Disorder and circadian periodicity in within-day variability of sinusal R-R intervals in myocardial infarcted patients


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Disorder and Circadian Periodicity in Within-Day Variability of Sinusal R-R Intervals in Myocardial Infarcted Patients

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The present study investigates whether the disorder in nonlinear variability of human heart rate shows a periodic pattern along the 24-h scale in postinfarct patients (PIP). The aim is to detect whether there are chronoalterations between disorder and periodicity in heart rate variability (HRV) that can contribute to explaining the postinfarct risk of sudden cardiac death.

The study was performed in 7 asymptomatic PIP who have had an acute myocardial infarction, complicated by ventricular arrhythmias, three months prior to the research. The control group was constituted by 10 clinically healthy subjects (CHS). Each one of the CHS and PIP underwent a Holter electrocardiogram. The sinusal R-R intervals (SRRI) of each dynamic Holter monitoring were detected and partitioned in units of one hour to cover the 24-h span. The hourly-qualified values of the SRRI were analyzed in their disorder using the Information Entropy (E) method. The hourly-qualified mean values of both the SRRI and E were, further, analyzed for their eventual circadian rhythm (CR), via the Cosinor method.

A clear nyctohemeral variability was found in the hourly-qualified mean values of both the SRRI and E. This variability during the day was found to have a significant CR. However, the oscillatory extent for the E CR was found to be less pronounced in PIP as compared to CHS. In addition, the oscillatory acrophase of the E CR was found to be shifted to the night in PIP as compared to CHS.

The lack of the matutinal increase of disorder in HRV may be speculatively regarded as a mechanism for explaining why the PIP are more exposed to the risk of sudden cardiac death in the morning hours. *J Clin Basic Cardiol* 2000; 3: 53–8.

Key words: chaos, chronobiology, entropy, heart rate, Holter monitoring, nonlinear dynamics
ing individuals having a hidden IHD. As a matter of fact, ethical reasons prevent performing an investigative coronaryography on asymptomatic subjects who appear to be in good health at a conventional clinical check up including physical examination and laboratory data. On the other hand, the age-related difference in HR is not so crucial between the third and fourth decade of life in normotensive human beings, despite of a reducing effect of old age and arterial hypertension on HRV [17]. Informed consent to be investigated was obtained from each participant. The study was carried out according to the Declaration of Helsinki.

The PIP were concordant in some clinical features: the mildly compromised ventricular function, the stability of the electrocardiographic and echographic signs of the healed infarction, the lack of any symptomatology at rest and during a mild-to-moderate exercise, the absence of silent angina and arrhythmias (documented by ECG monitoring), the absence of concomitant diseases, the common therapy of low-dose aspirin and nitrates. Criteria for exclusion were the use of cardiac glycosides, diuretics, ACE-inhibitors and antiarrhythmic drugs, including the beta-adrenergic blocking agents, a positive personal history of smoking, alcohol abuse, stressful activities, insomnia and anxiety.

Both the CHS and PIP underwent a 24-h continuous ECG monitoring by means of the ambulatory three-channel Holter recorder, manufactured by Rozinn (New York, USA). The PIP underwent the Holter ECG in pharmacological washout by 24-h. The monitored data were analyzed by means of a computerized system which automatically identifies the normal QRS complexes, and measures the SRRI between two juxtaposed normal QRS, taking into account both the minimal and maximal physiological durations between these waves.

Data analysis

**Hourly-qualified partitioning of the 24-h sinus R-R intervals**

The daily series of the SRRI of each ECG monitoring was partitioned into periods of 1 hour in order to have the hourly-qualified interbeat durations over the whole 24-h span. The hourly-qualified values of the SRRI were averaged in order to obtain their mean for each hour of the day-night period. The hourly qualified means of the SRRI were summarized per group in order to obtain the hourly-qualified mean values of the SRRI with their standard deviation (SD), ie, the mean chronogram, for CHS and PIP.

**Method for quantifying the disorder**

The individual hourly-qualified values of the SRRI were analysed for the disorder of their NLV by means of the Information Entropy method according to Shannon and Weaver [18]. In so doing, the entropy (E) was estimated as an adimensional measure (see Appendix) of the amount of disorder in the SRRI for each hour of the day-night span. The individual hourly-qualified values of E were, in turn, summarized per group in order to have their mean (± SD) for CHS and PIP.

**Rhythm biometry**

The individual hourly-qualified mean values of the SRRI were analyzed for their circadian rhythm (CR) by means of the Cosinor method [19, 20] with three harmonic components (see Appendix). The same approach was applied to the individual hourly-qualified values of E.

The individual rhythmometric estimates of both the hourly-qualified mean values of the SRRI and of the hourly-qualified values of the E were summarized per group in order to obtain their mean (± SD) in CHS and PIP. These mean estimates served to construct the oscillatory curve fitting the experimental data for each group (mean cosinorgram).

**Results**

**Hourly-qualified mean values of the sinus R-R intervals**

Figure 1 displays, in the left top panel, the hourly-qualified mean values (± SD) of the SRRI in CHS. The mean chronogram shows a manifest within-day variability. The ANOVA of this variability gave a significant result (p < 0.010) for the variance ratio between the columns (the hours of the day) and the rows (the individual hourly qualified mean values), demonstrating that there is a significant effect of time on the within-day variability of the SRRI in CHS.

Figure 1 illustrates, in the left bottom panel, the mean oscillatory curve that results from the fit of the three-component harmonic model to the hourly-qualified mean values of the SRRI in CHS. The mean cosinorgram shows a composite oscillation whose prominent wave corresponds to the hours of the night.

The rhythmic properties of the above-fitted mean cosinorgram in CHS are listed in Table 1 (left column). As documented by the significant overall p, the oscillatory curve is wide enough to reject the null-hypothesis of zero-amplitude. As demonstrated by the p values of each harmonic component, only the wave with a 24-h period has an amplitude which rejects the zero-amplitude assumption of a significant p level of probability, suggesting that the main oscillatory component of the nychtohemeral variability of the SRRI in CHS has a 24-h period. As documented by the acrophase of the first harmonic component, this CR shows the peak of the highest duration in SRRI during the night.

Figure 1 displays, in the right top panel, the hourly-qualified mean values (± SD) of the SRRI in PIP. The mean chronogram shows a certain within-day variability. The ANOVA of this variability gave a significant result (p < 0.010), demonstrating that the effect of time on the within-day variability of the SRRI is detectable also in PIP.

Figure 1 illustrates, in the right bottom panel, the mean cosinorgram provided by the fit of the three-component harmonic model to the hourly-qualified mean values of the SRRI in PIP. The oscillation shows a composite profile whose prominent wave corresponds to the hours of the afternoon.

The rhythmic properties of the above-fitted oscillation in PIP are listed in Table 1 (right column). As documented by the significant overall p, the oscillation results wide enough to reject the zero-amplitude assumption. As demonstrated by the p values of each harmonic component, the fitted wave with a 24-h period has an amplitude whose extent rejects the null-hypothesis of zero-amplitude, suggesting that the nychtohemeral variability of the SRRI is structured as a CR also in PIP. As documented by the acrophase of the first harmonic wave, this CR shows the highest duration of the SRRI during the night. However, as documented by the significant p value of the second harmonic wave, the hourly-qualified mean values of the SRRI in PIP can be approximated by an oscillation having a 12-h period. This finding suggests that the within-day variability of the SRRI in PIP results from the modulation of an additional oscillatory component with a frequency of fluctuation that is twice the circadian cycle. Such a 12-h component can be invoked to explain the postmeridian elongation of duration showed by the SRRI in PIP.

Interestingly, the circadian amplitude of the hourly-qualified mean values of the SRRI appears to be relatively less pronounced in PIP as compared to CHS. A t test of this difference gave a significant result (p < 0.001), demonstrating that
the circadian oscillation of the SRRI in PIP occurs within more restricted margins of variability.

**Hourly-qualified values of the entropy in the sinusal R-R intervals**

Figure 2 illustrates, in the left top panel, the hourly-qualified values of the E in CHS. The mean chronogram shows an overt within-day variability. The ANOVA of this variability provided a significant result (p < 0.010), demonstrating that there is a significant effect of time on the amount of disorder that is present in the hourly-qualified values of the SRRI in CHS.

![Figure 2](image-url)  
*Figure 2. Mean chronogram (top panel) and mean cosinogram (bottom panel) for the hourly-qualified values of sinusal R-R intervals in clinically healthy subjects (left panels) and postinfarct patients (right panels)*

The rhythmic properties of the above-fitted mean cosinogram in CHS are listed in Table 2 (left column). According to the significant overall p, the undulatory curve rejects the null-hypothesis of zero-amplitude. As demonstrated by the p values of each fitted harmonic wave, only the oscillatory component with a 24-h period shows a crest which rejects the null-hypothesis of zero-amplitude at a significant p level of probability. This means that the nychthemeral variability of the disorder in the SRRI of CHS corresponds to a CR (periodically structured disorder). As documented by the acrophase of the first harmonic component, the CR of the disorder shows its highest expression early in the morning.

![Figure 2](image-url)  
*Figure 2 displays, in the left bottom panel, the mean cosinogram that results from the adaptation of the three-component harmonic model to the hourly-qualified values of the E in CHS. The oscillatory profile shows a composite fluctuation whose prominent wave corresponds to the morning hours.*

**Table 1. Rhythmic biometry of the hourly-qualified values of sinusal R-R intervals in clinically healthy subjects (CHS) and postinfarct patients (PIP)**

<table>
<thead>
<tr>
<th>Rhythmic parameters</th>
<th>CHS</th>
<th>PIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall p</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mesor</td>
<td>0.8011 ± 0.3162</td>
<td>0.7800 ± 0.0150</td>
</tr>
<tr>
<td><strong>First harmonic wave with a 24-h period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.001</td>
<td>= 0.045</td>
</tr>
<tr>
<td>Amplitude (sec)</td>
<td>0.0727 ± 0.0297</td>
<td>0.0190 ± 0.0180</td>
</tr>
<tr>
<td>Acrophase (h:min)</td>
<td>03:08 ± 00:28</td>
<td>12:20 ± 03:28</td>
</tr>
<tr>
<td><strong>Second harmonic wave with a 12-h period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>= 0.144</td>
<td>= 0.001</td>
</tr>
<tr>
<td>Amplitude (sec)</td>
<td>0.0352 ± 0.0537</td>
<td>0.0280 ± 0.0150</td>
</tr>
<tr>
<td>Acrophase (h:min)</td>
<td>03:28 ± 01:52</td>
<td>05:16 ± 01:16</td>
</tr>
<tr>
<td><strong>Third harmonic wave with a 8-h period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>= 0.621</td>
<td>= 0.673</td>
</tr>
<tr>
<td>Amplitude (sec)</td>
<td>0.0186 ± 0.0278</td>
<td>0.0070 ± 0.0020</td>
</tr>
<tr>
<td>Acrophase (h:min)</td>
<td>12:04 ± 03:40</td>
<td>13:44 ± 11:00</td>
</tr>
</tbody>
</table>

± standard deviation
Figure 2. Mean chronogram (top panel) and mean cosinorgram (bottom panel) of the hourly-qualified values of entropy in clinically healthy subjects (left panels) and postinfarct patients (right panels)

Figure 2 depicts, in the right bottom panel, the mean cosinorgram provided by the three-component harmonic model applied to the hourly-qualified values of the E in PIP. The mean oscillatory curve shows a fluctuation in which it is difficult to detect a prominent wave.

The rhythmic properties of the above-fitted mean cosinorgram in PIP are listed in Table 2 (right column). As documented by the significant overall p, the oscillatory curve is characterized by an amplitude wide enough to reject the null-hypothesis of zero-amplitude. As demonstrated by the p values of each fitted harmonic wave, only the oscillatory component with a 24-h period exhibits an amplitude which rejects the zero-amplitude assumption of a significant p level of probability, suggesting that the nyctohemeral variability of the E shows a periodic recursivity of circadian type (periodically structured disorder) also in PIP. As documented by the acrophase of the circadian wave, the crest for the CR of the E in PIP is located during the night.

Interestingly, the circadian acrophase of the E appears to be relatively earlier in PIP as compared to CHS. A test of this difference gave a significant result (p < 0.001), demonstrating that the disorder in the SRRI is significantly shifted to the night in PIP.

Discussion

In discussing the results of the present study, it is important to consider by comparison the findings obtained in CHS and PIP, respectively.

The study in CHS provided evidence that the SRRI shows a nyctohemeral variability which is the expression of a CR. Accordingly, it can be argued that the HRV reflects in its physiological daily pattern a deterministic periodic order whose regimen of repetition has a 24-h period.

The study in CHS was also able to document that the within-day variability in the SRRI is significantly characterized by a disor-

Table 2. Rhythmic biometry of the hourly-qualified values of entropy in clinically healthy subjects (CHS) and postinfarct patients (PIP)

<table>
<thead>
<tr>
<th>Rhythmic parameters</th>
<th>CHS Estimates</th>
<th>PIP Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall p</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mesor</td>
<td>1.0709 ± 0.3162</td>
<td>0.8333 ± 0.4471</td>
</tr>
<tr>
<td>First harmonic wave with a 24-h period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.008</td>
<td>= 0.0140</td>
</tr>
<tr>
<td>Amplitude (Units)</td>
<td>0.0674 ± 0.0610</td>
<td>0.0780 ± 0.0632</td>
</tr>
<tr>
<td>Acrophase (h:min)</td>
<td>07:54 ± 02:28</td>
<td>00:04 ± 02:51</td>
</tr>
<tr>
<td>Second harmonic wave with a 12-h period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>= 0.070</td>
<td>= 0.5842</td>
</tr>
<tr>
<td>Amplitude (Units)</td>
<td>0.0522 ± 0.0357</td>
<td>0.0301 ± 0.0767</td>
</tr>
<tr>
<td>Acrophase (h:min)</td>
<td>17:28 ± 04:15</td>
<td>12:00 ± 08:59</td>
</tr>
<tr>
<td>Third harmonic wave with a 8-h period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.216</td>
<td>= 0.9598</td>
</tr>
<tr>
<td>Amplitude (Units)</td>
<td>0.0421 ± 0.0304</td>
<td>0.0084 ± 0.0794</td>
</tr>
<tr>
<td>Acrophase (h:min)</td>
<td>01:52 ± 06:23</td>
<td>00:20 ± 03:49</td>
</tr>
</tbody>
</table>

± standard deviation
Heart Rate, Disorder and Periodicity in Postinfarct Patients

J Clin Basic Cardiol 2000; 3: 57

Appendix

Information Entropy determination

The Information Entropy (E) of a data series provides a quantitative measure of the amount of disorder contained in the sequence. Its evaluation depends on the normalized histogram of the data, i.e., the function f(x) which gives the frequency of occurrence of the value x in the data. The Information E is defined by the formula

\[ E = \sum f(x) \log f(x) \]

where the sum runs over all the values assumed by the data. The Information E measure is an adimensional value which depends on a probability distribution.

Rhythm analysis

The hourly-qualified mean values of the SRRI and the hourly-qualified values of the E were analyzed via the Cosinor method, according to Halberg et al. [16, 17], by using a three-component harmonic model with the period \( T = 24-h, 12-h \), and 8-h, respectively for the first, second and third harmonic wave. The three-component model was chosen in order to optimize the variance expressed by the periodic regression, covering the temporal data above and below their mean level for a different duration of time during the day-night period.

The three-component method applies the formula

\[ Y_t = M + A_1 \cos \left( \frac{2\pi}{\tau_1} t + \phi_1 \right) + A_2 \cos \left( \frac{2\pi}{\tau_2} t + \phi_2 \right) + A_3 \cos \left( \frac{2\pi}{\tau_3} t + \phi_3 \right) \]

Each parameter of the formula represents a rhythm property, i.e., \( M \) (mesor, acronym of midline estimating statistic of rhythm); the rhythm-adjusted mean; \( A \) (amplitude): the oscillatory extent from \( M \); \( \tau \): the fitted period; \( \phi \): a given temporal instant of the fitted period; \( \phi \): (acrophase): the temporal location of the oscillatory crest with a respect to a local reference time (which in case of a CR is the local midnight). The acrophase, computed in negative sexagesimal degrees (°), is transformed into hours and minutes, considering that 360° correspond to 24 hours, 15° to 1 hour, and 1° to 4 minutes. Importantly, the periodic regression method derives the rhythmic parameters via the best fitting sinusoidal wave (cosinorgram). The cosinorgram is fitted using the least squares method in order to minimize the sum of the squared residuals. The F ratio between the variance expressed by the regression and the variance of the raw discrete temporal data allows us to know whether or not the cosinorgram is characterized by an oscillation with an amplitude wide enough to reject the null-hypothesis of zero-amplitude at a significant p level of probability (p ≤ 0.05).

The three-component harmonic analysis was adapted to the hourly-qualified mean values of the SRRI (sec) and to the hourly-qualified values of the E (Units).

References


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