Circadian variation of variability and irregularity of heart rate in patients with permanent atrial fibrillation: relation to symptoms and rate control drugs

Valentina D. A. Corino,1 Pyotr G. Platonov,2 Steve Enger,3 Arnjot Tveit,3 and Sara R. Ulimoen3

1Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milano, Italy; 2Center for Integrative Electrocardiology at Lund University, Department of Cardiology, Clinical Sciences, Lund University and Arrhythmia Clinic, Skåne University Hospital, Lund, Sweden; and 3Department of Medical Research, Bærum Hospital, Vestre Viken Hospital Trust, Rud, Norway

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Corino VD, Platonov PG, Enger S, Tveit A, Ulimoen SR. Circadian variation of variability and irregularity of heart rate in patients with permanent atrial fibrillation: relation to symptoms and rate control drugs. Am J Physiol Heart Circ Physiol 309: H2152–H2157, 2015. First published October 23, 2015; doi:10.1152/ajpheart.00300.2015.—The aim of the present study was to evaluate diurnal variations of the variability and irregularity of heart rate (HR) in patients with permanent atrial fibrillation (AF) with and without rate control drugs. Thirty-eight patients with permanent AF were part of an investigator-blind crossover study comparing diltiazem, verapamil, metoprolol, and carvedilol. We analyzed five Holter recordings per patient: at baseline (no rate control drug) and with each of the four drug regimens. HR, variability (SD; percentages of interval differences of successive RR intervals of >20, 50, and 80 ms; and root of the mean squared differences of successive RR intervals), and irregularity (approximate and sample entropy) parameters were computed in 20-min long nonoverlapping segments. Circadian rhythm was evaluated using cosinor analysis to each parameter series, which is characterized by the 24-h mean [midline statistic of rhythm (MESOR)] and excursion over the mean (amplitude). Arrhythmia-related symptomatic symptoms were assessed by a questionnaire measuring symptom severity and frequency. HR and variability parameters showed a significant circadian variation in most patients, whereas only a small minority of the patients had circadian variations of irregularity parameters. Patients with circadian approximate entropy n at baseline had more severe symptoms (symptom severity: 9 ± 4 vs. 6 ± 5, P < 0.05, circadian vs. noncircadian variations). All drugs decreased the MESOR of HR and increased the MESOR of variability parameters. Only carvedilol and metoprolol decreased the normalized amplitude over 24 h of all parameters and HR. In conclusion, HR and RR variability parameters present a circadian variation in patients with permanent AF, whereas few patients demonstrated circadian fluctuations in irregularity parameters, suggesting different physiological mechanisms.

circadianity;variability;irregularity;β-blockers;calcium channel blockers

NEW & NOTEWORTHY

Patients with permanent atrial fibrillation showed a circadian variation in heart rate and ventricular response variability parameters in most patients. In contrast, few patients showed circadian variations in irregularity parameters, and these were more symptomatic than other patients. β-Blockers and Ca2+ channel blockers influenced irregularity parameters differently.

IRREGULARITY MEASURES have been suggested as risk indicators in patients with atrial fibrillation (AF). Studies that have analyzed the variability and irregularity of the RR series have found that a reduced irregularity of RR intervals in permanent AF is associated with poor outcome (5, 14, 15, 22). Despite the accumulating data that suggest potential use of irregularity measures as risk indicators in patients with AF, it is not known to what extent they are affected by a variation of autonomic tone over 24 h and whether diurnal variation of these parameters, if exists, is affected by commonly used rate control drugs.

Recently, the Rate Control in AF (RATAF) study compared the effects of four once-daily drug regimens (metoprolol, diltiazem, verapamil, and carvedilol) on ventricular heart rate (HR) and arrhythmia-related symptoms in patients with permanent AF (21). In a recent study (3), we analyzed the RATAF data and found that Ca2+ channel blockers and β-blockers influenced atrioventricular (AV) node conduction differently. Both Ca2+ channel blockers and β-blockers reduced HR and increased time-domain measures of HR variability, but only β-blockers increased the irregularity measures.

However, 24-h variations of variability and irregularity measures in patients with AF have not been evaluated in controlled settings with and without rate-reducing drug administration.

Few studies have investigated circadian variations in patients with AF. Hayano et al. (7, 8) examined circadian variations in AV conduction properties during AF by a technique based on the Lorenz plot of successive ventricular response intervals. Their results suggested that AV node properties during AF may show a circadian rhythm that could contribute to the circadian variation of the ventricular response. Moreover, they found that the circadian rhythm was attenuated in patients with congestive heart failure (8) and that the circadian rhythm of AV conduction was an independent risk for cardiac death in patients with chronic AF (7). Sandberg et al. (19) explored the circadian variation in AF rate and showed that a circadian variation was present in most patients with long-standing persistent AF, although the short-term variation in the AF frequency was considerable and should be taken into account.

Irregularity of the ventricular response obtained from short-time recordings during AF have demonstrated their value for prediction of outcome (5, 14, 15, 22); however, the limits of applicability of this methodology remain to be delineated, including the optimal recording length, time of day, and potential impact of rate control drugs, which are commonly used in patients with AF. The possible prognostic meaning of a circadian variation of these same parameters is not known, and we have recently shown that some of these parameters can be affected by drug treatment (3). The present study is the first to address these questions. Our objective was to evaluate 24-h
variations of variability and irregularity of RR intervals in patients with permanent AF at baseline and during metoprolol, carvedilol, diltiazem, and verapamil administration.

MATERIALS AND METHODS

Protocol

The RATAF study was a prospective, randomized, investigator-blind, crossover study designed to compare four drug regimens used to reduce HR in patients with permanent AF. Patients without congestive heart failure or ischemic heart disease were recruited from the AF outpatient clinic at Bærum Hospital (Bærum, Norway) from May 2006 to June 2010. The detailed protocol of the study has been described elsewhere (21). The study was approved by the regional ethics committee and Norwegian medicines agency, and all patients signed informed consent. Clinical characteristics are shown in Table 1.

Participants received the following drug regimens in a randomized crossover design: 1) metoprolol slow-release tablets (100 mg/day), 2) diltiazem sustained-release capsules (360 mg/day), 3) verapamil modified-release tablets (240 mg/day), and 4) carvedilol immediate-release tablets (25 mg/day). Each drug was given for at least 3 wk to ensure steady-state plasma concentrations and an adequate period of washout of the previous treatment.

Arrhythmia-related symptoms were assessed using a self-administered questionnaire (21): the Symptom Checklist–Frequency and Severity in Norwegian translation. The questionnaire evaluated the frequency and severity of 16 symptoms potentially associated with arrhythmias, thereby generating frequency and severity scores, with higher scores representing worse symptoms. Total scores of symptom frequency and severity were calculated on the basis of all 16 symptoms included in the checklist. Patients were given the questionnaires on each visit, i.e., at the end of washout and at the end of each treatment period. Patients filled them out at home and returned them the next day.

Ventricular Response Analysis

We analyzed five Holter recordings per patient: at baseline (no rate-reducing drug) and with each of the four drug regimens. Variability and irregularity parameters were computed in 20-min long nonoverlapping segments; therefore, for each parameter, a series of $N$ values was obtained (where $N = 24 \times 3 = 72$ if the recording lasted exactly 24 h). Variability and irregularity are not synonyms: variability is related to the dispersion of data, whereas irregularity is related to the degree of unpredictability of the data fluctuations. Therefore, they offer complementary information. A visual explanation of the difference between variability and irregularity is shown in Fig. 1.

RR variability. Time-domain analysis included the HR, SD of all normal RR intervals, root of the mean squared differences of successive RR intervals (rMSSD), and percentages of interval differences of successive RR intervals of $\geq 20$, 50, and 80 ms (20a).

RR irregularity. Irregularity of RR intervals was assessed by approximate entropy (ApEn) and sample entropy (SampEn). ApEn is a regularity statistic quantifying the unpredictability of fluctuations in a time series such as an instantaneous HR time series. The presence of repetitive patterns of fluctuation in a time series makes it more predictable than a time series in which such patterns are absent. ApEn reflects the likelihood that similar patterns of observa-
tions will not be followed by additional similar observations. A time series containing many repetitive patterns, i.e., a regular and predictable series, has a relatively small ApEn; a less predictable, i.e., more complex, process has a higher ApEn (13). The ApEn algorithm counts each sequence as matching itself, and this makes the ApEn biased. Therefore, SampEn, not counting self-matches, has been introduced (18).

Circadian Analysis

To evaluate the circadian rhythmicity of the variations, cosinor analysis was applied, i.e., a single-component cosinor with a 24-h period is fitted to the parameter series to determine if there is a circadian variation. Briefly, the following variables that characterize circadian rhythmicity were estimated (see Fig. 2): the midline statistic of rhythm (MESOR; a rhythm-adjusted mean), amplitude (A; a measure of half the extent of predictable variation within a cycle), and acrophase (a measure of the time of overall high values recurring in each cycle). The period (duration of one cycle) was supposed to be known and equal to 24 h. Normalized amplitude was also computed as A/MESOR for a better comparison among patients and phases, i.e., normalized amplitude is the percentage of variation during the day over the average value (MESOR). The three parameters (MESOR, A, and acrophase) were determined using a nonlinear least-squares method (1).

Statistical Analysis

To determine whether a circadian variation was present, the zero-amplitude test was used. Briefly, the sum of squared differences between the estimated values based on the fitted model and the arithmetic mean (MSS) and the sum of squared differences between the data and estimated values from the fitted model (RSS) were computed. The model is statistically significant when the model sum of squares (MSS) is large relative to the residual sum of squares (RSS), as determined by the following F-test: $F = (MSS/2)/[RSS/(N - 3)]$, where 2 and $(N - 3)$ are the numbers of degrees of freedom attributed to the model ($k = 3$ parameters $- 1$) and to the error term ($N - k$). The null hypothesis that there was no rhythm (the amplitude is zero) was rejected when $F > F_1 - \alpha(2, N - 3)$, where $\alpha$ relates to the chosen probability level for testing the null hypothesis and was chosen as equal to 0.001 (4).

One-way repeated-measures ANOVA was performed to compare the computed parameters during baseline and drug regimens; if the $P$ value of the ANOVA was significant, a paired $t$-test or Wilcoxon test with Holm’s correction was applied.

The Wilcoxon rank-sum test was used to test symptom scores between patients who presented circadian variation and those who did not.

$P$ values of $<0.05$ were considered statistically significant. All analyses and statistical tests were performed using MATLAB R2012b (The MathWorks).

RESULTS

Patient Characteristics and Data Availability

In total, 60 patients (age: 71 ± 9 yr, 42 men and 18 women) with permanent AF were included in the RATAF study. For the present analyses, we included the 38 patients that had 5 ECG recordings lasting ≥ 20 h (minimum duration for circadian analysis). Clinical characteristics are shown in Table 1.

Twenty-Four-Hour Variation at Baseline

Figure 3 shows an example of 24-h trends for HR, variability (rMSSD), and an irregularity parameter (SampEn) for one patient. As shown in Fig. 3, both HR and rMSSD showed a circadian variation, whereas SampEn did not. These results were confirmed for the whole database and for all parameters, as shown in Table 2, which shows the number of patients whose parameters were found to present a circadian variation, as established by the zero-amplitude test. At baseline, variability parameters showed a circadian variation in 87% of the patients (range: 82–95%), whereas one-third of patients had a circadian rhythm in irregularity parameters.

Rate Control Drug Effect: 24-Hour Variation

HR. Figure 3, top, shows an example of 24-h trends for HR for one patient. As shown in Fig. 3, top, a significant circadian variation was present in HR trends during all drug administration; however, the MESOR and amplitude were lower compared with baseline. These results were confirmed for the whole database, as shown in Tables 3 and 4.

Figure 4 shows an average cosinor of HR for all patients during the five phases of analysis after normalization by the average MESOR and considering the same acrophase for all, to emphasize the difference in the normalized amplitude. It can be observed that all drugs decreased the normalized amplitude, with diltiazem as the drug that maintained the maximal excursion in HR. This result was confirmed in almost all parameters, as shown in Table 4. Only verapamil significantly decreased the normalized amplitude of HR compared with the baseline value.
Variability parameters. Figure 3, middle, shows an example of 24-h trends for a variability parameter (rMSSD) for one patient. rMSSD showed a circadian variation during drug administration and a larger MESOR compared with baseline. Table 3 shows that the MESOR of variability parameters was higher during drug administration compared with baseline. Diltiazem was the drug that increased the MESOR of variability parameters the most. The normalized amplitude using the β-blockers carvedilol and metoprolol was lower than during baseline.

Irregularity parameters. Figure 3, bottom, shows an example of 24-h trends on an irregularity parameter (SampEn) for one patient. SampEn did not show any significant circadian variation during baseline or drug administration. For the whole database (Table 3), the MESOR of irregularity parameters was higher during β-blocker administration compared with baseline, whereas there was no significant difference when Ca²⁺ channel blockers were used.

The normalized amplitude for the irregularity parameters using the β-blockers carvedilol and metoprolol was lower than at baseline.

Circadianity and Symptoms

We investigated the relation between symptoms and the presence of circadian rhythm in variability and irregularity parameters. A trend between symptoms and circadian variation in both variability and irregularity parameters was observed: patients with a circadian variation in variability parameters had less frequent and less severe symptoms. In contrast, patients with a circadian variation in irregularity parameters had more frequent and more severe symptoms. At baseline, significant differences in symptom severity were found in rMSSD and ApEn (rMSSD: 6 ± 5 vs. 11 ± 5 and ApEn: 9 ± 4 vs. 6 ± 5, circadian vs. noncircadian variations). Patients with a circadian variation in irregularity parameters tended to have lower actual irregularity (as an example, during baseline, ApEn was 1.79 ± 0.10 vs. 1.91 ± 0.07, P < 0.0001, circadian vs. noncircadian variations).

DISCUSSION

In normal subjects, a lower HR during sleep is well established, although few studies (11, 12) have undertaken a detailed analysis of the circadian properties of the curve, as both HR and HR variability depend on the autonomic nervous system.
system. In addition, previous studies (16, 17) have suggested that in normal subjects as well, the complexity of a short-term RR series depends on the state of the autonomic nervous system: it is usually reduced during experimental conditions, inducing an increase of the sympathetic modulation. A reduction of RR series complexity during tilt was also found in a small group of patients with AF (2). However, to the best of our knowledge, this is the first time that the effect of rate control drugs on HR variability and irregularity over 24 h was assessed in patients with AF in the setting of a randomized prospective crossover designed study.

The main findings of this study were 1) the existence of a circadian variation in HR and variability parameters in almost all patients at baseline, 2) the lack of circadianity in irregularity parameters in most of the patients, 3) both β-blockers and Ca2+-channel blockers decreased the 24-h mean (MESOR) of HR and increased the MESOR of variability parameters, and 4) β-blockers decreased the normalized amplitude over the 24 h, i.e., the excursion of variation of all parameters and HR.

The existence of a circadian variation in HR and variability parameters in patients with AF can be considered a sign that the autonomic nervous system still works properly in these patients.

The effect of the autonomic nervous system during AF has been highlighted in recent studies on arterial blood pressure, where fluctuations in the low-frequency band have been related to the influence of sympathetic fibers acting on the cardiovascular system (9). Moreover, a previous study (10) has suggested that the blunted circadian rhythms of AV conduction properties may reflect blunted circadian rhythm of autonomic cardiac modulation, which may be in accordance with the fact that a reduced circadian variation in HR variability, an index of cardiac autonomic activity, is associated with an increased risk of mortality in patients after myocardial infarction.

We have recently shown that Ca2+-channel blockers and β-blockers influence AV node conduction differently. Both Ca2+-channel blockers and β-blockers reduced HR and increased time-domain measures of HR variability, but only β-blockers increased the irregularity measures (3), and the present results on the MESOR are in agreement with the previous ones. β-Blockers decreased the normalized amplitude over 24 h, i.e., the excursion of variation of all parameters and HR. A previous study (20) has showed a marked attenuation in the circadian variation of the low-frequency component after β-blockade.

Even if irregularity parameters have been shown to be good risk indicators in patients with AF (5, 14, 15, 22), interpretation of the prognostic impact of RR irregularity is rather complex. The few studies analyzing variability and irregularity of the RR series showed that a reduced irregularity of RR intervals in permanent AF was associated with poor outcome. Reduced variability and irregularity of RR intervals during AF were found to be independent predictors of all-cause mortality in patients with left ventricular dysfunction after myocardial infarction (14) and in patients with mild to moderate heart failure (5), respectively. In the present study, irregularity measures showed circadian behavior in a minority of patients (~1/3). Patients who had a circadian variation in irregularity parameters tended to have worse and more frequent symptoms; these

Table 3. **MESOR for all parameters during baseline and during drug administration**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Carvedilol</th>
<th>Metoprolol</th>
<th>Diltiazem</th>
<th>Verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>96 ± 12</td>
<td>85 ± 11*</td>
<td>83 ± 12†</td>
<td>77 ± 10‡</td>
<td>81 ± 12†§</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>154 ± 32</td>
<td>171 ± 37*</td>
<td>182 ± 43†</td>
<td>194 ± 46‡</td>
<td>177 ± 40§</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>89 ± 3</td>
<td>91 ± 2*</td>
<td>91 ± 2*</td>
<td>91 ± 3*</td>
<td>90 ± 2*</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>73 ± 6</td>
<td>78 ± 4*</td>
<td>79 ± 5*</td>
<td>79 ± 6*</td>
<td>77 ± 5§</td>
</tr>
<tr>
<td>pNN80, %</td>
<td>60 ± 7</td>
<td>66 ± 6*</td>
<td>67 ± 6*</td>
<td>68 ± 8*</td>
<td>65 ± 6§</td>
</tr>
<tr>
<td>rMSSD, ms</td>
<td>206 ± 43</td>
<td>234 ± 50*</td>
<td>248 ± 58†</td>
<td>266 ± 69‡‡</td>
<td>238 ± 57§§</td>
</tr>
<tr>
<td>ApEn, au</td>
<td>1.88 ± 0.10</td>
<td>1.92 ± 0.07*</td>
<td>1.93 ± 0.06*</td>
<td>1.90 ± 0.07</td>
<td>1.90 ± 0.07‡‡</td>
</tr>
<tr>
<td>SampEn, au</td>
<td>1.72 ± 0.14</td>
<td>1.78 ± 0.11*</td>
<td>1.78 ± 0.10*</td>
<td>1.76 ± 0.11</td>
<td>1.75 ± 0.10</td>
</tr>
</tbody>
</table>

Values are means ± SD. MESOR, midline statistic of rhythm; SDNN, SD of NN intervals; au, arbitrary units. *P < 0.05 compared with baseline; †P < 0.05 compared with metoprolol; §P < 0.05 compared with diltiazem.

Table 4. **Percentage of the variation over the average (MESOR) during the day (normalized amplitude)** for all parameters during baseline and drug administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Carvedilol</th>
<th>Metoprolol</th>
<th>Diltiazem</th>
<th>Verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>17 ± 6</td>
<td>10 ± 4†</td>
<td>13 ± 6‡</td>
<td>16 ± 7§</td>
<td>15 ± 6†</td>
</tr>
<tr>
<td>SDNN</td>
<td>20 ± 1</td>
<td>13 ± 6*</td>
<td>15 ± 7*</td>
<td>21 ± 10§</td>
<td>17 ± 9</td>
</tr>
<tr>
<td>pNN50</td>
<td>3 ± 2</td>
<td>1 ± 1*</td>
<td>2 ± 1†</td>
<td>3 ± 4</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>pNN50</td>
<td>8 ± 6</td>
<td>4 ± 3*</td>
<td>5 ± 3*</td>
<td>7 ± 8</td>
<td>6 ± 6</td>
</tr>
<tr>
<td>pNN80</td>
<td>13 ± 8</td>
<td>7 ± 4*</td>
<td>7 ± 5*</td>
<td>11 ± 10</td>
<td>10 ± 8</td>
</tr>
<tr>
<td>rMSSD</td>
<td>22 ± 11</td>
<td>14 ± 7†</td>
<td>17 ± 8*</td>
<td>23 ± 11‡§</td>
<td>18 ± 10</td>
</tr>
<tr>
<td>ApEn</td>
<td>2 ± 2</td>
<td>1 ± 2*</td>
<td>1 ± 1*</td>
<td>2 ± 3</td>
<td>3 ± 3§</td>
</tr>
<tr>
<td>SampEn</td>
<td>5 ± 5</td>
<td>3 ± 3*</td>
<td>2 ± 2*</td>
<td>3 ± 4</td>
<td>5 ± 5</td>
</tr>
</tbody>
</table>

*P < 0.05 and †P < 0.001 compared with baseline; ‡P < 0.05 compared with carvedilol; §P < 0.05 compared with metoprolol.
same patients had lower irregularity, which has been shown to be a poor prognostic sign (5, 14, 15, 22).

In conclusion, in the majority of patients, HR and RR variability parameters present a circadian variation as in normal subjects, showing that the autonomic nervous system works quite properly even in patients with permanent AF. In contrast, irregularity parameters have a circadian variation only in a few patients. The circadianity parameter MESOR is influenced by Ca\(^{2+}\) channel blockers and β-blockers, whereas the normalized amplitude is attenuated only by β-blockers, i.e., HR and variability and irregularity parameters are forced to have a smaller range of variation. Finally, irregularity parameters do not generally demonstrate circadian fluctuations, which may suggest that they may prove to be more robust as risk predictors in patients with AF.

REFERENCES