Quantitative Analysis of Circadian Variation in Atrial Fibrillation Frequency

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Abstract

Circadian variation in atrial fibrillation (AF) frequency is explored in this paper by employing recent advances in signal processing. Once the AF frequency has been estimated and tracked by a hidden Markov model approach, the resulting trend is analyzed for the purpose of detecting and characterizing the presence of circadian variation. With cosinor analysis, the results show that the short-term variations in AF frequency exceeds the variation that may be attributed to circadian. Using the autocorrelation method, circadian variation was detected in 13 of 18 ambulatory ECG recordings (Holter) acquired from patients with long standing persistent AF. Using the ensemble correlation method, the highest AF frequency usually occurred during the afternoon, whereas the lowest usually occurred during late night. It is concluded that circadian variation is present in most patients with long standing persistent AF but the short-term variation in AF frequency is considerable.

1. Introduction

Nearly all functions of the body exhibit circadian variation. Such variation is important to study as knowledge about it may help to establish proper timing of drug administration (chronotherapy), being essential to maximize drug effect as well as to reduce side effects.

Circadian variation in AF frequency has been studied using 24-hour Holter recordings from which sparse measurements of AF frequency were obtained. Based on AF frequency obtained from 1-minute segments every sixth hour (16h, 22h, 4h, and 10h) from 30 patients, it was concluded that AF frequency was significantly lower during night-time than daytime [1]. In another study involving 21 patients, a nocturnal decrease of the normalized AF frequency was observed when the data series was defined by 5-minute segments every hour [2]. The mean length of the recordings were 15.5 h with certain recordings being as short as 12 h.

In this study we investigate the AF frequency trend with respect to the presence of circadian variation, using three different methods which provide complementary information. The cosinor method (Sec. 2.2) assumes that the variation is characterized by a single sinusoidal with a 24-hour period, thus imposing a functional shape on the variation. In contrast to the cosinor method, neither the autocorrelation method (Sec. 2.3) nor the ensemble correlation method (Sec. 2.4) impose a functional shape of the circadian variation, but exploits the correlation in time or across the ensemble.

2. Methods

2.1. Frequency trend estimation

The ECG signals were subjected to preprocessing in terms of baseline wander removal, using linear time-invariant highpass filtering, and atrial activity extraction, using spatiotemporal QRST cancellation [3]. These preprocessing steps are identical to those which have been employed in our previous studies, see, e.g., [4]

The AF frequency trend is estimated from short-term Fourier analysis of the atrial activity. Since the presence of intermittent noise causes the AF frequency estimates to become unreliable with this analysis, HMM-based AF frequency tracking is considered. The HMM method produces an optimal AF frequency trend from a sequence of observed AF frequencies, using a priori knowledge about the likelihood of AF frequency changes and the frequency estimation method employed. A short summary of the method is presented below; the details of the method can be found in [5].

First, the Fourier transform of the extracted atrial activity is calculated for each 2-s segment. The maximum peak of the periodogram is chosen as the observed AF frequency of the segment, provided that the peak is contained in the interval 3 to 12 Hz and that its magnitude exceeds a predefined detection threshold. Then, an observation sequence denoted $[z_m(1), z_m(2), \ldots, z_m(N_m)]$ is created which contains the different states that correspond to the frequency estimates; N_m denotes the length of $z_m(n)$. The HMM is characterized by a state transition matrix, defining the likelihood of AF frequency changes, and an observation matrix, defining the likelihood of estimating the correct frequency. The Viterbi algorithm creates a new sequence of AF frequency estimates, $[x_m(1), x_m(2), \ldots, x_m(N_m)]$, optimized with respect to the a priori knowledge contained in the above-mentioned HMM matrices. Those frequency estimates $z_m(n)$ that differ significantly from the observed trend are either excluded or replaced in $x_m(n)$ by estimates based on the adjacent AF frequencies. Hence, the HMM can be viewed as a postprocessing step which reduces the presence of outliers in the trend.

The AF frequency trend is first obtained separately for each of the ECG leads and then the trend with the least number of excluded frequency estimates is selected for further analysis. A robust one-minute resolution AF frequency trend is produced by taking the median of each segment of 30 consecutive 2-s AF frequency estimates. In the following, the AF frequency trend is denoted $x_m(n)$ where m refers to patient number.

2.2. The cosinor method

In this method, a single sinusoid $y_m(n)$ with a 24-hour period is fitted to $x_m(n)$ so as to determine if there is a circadian variation in AF frequency. The sinusoid is defined by

$$y_m(n) = a_m + b_m \cos\left(\frac{2\pi(n - n_{0,m})}{24}\right), \qquad (1)$$

where the three parameters a_m, b_m, and $n_{0,m}$ are determined using a nonlinear least squares method [6]. In the literature, a_m is usually referred to as midline estimating statistic of rhythm (MESOR), b_m as amplitude, and the time at which the fitted curve reaches its maximal value $n_{0,m}$ is referred to as acrophase.

The goodness-of-fit measure γ_m^2 indicates how well the variation in $x_m(n)$ is explained by the fitted curve $y_m(n)$. This measure is defined as the ratio between the variance of $y_m(n)$ and the variance of $x_m(n)$, i.e., $\gamma_m^2 = \sum_{n=1}^{N_m}(y_m(n) - \bar{x}_m)^2 / \sum_{n=1}^{N_m}(x_m(n) - \bar{x}_m)^2$, where $\bar{x}_m$ denotes mean AF frequency. The measure γ_m^2 can take on values between 0 and 1 where larger values indicate a better fit.

2.3. The autocorrelation method

In contrast to the cosinor method, this method does not impose a functional structure on the variation, but only establishes whether or not circadian variation is present in $x_m(n)$ [7]. Evidently, the autocorrelation function $r_m(k)$ indicates to what degree two samples are correlated with each other, being k samples apart. This function is estimated using the following expression,

$$\hat{r}_m(k) = \frac{1}{N_m} \sum_{n=1}^{N_m - k} (x_m(n) - \bar{x}_m)(x_m(n+k) - \bar{x}_m). \qquad (2)$$

When $x_m(n)$ is periodic with length T, $r_m(k)$ is positive-valued at $k = pT$, $p = 0, 1, 2, \ldots$, since $x_m(n)$ deviates from $\bar{x}_m$ in the same direction for these time lags. When $x_m(n)$ exhibits circadian variation, $r_m(k)$ has a U-shaped appearance, i.e., the autocorrelation is positive-valued at 0 and 24 hour lags and negative-valued at intermediate lags.

The autocorrelation function $r_m(k)$ is judged to reflect circadian variation if it differs significantly from the autocorrelation function $r_{w,m}(k)$ that corresponds to white noise. The difference between $r_m(k)$ and $r_{w,m}(k)$ is quantified by calculating a χ_m^2-value being defined by

$$\chi_m^2 = \sum_{k=1}^{N_m - 1} \left(\frac{\hat{r}_m(k) - \hat{r}_{w,m}(k)}{\delta(\hat{r}_m(k))}\right)^2, \qquad (3)$$

where $\hat{r}_{w,m}(k)$ is estimated using $\hat{r}_m(k)$ and the standard error $\delta(\hat{r}_m(k))$ is obtained using a bootstrapping technique [7]. If χ_m^2 with $N_m - 1$ degrees of freedom is significant and $\hat{r}_m(k)$ is U-shaped, $x_m(n)$ is said to exhibit a circadian variation. The autocorrelation method was applied to hourly averaged AF frequency estimates. Accordingly, each AF frequency trend was averaged so that $[x_{h,m}(1), x_{h,m}(2), \ldots, x_{h,m}(N_{h,m})]$ contains the average frequency of each hour.

2.4. The ensemble correlation method

The ensemble correlation method can be used to reveal joint variational patterns among the ensemble of data $x_1(n), \ldots, x_M(n)$, e.g., increased or decreased AF frequency during a certain period of the day common to all patients. Below, we will summarize the main steps of how to compute the ensemble average and correlation; see [8] for a detailed description of the method. In this study, deviations from the mean AF frequency are analyzed and, therefore, the following ensemble average is computed,

$$\mu_{\Delta x}(n) = \frac{1}{M} \sum_{m=1}^{M} \Delta x_m(n), \qquad (4)$$

where $\Delta x_m(n) = x_m(n) - \bar{x}_m$ and M is the number of frequency trends.

The samples of $\mu_{\Delta x}(n)$ are weighted so that samples with a large correlation across the ensemble are assigned a larger weight and vice versa. The weights $w(n)$ is obtained using a nonlinear transformation of the ensemble correlation $\rho(n)$, which quantifies the degree of correlation between a set of signals at the time instant n. The ensemble correlation is estimated using

$$\hat{\rho}(n) = \frac{\sum_{i=1}^{M}\sum_{j=1,i\neq j}^{M} \Delta x_i(n)\Delta x_j(n)}{(M-1)\sum_{i=1}^{M} \Delta x_i^2(n)}. \quad (5)$$

In order to robustify the estimate, the correlation between $\Delta x_i(n)$ and $\Delta x_j(n)$ may be averaged over $2W+1$ samples.

3. Database

Eighteen 24-hour recordings from different patients with long standing persistent AF were used in this study. All recordings were acquired at baseline with two leads at a sampling rate of 128 Hz, but digitally upsampled to 1000 Hz in order to comply with the requirements of the software used for beat detection/clustering and atrial activity extraction.

In order to ensure that all recordings started at the same time when applying the ensemble correlation method, the AF frequency trends $x_m(n)$ were subjected to shifting so as to get the same onset time. Therefore, the segment occurring before the onset time was shifted to the corresponding hour of the subsequent day, and, conversely, the segment occurring after the end time was shifted to the corresponding hour of the preceding day. No shifting was required for the cosinor and autocorrelation methods.

4. Results

The mean AF frequency $\bar{x}_m$ was computed for each of the 18 recordings and was found to be 6.74 ± 0.77 Hz (range 5.16 – 8.27 Hz). The standard deviation σ_m of the 24-hour AF frequency trend was 0.30 ± 0.07 Hz (range 0.19 – 0.45 Hz), demonstrating that the variation in AF frequency is quite substantial.

The nature of this variation is illustrated by the AF frequency trends displayed in Fig. 1. The long-term variations in AF frequency are small in amplitude and do not follow a regular pattern, whereas short-term variations are quite large.

Using cosinor analysis, the amplitude b_m of the variation was found to be 0.15 ± 0.09 Hz (range 0.05 – 0.30 Hz). The amplitude b_m was not correlated with $\bar{x}_m$ ($r = -0.26$). The acrophase $n_{0,m}$ occurred typically in the afternoon or evening (median time was at 15h48). The goodness of fit γ_m^2 of the sinusoid to the observed trend was 0.15 ± 0.13 (range 0.008 – 0.446), indicating that only a small portion of the variation in AF frequency is accounted for by the fitted sinusoids. The upper frequency trend in Fig. 1 (case #1) corresponds to the recording with

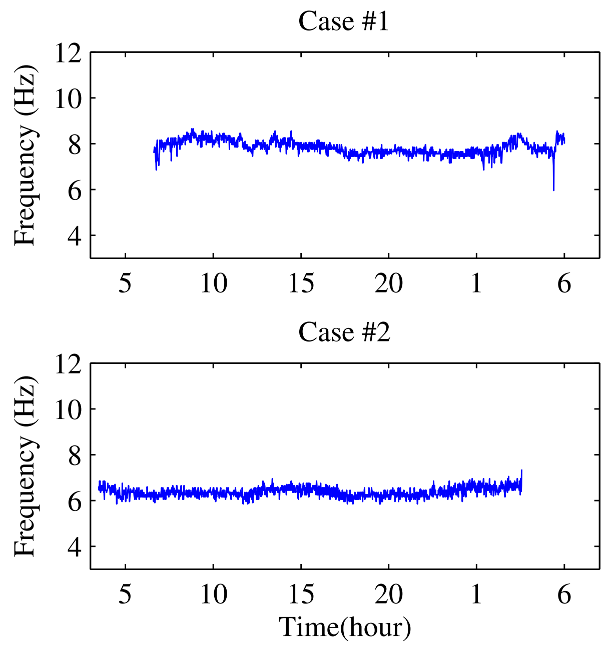

Figure 1. Two examples of AF frequency trends corresponding to (a) largest b_m and (b) smallest b_m.

the largest value of b_m, possibly indicative of circadian variation, whereas the lower frequency trend in Fig. 1 (case #2) corresponds to the smallest value.

Out of the 18 autocorrelation functions $\hat{r}_m(k)$, 14 have a U-shaped appearance. The χ_m^2/degree of freedom values of these 14 $\hat{r}_m(k)$ were 32 ± 33 (range $1 - 113$) indicating that all $\hat{r}_m(k)$ except one differ significantly from an autocorrelation function corresponding to white noise ($p < 0.0005$). Hence, circadian variation was detected in 13 out of 18 AF frequency trends using the autocorrelation method.

The ensemble average of the deviations from the mean AF frequency, $\mu_{\Delta x}(n)$, and the related ensemble correlation, $w(n)$, are presented in Fig. 2 as functions of the time of the day. It is evident from Fig. 2(a) that the highest mean AF frequency occurs in the afternoon (about 15h to 17h), while the lowest occurs late in the night (about 1h to 6h). These two periods of the day are associated with the most pronounced joint variation as reflected by the ensemble correlation, see Fig. 2(b). The magnitude of the ensemble average variation is approximately ± 0.15 Hz.

5. Discussion and conclusions

The main result of the present study is that there is a small circadian variation in AF frequency, though the short-term variation dominates, cf. Fig. 1. In previous studies [1,2] the AF frequency was sparsely measured and, hence, the short-term variation in AF frequency was disre-

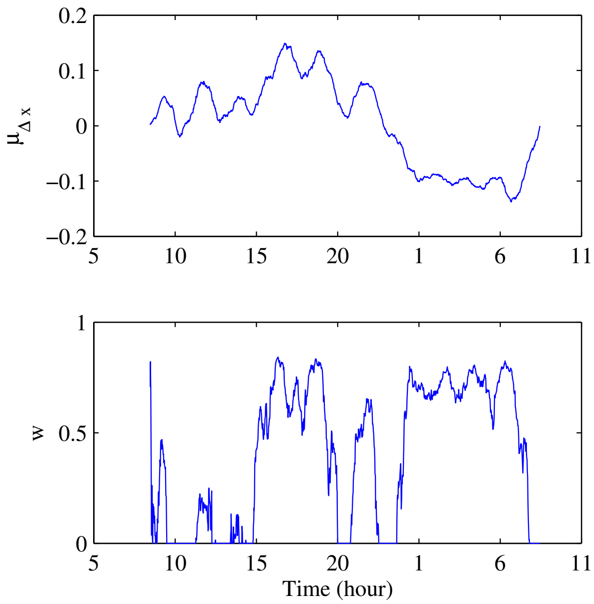

Figure 2. (a) The ensemble average of the deviations from the mean AF frequency $\mu_{\Delta x}(n)$ and (b) the corresponding ensemble correlation $w(n)$. The ensemble correlation is computed with a window length of $2W + 1 = 60$ samples, corresponding to one hour. For this illustration, the ensemble average $\mu_{\Delta x}(n)$ is filtered using a moving average filter with the length of 60 samples, corresponding to one hour.

garded as it could not be observed. The magnitude as well as the characteristics of the circadian changes in AF frequency were in relative agreement with the results reported in previous studies where it was shown that AF frequency decreases at night and increases in the morning [1, 2].

The results are established on a group of patients with long standing persistent AF who, in general, exhibit a higher AF frequency than do patients with new onset or paroxysmal AF; the mean AF frequency $\bar{x}_m$ was equal to 6.74 Hz during the 24 hours. It may be speculated that patients with long standing persistent AF are associated with less circadian variation due to reduced autonomic modulation, however, such a relation yet remains to be established.

A limitation with the present study is that the dataset is relatively small. Yet, the current dataset is homogenous and the size of it is enough to demonstrate that circadian variation is smaller than short-term variation in patients with long standing persistent AF. The data shifting, required to make all recordings start at the same time, represents another limitation of the present study as data from different days are spliced together; this procedure was only needed when performing ensemble correlation analysis. Such a procedure was, however, inevitable to employ when considering that only 24-hour recordings were available.

References

[1] Bollmann A, Sonne K, Esperer H, Toepffer I, Klein H. Circadian variations in atrial fibrillatory frequency in persistent human atrial fibrillation. PACE 2000;23:1867–1871.

[2] Meurling C, Waktare J, Holmqvist F, Hedman A, Camm A, Olsson S, Malik M. Diurnal variations of the dominant cycle length of chronic atrial fibrillation. Am J Physiol 2001; 280:H401–H406.

[3] Stridh M, Sörnmo L. Spatiotemporal QRST cancellation techniques for analysis of atrial fibrillation. IEEE Trans Biomed Eng 2001;48:105–111.

[4] Stridh M, Sörnmo L, Meurling C, Olsson S. Sequential characterization of atrial tachyarrhythmias based on ECG time–frequency analysis. IEEE Trans Biomed Eng 2004;51:100–114.

[5] Sandberg F, Stridh M, Sörnmo L. Frequency tracking of atrial fibrillation using hidden Markov models. IEEE Trans Biomed Eng 2008;55:502–511.

[6] Branch MA, Coleman TF, Li Y. A subspace, interior, and conjugate gradient method for large-scale bound-constrained minimization problems. SIAM J Sci Comput 1999;21:1–23.

[7] Watanabe MA, Alford M, Schneider R, Bauer A, Barthel P, Stein PK, Schmidt G. Demonstration of circadian rhythm in heart rate turbulence using novel application of correlator functions. Heart Rhythm 2007;4:292–300.

[8] Sörnmo L, Laguna P. Bioelectrical Signal Processing in Cardiac and Neurological Applications. Amsterdam: Elsevier, 2005.

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