Rhythms

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Abstract: In the present work, f-wave morphology is characterized by principal component analysis and a novel temporal parameter defined by the cumulative normalized variance of the 3 largest principal components (r_3). The 7-day behavior of persistent atrial fibrillation (AF) was studied in 9 patients using r_3, AF frequency, and sample entropy (*SampEn*). Detection of circadian rhythms depended on the parameter considered: rhythms were found in 6 (r_3, *SampEn*) and 5 (AF frequency) patients, but interestingly not always in the same patients. Two patients had significant circadian rhythm in all parameters. When a circadian rhythm was significantly present in 7 days, it was usually only significantly present in some of the 24-h segments. It is concluded that detailed AF characterization can be achieved with complementary parameters.

1 INTRODUCTION

Atrial activity during atrial fibrillation (AF) has often been studied as a random phenomenon, nonetheless, several studies have demonstrated the presence of organization during AF, indicating that a certain degree of local organization exists, likely caused by deterministic mechanisms of activation (Bollmann et al., 2006). Given the heterogeneity of the underlying AF pathophysiology and its different symptomatic impact on each patient, different treatment strategies should be adopted. The efficacy of treatment may be determined by accurate characterization of each particular case.

Several studies have investigated AF frequency, estimated from the surface ECG, as a marker of AF organization. However, no single parameter is likely to be sufficient for characterizing such a complex arrhythmia as AF, but a set of parameters is rather needed. Parameters reflecting irregularity (Alcaráz and Rieta, 2008) and changes in f-wave morphology (Stridh et al., 2009) may be complementary in conveying information on AF organization. Virtually all studies on AF organization have been conducted on short recordings, whereas the characterization of AF evolution over several days remains to be addressed. Such information will help to understand pathophysiological aspects of AF as well as to distinguish between different types of AF.

Despite the fact that the assessment of circadian rhythms in 24-h recordings has limited statistical significance, circadian variations in AF frequency have nevertheless been investigated using such recordings (Bollmann et al., 2000; Sandberg et al., 2010). Long-term monitoring makes it possible to determine more accurately the existence of circadian rhythms than when using 24-h.

The aim of this work is threefold. First, time domain characterization of f-wave morphology, based on principal component analysis (PCA), is proposed. This parameter, denoted r_3, is defined as the percentage of the cumulative normalized variance of the 3 largest principal components (PCs). Second, 7-day evolution of AF frequency, *SampEn*, and r_3 is studied for the first time, previously only studied in 24-h recordings or shorter. Finally, the reproducibility of circadian patterns is studied for the purpose of comparing detection performance when analyzing 24-h and 7-day data.

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2 METHODS

2.1 Dataset and Preprocessing

Our database consisted of 14 7-day Holter recordings from patients with persistent AF. The orthogonal X,Y,Z leads were acquired using a commercially available device (Lifecard CF^{TM}, Del Mar Reynolds).

Since QRST cancellation of the entire recordings was not possible due to computational restrictions, the first 5 min of each hour throughout the 7 days were analyzed. The residual ECG was obtained using spatiotemporal QRST cancellation. Furthermore, QRST-related residuals were replaced by spline interpolation if they exceeded ± 6 times the standard deviation of the residual.

Despite preprocessing, 5 recordings still had significant QRS-related residuals and had to be excluded since f-waves characterization could not be done. Thus, the remaining dataset consisted of 9 recordings.

2.2 Morphology, Frequency and Irregularity Parameters

The morphology of f-waves is characterized in individual leads using PCA information (Jackson, 1980). For this purpose, the parameter r_3 is introduced, which exploits the short-term temporal redundancy in the AF signal. It is obtained by first dividing each 5-min segment into 1-s segments, and then computing the sample covariance matrix from the resulting 300 segments. The resulting eigenvectors are arranged in order of decreasing eigenvalues λ_i. The variance concentrated to the 3 largest eigenvalues can be assessed by the percentage of their cumulative normalized variance r_3, i.e.,

$$r_3 = \frac{\sum_{i=1}^{3} \lambda_i}{\sum_{i=1}^{300} \lambda_i} \cdot 100. \quad (1)$$

This parameter is computed for each 5-min segment throughout the 7-day recordings, and thus provides an hourly characterization. Higher values of r_3 reflect more regular and organized f-wave morphology since the 3 first PCs explain most of the variance, and vice versa. An advantage with r_3 is that no assumption is required on an underlying signal model.

The AF frequency, which reflects the repetition rate of the f-waves, plays a central role when analyzing atrial activity. Several studies have demonstrated a significant correlation between AF frequency and the likelihood of spontaneous or drug-induced AF termination (Mainardi et al., 2009; Bollmann et al., 2006; Nilsson et al., 2006). The AF frequency trend is here estimated by short-term Fourier analysis of the residual signal. In order to reduce the influence of intermittent noise, HMM-based tracking is employed which yields an optimal trend from a sequence of observed AF frequencies (Sandberg et al., 2008). AF frequency is determined every 5 min to be comparable with the other parameters.

SampEn holds certain properties which are suitable for the study of physiological signals (Richman and Moorman, 2000). *SampEn* is the negative natural logarithm of the conditional probability that two sequences which are similar for m points remain similar for $m+1$ points. In order to compute *SampEn*, the embedded dimension m, i.e., the length of the vectors to be compared, and the noise filter threshold r need to be specified. For the AF signal different values for m and r were estudied in (Alcaráz and Rieta, 2008), accordingly *SampEn* is computed for every 5-min segment, using $m = 2$ and $r = 0.2 \cdot$ the standard deviation of the signal segment.

2.3 Circadianity Analysis

Circadian rhythms are assessed in 7-day recordings using hourly values of the parameters under study. The data sequence can be represented by a temporal regression model known as the cosinor model (Bingham et al., 1982), defined by

$$y_n = M + A_0 \cos(2\pi f_0 t_n + \phi_0) + e_n, \quad (2)$$

where M denotes the rhythm-adjusted mesor (i.e., mean value), A_0 the fitted cosine amplitude, f_0 the fundamental frequency (set to 24 hours) and ϕ_0 the acrophase (i.e., the lag from a defined reference time point to the crest time in the cosine curve fitted to the data). The random variable e_n corresponds to the residuals, this is, the difference between the observed sample y_n and the value provided by the estimated regression model $\hat{y}_n$. The least squares method is applied to determine the regression parameters.

The significance of a circadian rhythm is determined here by means of a bootstrap hypothesis test (Efron and Tibshirani, 1993). The circadian model ($\hat{y}_n$) is compared against a model consisting of the mesor component (M). The mean square error between the signal and each model ($E_{\hat{y}_n}$, E_M) is computed to obtain the difference between the residuals of the two models ($\Delta E = E_M - E_{\hat{y}_n}$). The statistical relevance of $\hat{y}_n$ versus M is assessed using a paired bootstrap hypothesis test. B random resamplings with replacement of residuals are made to obtain ΔE for each resampling ($B = 2500$). A suitable statistical hypothesis test contrasts the null hypothesis that the models have the same unexplained variance ($\Delta E = 0$) against the alternative hypothesis that both

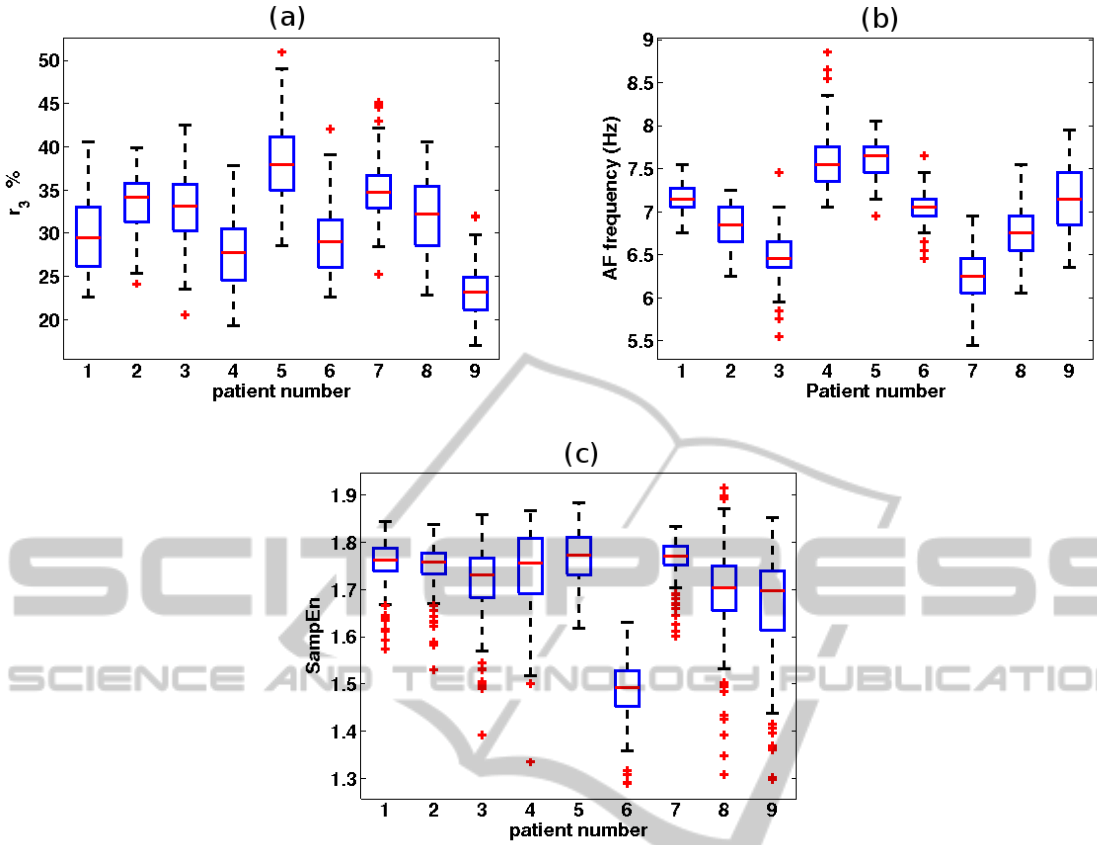

Figure 1: Boxplots for (a) r_3, (b) AF frequency, and (c) *SampEn* for each of the patients. For each box, the central mark is the median, the edges of the box are the 25th ($q1$) and 75th ($q3$) percentiles, the whiskers extend to the most extreme data points (excluding outliers), and outliers (points larger than $q3+1.5(q3-q1)$ or smaller than $q1-1.5(q3-q1)$) are plotted individually.

models have different unexplained variance ($\Delta E \pm 0$). The paired bootstrap hypothesis test determines that the circadian model is significant when at least 97.5% of the B values, for the estimated probability density function of ΔE, are on the right-hand side of 0.

The goodness of the model fit is quantified as the percentage of the signal variance explained by the circadian model with respect to the mesor,

$$P_m = \left(1 - \frac{\sum_{n=1}^{N}(y_n - \hat{y}_n)^2}{\sum_{n=1}^{N}(y_n - M)^2}\right) \cdot 100. \qquad (3)$$

The reproducibility of the circadian patterns is also studied in order to determine whether significant circadian rhythms can be consistently determined when analyzing 7-day and 24-h recordings.

3 RESULTS

3.1 AF Signal Characterization

Figure 1 shows boxplots of r_3, AF frequency, and *SampEn* for the 9 patients. There was a considerable inter-patient variability in r_3, and AF frequency, while this variability was less pronounced in *SampEn*.

Figure 2 displays four 4-s AF signals from patient #3, comparing high and low r_3 with high and low AF frequency. It can be seen that in situations when AF frequencies were very similar, e.g., 6.8 and 6.9 Hz, the f-wave morphology was quite different when quantified by r_3.

3.2 Circadian Rhythms

Significant circadian rhythm was found in 6 patients for r_3 and *SampEn*, and in 5 patients for AF frequency. Table 1 shows P_m and the hour M_h at which the maximum of the circadian model occurs, for each

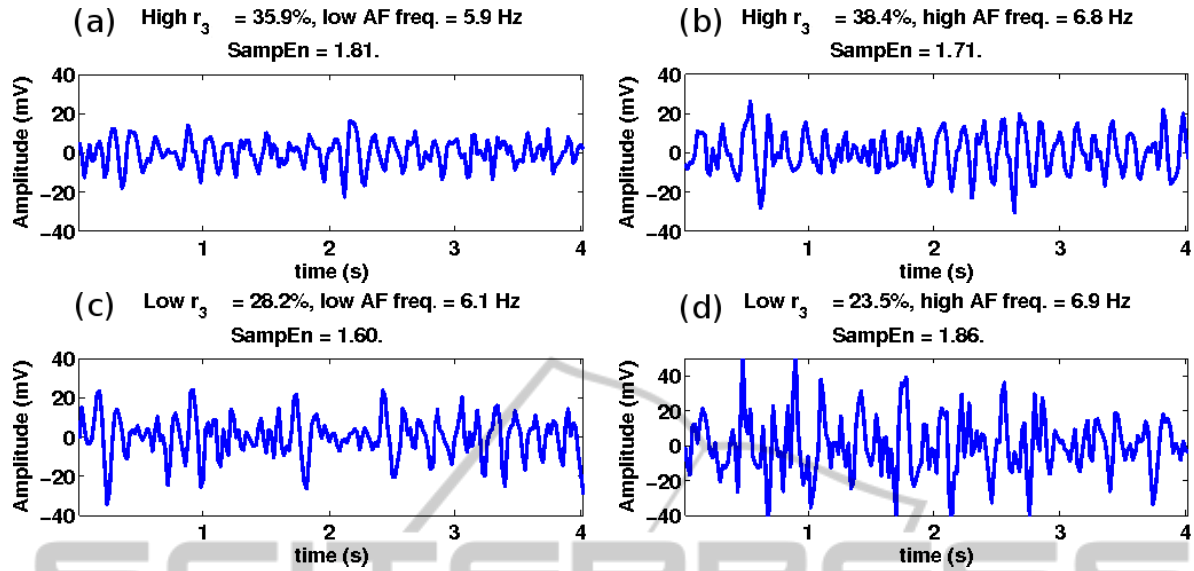

Figure 2: Patient #3. AF frequency versus r_3. (a) High r_3 and low AF frequency, (b) high r_3 and high AF frequency, (c) low r_3 and low AF frequency, (d) low r_3 and high AF frequency, corresponding to (a) 5 pm, (b) 11 pm, (c) 8 am, and (d) 6 am.

patient and each parameter. According to the circadian models, the highest r_3 was found in the morning for 3 patients and in the afternoon for the other 3 patients. The highest AF frequency was found in the morning for 3 patients and at night for 2 patients. Regarding *SampEn*, the highest irregularity was found in early morning or at late night.

Figure 3 shows the 7-day trend for patient #1, with r_3 and *SampEn* showing significant circadian variation, whereas AF frequency does not.

Circadian rhythms, found to be significant for the 7-day recordings, were usually significant only in some of the 7 24-h segments. The higher the value of P_m of the circadian rhythm for the 7-day signal, the more 24-h segments showed significant circadian rhythm. For example, patient #6 showed significant circadian variation in all 24-h segments for r_3 ($P_m = 54.5\%$), in three 24-h segments for *SampEn* ($P_m = 27.5\%$), and in one 24-h segment for AF frequency ($P_m = 14.1\%$).

4 CONCLUSIONS

The analysis of Holter recordings is typically synonymous to the analysis of AF signals corrupted by noise due to muscular activity or insufficient QRST cancellation. Of the studied parameters, AF frequency is probably the one to suffer the most from noise. *SampEn* is sensitive to high amplitude noise, since the noise threshold r is affected when outliers fall within a signal segment. Since r_3 is obtained from the 3 largest principal components the influence of noise is largely eliminated, thereby making characterization of f-wave morphology particularly well-suited for analysis of Holter recordings. The parameters r_1 and r_2 were also considered but there were not large differences between the three approaches, r_3 was finally selected since the transition between successive segments was smoother for this choice.

The time evolution over 7 days was assessed for r_3, *SampEn*, and AF frequency. The results showed that these parameters reflect complementary aspects of the AF signal since there was not always a correlation between their values. Higher AF frequency or higher irregularity parameters were frequently not followed by lower r_3. A more thorough investigation of r_3 will be done in a future study. The results reveal that these parameters vary considerable over time. The patterns differed from patient to patient, i.e., the highest values of a given parameter were not always found at the same time of the day for all patients. Such long-term information could be potentially useful in AF studies since short-term evaluation of parameters characterizing AF is prone to bias.

Significant circadian rhythms were found in most patients and reflected by most parameters—this is an additional piece of information about chronic AF mechanisms being related to the physiological equilibrium of patients and the long-term regulation mechanisms of the cardiovascular system. The aim of the circadian model is to extrat the daily component of the AF signal, rather than to be the best regression model in terms of lowest prediction error. A study on reproducibility of circadian rhythms verified that dif-

Table 1: Circadian rhythm. Percentage of the signal variance explained by the circadian model with respect to the mesor (P_m) and the hour of the maximum of the circadian model (M_h). "–" denotes absence of significant circadian variation.

Patient	r_3		*AF freq.*		*SampEn*	
	$P_m(\%)$	M_h	$P_m(\%)$	M_h	$P_m(\%)$	M_h
1	33.2	7 am	–	–	16.9	9 am
2	11.5	9 am	38.5	8 am	10.6	7 am
3	21.0	3 pm	22.2	7 am	–	–
4	11.1	4 pm	–	–	10.7	3 am
5	–	–	11.3	10 pm	8.6	6 am
6	54.5	8 am	14.1	12 pm	27.5	7 am
7	–	–	–	–	–	–
8	19.8	4 pm	14.2	7 am	–	–
9	–	–	–	–	11.3	7 am

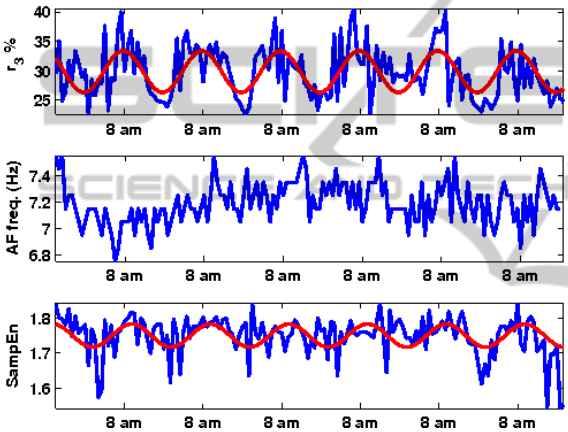

Figure 3: Circadian patterns. 7-day trends for patient #1, plotted together with the fitted circadian model (solid red line).

ferent results are obtained when using 24-h and 7-day recordings, the latter producing more accurate detection of circadianity.

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