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Evidence that the information entropy estimating the nonlinear variability of human sinusal R-R intervals shows a circadian rhythm

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The present study tries to detect whether the nonlinear variability of human electrocardiographic sinusal R-R intervals exhibits a circadian rhythm (CR). The sinusal R-R intervals were provided by the Holter ECG of 10 (5M, 5F, 23–30 years old) clinically healthy volunteers.

Sinusal R-R intervals were analysed by measuring the information entropy (E) of their nonlinear variability each hour of the Holter recording. The hourly-qualified E measurements were analysed for CR via a three-component harmonic regression method.

Hourly-qualified values of sinusal R-R intervals were seen to exhibit a variability which oscillates with a significant CR. Hourly-qualified values of heart rate (HR) were also seen to show a variability corresponding to a significant CR. Finally, hourly-qualified measurements of E were found to show a variability oscillating with a significant CR.

Hourly-qualified measurements of E document that the nonlinear variability of the human sinusal R-R intervals is characterized by a time structure. The CR of E documents that such a time structure is the expression of a biological rhythm oscillating with a 24-h period. Accordingly, one can argue that the nyctohemeral variability of human sinusal R-R intervals results from a combination of chaos and periodicity. The chaotic component seems to be periodic, since it is structured in an oscillatory fashion over a 24-h scale. *J Clin Basic Cardiol 1999; 2: 275–8.*

Keywords: chaos, chronobiology, circadian rhythms, entropy, heart rate, Holter monitoring, nonlinear dynamics

Temporal duration of the sinusal R-R intervals of the human dynamic electrocardiogram (ECG) is known to follow a nonlinear pattern: the interbeat time changes unpredictably in its sequence [1–4]. However, human heart rate (HR) is also known to show a periodic pattern, since it is possible to mathematically fit a cyclic oscillation with a 24-h period, otherwise known as circadian rhythm (CR), to its nyctohemeral variability [5–9].

Because of this chaotic and periodic complexity in human HR variability during the day, the present study is devoted investigating whether the nonlinear pattern of the sinusal R-R intervals shows a CR.

Methods

Subjects

The study was carried out on 10 clinically healthy subjects, 5 males and 5 females, ranging in age from 23 to 30 years, who underwent a 24-h continuous ECG according to Holter technique, maintaining their habitual psychophysical daily activities unchanged. Their clinical health was ascertained via physical examination and laboratory data (blood pressure, urinalysis, chest X ray, conventional ECG etc.). Informed consent was obtained from all the investigated subjects.

Ambulatory ECG monitoring

The 24-h continuous ECG was performed on each subject by means of the ambulatory three-channel Holter recorder, manufactured by Rozinn (New York, USA), equipped with a computerized analysing system for automatically identifying the normal QRS complexes as templates, and measuring the R-R intervals occurring between two normal juxtaposed templates, giving a minimal *"a priori"* defined percentage difference of duration to the previous beat (sinusal R-R intervals). The monitored data were transferred to an IBM-compatible microcomputer for further analysis.

Analysis of the nonlinear variability in the sinusal R-R intervals

The time series of the sinusal R-R intervals were analysed each hour of the day in their nonlinear variability via the measurement of the information entropy (E), according to Shannon and Weaver [10] (see Appendix). The software was developed by the mathematician of our research group.

Time series analysis

Hourly-qualified values of the sinusal R-R intervals, HR and E for each subject (individual chronograms) were biometrically analysed to estimate their variability during the day (conventional parametric biometry) as well as for validating the hypothesis of a CR (rhythm biometry).

Conventional parametric biometry

The variability during the day of each individual chronogram (sinusal R-R intervals, HR and E) was conventionally estimated using the measurement of central location (mean) and dispersion (SD) applied to the daily (from 00:00 to 24:00), diurnal (from 07:00 to 23:00) and nocturnal (from 23:00 to 07:00) values.

Rhythm biometry

Each individual chronogram of the sinusal R-R intervals, HR and E was rhythmometrically analysed for CR via a three-component harmonic method of periodic regression (see Appendix).

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Results

Conventional parametric biometry

Hourly-qualified values of the sinusal R-R intervals, HR and E are displayed in Figure 1 as mean chronograms provided by all the investigated subjects.

From the graphs can be seen that each daily profile is characterized by a time-dependent variability.

The conventional parametric biometry of this variability is given in Table 1.

The table shows that the sinusal R-R intervals are at a maximum during the night, while both HR and E show their highest values during the diurnal part of the day. A Run test found the variability during the day of the sinusal R-R intervals, HR and E to be highly statistically significant ($p < 0.001$). Because of the significant nyctohemeral variability in each mean chronogram it was clear that the hourly-qualified values of the sinusal R-R intervals, HR and E were eligible for the rhythm biometry of a possible CR.

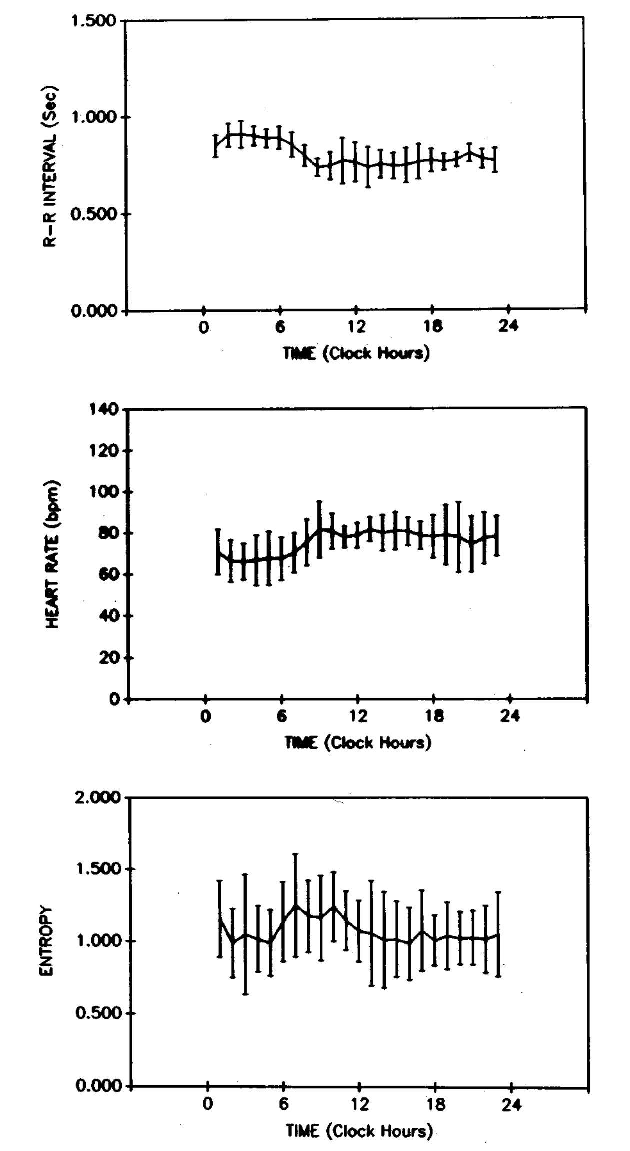

Figure 1. Mean chronograms provided by conventional parametric biometry applied to the hourly-qualified values of the sinusal R-R interval, heart rate and information entropy measurement in clinically healthy subjects

Rhythm biometry

A three-component harmonic curve-fitting of the above illustrated hourly-qualified profiles are displayed in Figure 2, as the mean of the cosinograms provided by all the investigated subjects.

From the graphs it can be derived that each 24-hour profile can be effectively approximated by a plurimodal curve having three oscillatory components.

The rhythmometric biometry of these oscillatory curves is displayed in Table 2.

It can be derived from the table that the profiles of the sinusal R-R intervals, HR and E show a significant CR, as it is proven by the overall P values of the multicomponent harmonic regression. It is important to stress that the oscillation characterized by a 24-h period was found to be the only harmonic component whose fluctuation was wide enough to reject the null-hypothesis of zero-amplitude at a probability of $p < 0.05$. According to the acrophases of the dominant circadian component it can be seen that the sinusal R-R intervals show a nocturnal crest, while both the HR and E show a diurnal periodic elevation.

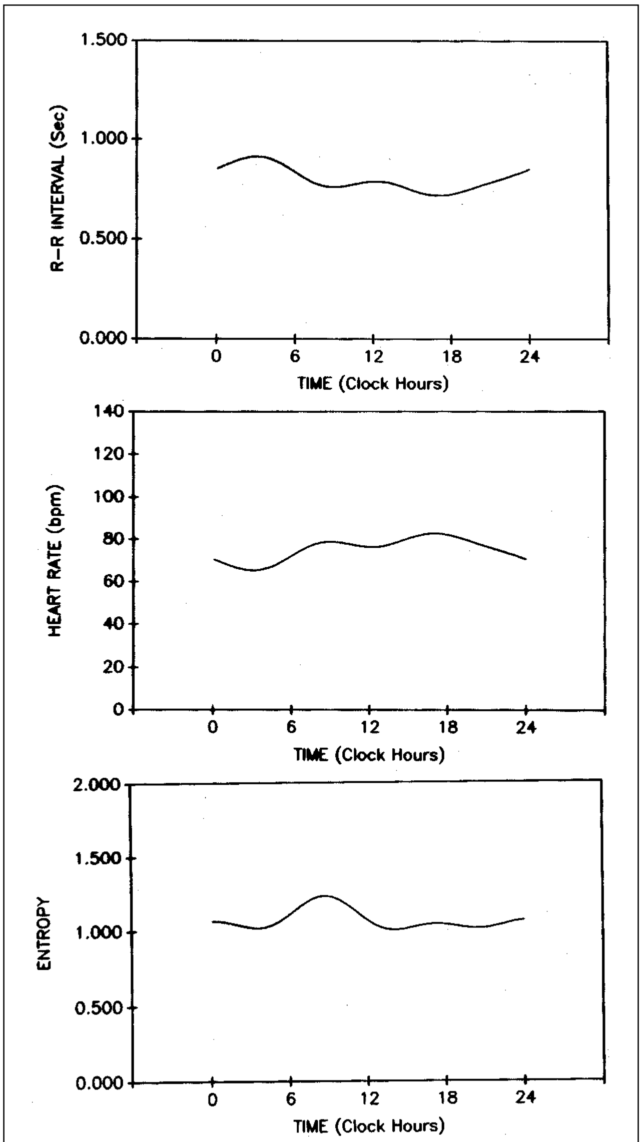

Figure 2. Mean cosinograms provided by the three-component harmonic method applied to the hourly-qualified values of the sinusal R-R interval, heart rate and information entropy measurement in clinically healthy subjects

Table 1. Conventional parametric biometry of the hourly-qualified values of sinusal R-R intervals, heart rate and entropy in clinically healthy subjects

	Nyctohemeral variability			
Variables	**Daily mean**	**Diurnal (D) mean**	**Nocturnal (N) mean**	**D-N mean difference**
R-R Interval (sec)	0.7990 ± 0.0595	0.7606 ± 0.0205	0.8586 ± 0.0506	-0.0980 ± 0.0390
HR (bpm)	75 ± 5	79 ± 2	70 ± 4	9 ± 2
Entropy	1.0726 ± 0.0779	1.0733 ± 0.0734	1.0715 ± 0.0844	0.0018 ± 0.0110

± Standard Deviation

Table 2. Rhythm biometry of the hourly-qualified values of sinusal R-R intervals, heart rate and entropy in clinically healthy subjects

			First harmonic component (24-h period)			Second harmonic component (12-h period)			Third harmonic component (8-h period)		
Variables	**Overall p**	**Mesor**	**p1**	**A_1**	**$\phi 1$**	**p2**	**A_2**	**$\phi 2$**	**p3**	**A_3**	**$\phi 3$**
R-R Interval (sec)	< 0.001	0.8011 ± 0.3162	< 0.001	0.0727 ± 0.0297	03:08 ± 00:28	= 0.144	0.0352 ± 0.0537	03:28 ± 01:52	= 0.621	0.0186 ± 0.0278	12:04 ± 03:40
HR (bpm)	< 0.001	75 ± 3	< 0.001	7 ± 3	15:04 ± 01:17	= 0.070	3 ±3	15:16 ± 05:34	= 0.634	1.64 ± 3	00:12 ± 11:00
Entropy	< 0.001	1.0709 ± 0.3162	= 0.008	0.0674 ± 0.0610	07:54 02:28	= 0.070	0.0522 ± 0.0357	17:28 ± 04:15	= 0.216	0.0421 ± 0.0304	01:52 ± 06:23

± Standard Deviation

Discussion

The present study formulated the hypothesis that the nonlinear variability of the sinusal R-R intervals might be characterized by a periodic pattern over the 24-h scale. Therefore, the time-qualified values of the sinusal R-R intervals were analysed in their nonlinear variability each hour of the day via the measurement of the information E. In this way the hourly-qualified estimates were tested for a significant CR.

The formulated hypothesis was confirmed in that the hourly-qualified values of E were found to show a variability during the day, which is the expression of a CR. To be exact, the three-component harmonic regression analysis fitted the hourly-qualified values of E optimally to a 24-h cosine curve, with a highly statistically significant oscillation.

How can a chaotic disorder which coexists with a periodic order be interpreted? Several mathematical and medical reports have already demonstrated that the systems characterized by periodic dynamics may well show a transition to chaos which depends on the 'complexity' of their oscillatory structure, given the initial conditions of their dynamics [11–25]. In line with this idea it can be inferred that the chaotic pattern of the sinusal R-R intervals might be a 'time-dependent repetitive phenomenon structured in fractals' which is bound to the complexity of the periodic mechanisms which physiologically regulate the circadian rhythmicity of human HR. The fractal scaling in heart rate variability is in somewhat considered [6, 26].

Assuming the chaos to be periodic in its within-day expression, how should the fact that the E of the sinusal R-R intervals shows a diurnal acrophase be explained? The interpretation can be given on a theoretical basis, considering that the HR within-day variability is regulated by parasympathetic and sympathetic mechanisms, which, in turn, show CRs whose acrophases are respectively nocturnal and diurnal [27–34]. Because of the specific circadian phase of oscillation in neurovegetative activity, it can be argued that the diurnal prominence of the circadian chaos for the sinusal R-R intervals might be dependent on the relative prevalence of the sympathetic tone. Such an adrenergic influence is plausible when considering that the sympathetic activity shows its periodic increase to be only located in the early morning hours.

Appendix

Determination of information entropy

The information entropy (E) of a sequence of data provides a quantitative measure of the amount of information contained in the sequence. Its evaluation depends on the normalized histogram of the data, ie, the function F(s) which gives the frequency of occurrence of the value *s* in the data. The information E is defined by the formula

$$E = \sum_s \mathrm{F}(s)\log[1/\mathrm{F}(s)]$$

where the sum runs over all the values given by the data. Information E measurement is a non-dimensional parameter which depends essentially on a probability.

Rhythm biometry

The three-component method of harmonic regression uses the formula

$$Y_{(t)} = M + \sum_{i=1}^{3} [A_i \cdot \cos(\omega_i \cdot t + \phi_i)]$$

Each parameter of the formula represents a rhythmic property, ie, M (mesor) is the rhythm-adjusted mean; A (amplitude) is the oscillatory extent from M; ω is the angular frequency given by 2π/τ (τ = oscillatory period); t is a given temporal instant of the oscillatory period; ϕ (acrophase) is the temporal location of the oscillatory crest with respect to a local reference time, which in the case of a CR (τ = 24-h) is the local midnight. The acrophase is computed in negative sexagesimal degrees (°), which can be transformed into hours and minutes in that 360° correspond to 24 hours, 15° to 1 hour, and 1° to 4 minutes. Importantly, the periodic regression method derives the rhythmometric parameters via the best fitting sinusoidal wave (cosinogram), using the least squares method in order to minimize the sum of the squared residuals [35, 36]. According to the F ratio between the variance expressed by the regression and the variance of the raw discrete temporal data, it is possible to see whether or not the fitted wave shows an oscillation whose amplitude is wide enough to reject the null-hypothesis of zero-amplitude at a significant P level of probability (p ≤ 0.05).

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