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Is a Reduced Entropy in Heart Rate Variability an Early Finding of Silent Cardiac Neurovegetative Dysautonomia in Type 2 Diabetes Mellitus?

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The present study estimates the entropy (E), say the amount of disorder, that is detectable in non-linear variability (NLV) of electrocardiographic sinus R-R intervals (SRRI) in apparently uncomplicated diabetic patients (DP) affected by type 2 diabetes mellitus (NIDDM). The aim is to detect whether a reduction of the expected disorder in heart rate (HR) variability (V) can be taken as an early finding of cardiac dysautonomia in type 2 DP. The SRRI were provided by the Holter ECG of 10 type 2 DP (5 M and 5 F, mean age = 41 ± 5 years), who were metabolically compensated, via a hypoglycaemic diet, and lacking of apparent clinical and instrumental signs of cardiac neurovegetative involvement. Control data were obtained by the Holter ECG of 10 clinically healthy subjects (CHS, 5 M and 5 F, mean age = 38 ± 6 years). The E in SRRI NLV was estimated per each hour of the Holter recording. The hourly-qualified series of SRRI, HR and E were, thus, analyzed via methods of conventional statistics and chronobiology, the latter ones being used for assessing whether or not a reduced disorder could depend on the disappearance of HR circadian rhythm (CR). Notwithstanding the comparability of the conventional and chronobiological estimates regarding both the SRRI and HR, the E was found to be significantly lower in its daily, diurnal and nocturnal mean level in type 2 DP in comparison with CHS. However, the hourly-qualified values of SRRI, HR and E were seen to maintain the expected CR. The reduced E in hourly-qualified series of SRRI suggests that a less pronounced disorder is detectable in HRV of type 2 DP. Importantly, such a reduced disorder seems not to be associated with the disappearance of HR CR, whose abolition is regarded to be a sign of an established cardiac neurovegetative complication in DP. Considering that the investigated DP were lacking of documentable signs of cardiac neuropathy, one can argue that the measurement of E in HRV might be considered as an early tool for detecting a silent cardiac neurovegetative dysautonomia complicating the NIDDM. *J Clin Basic Cardiol* 2001; 4: 289-94.

Key words: chaos; chronobiology; circadian rhythms; diabetes mellitus, electrocardiogram; entropy; heart rate, Holter monitoring; non-linear dynamics

A non-linear variability (NLV) is known to characterize the within-day pattern of sinus R-R intervals (SRRI) of human electrocardiogram [1-4]. Because of this non-linear pattern, it can be assumed that human heart rate (HR) shows in its within-day variability a certain amount of unpredictability, which can be defined "chaotic disorder".

It has been demonstrated that human HR is a haemodynamic parameter which shows the properties of a biological circadian rhythm [5-10]. Because of this periodic pattern, it can be argued that human HR shows in its 24-h variability a certain amount a predictability, which can be defined as "periodic order".

Methodologically, the chaotic disorder in a given non-linear series of experimental data can be investigated via several methods, which belong to the chaos mathematics. These methods include the information entropy (E) analysis which provides a quantitative estimate, whose value is positively related to the amount of unpredictable variation that is present in a given series under scrutiny. Therefore, the greater the estimated E, the greater the amount of disorder in a given biological phenomenon which is characterized by a NLV in its dynamic pattern.

Interestingly, our research group has demonstrated that the chaotic disorder in HR NLV is a phenomenon which is itself structured in a periodic fashion as a circadian rhythm [11]. Such a demonstration was given via a chronobiological analysis of the E values estimated on the SRRI per each hour of the day-night Holter monitoring.

Type 2 diabetes mellitus (NIDDM) is an endocrino-metabolic disease that is known to be complicated by disturbances in HRV, which can be taken as a finding of cardiac autonomic neuropathy [12-21]. The disturbances in HRV can be so marked that a relevant sign of an established diabetic cardiac neurovegetative dysfunction is the disappearance of HR circadian rhythm [10].

Because of the diabetic involvement of cardiac neurovegetative regulation, our research group found scientific interest in expanding the investigation on the E in NIDDM patients, who were lacking of apparent clinical and instrumental signs of cardiac dysautonomia (silent autonomic dysfunction), hypothesizing that a reduced disorder in HRV could document *per se* the beginning of the cardiac neurovegetative dysfunction, in the presence of a normal HR circadian rhythm.

Methods

Subjects and protocol

The study was carried out on 10 non-smoking diabetic patients (DP) affected by NIDDM (5 males and 5 females, mean age: 41 ± 5 years), whose diagnosis was performed via clinical examination and laboratory data. Importantly, these investigated DP were all ascertained not to show apparent clinical and instrumental findings of cardioneuropathy, cardiomyopathy and coronary ischaemic disease at the Holter ECG (time domain analysis: SDNN, SDANN, SDNNi,

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rMSSD, NN50, pNN50; frequency domain analysis: power spectral method for low- and high-frequency oscillatory components as relative indices of sympathetic and vagal activity; QT lengthening, etc.), echocardiography (M- and B-mode, colour-Doppler), cardiovascular tests (deep breathing, Valsalva manoeuvre, lying to standing, postural hypotension, tilt test), myocardial scintigraphy (^{123}I meta-iodobenzylguanidine [MIBG]; $^{99\text{m}}\text{Tc}$ methoxyisobutylisonitrile [$^{99\text{m}}\text{Tc}$ -MIBI]).

In addition, all the investigated DP were complying with the following criteria for inclusion, ie, normotension, normal microalbuminuria and renal function, non-glycosuria, non-ketonaemia, normoglycaemia via a hypocalbohydrate diet, normal glycated haemoglobin, abstinence from smoking, absence of psychoneurotic disturbances, including insomnia, eating and drinking disorders.

The control group was constituted by 10 sedentary non-smoking clinically healthy subjects (CHS), 5 men and 5 women (mean age: 38 ± 6 years), whose good health status was established via clinical examination and laboratory data.

Importantly, the results obtained by time domain analysis as well as frequency domain analysis were not significantly dissimilar in CHS and type 2 DP, with reference to the estimates given by the Task Force of the European Society of Cardiology, and North American Society of Pacing Electrophysiology [22].

All the participants volunteered with informed consent to the study. The investigation was performed in conformity to the principles outlined in the declaration of Helsinki.

Dynamic ECG monitoring

The variability in SRRI was investigated by means of a dynamic Holter ECG which was performed on an ordinary day of the week during the winter season. The ECG recorder was applied to each investigated subject at the same hour of the day (at 11:00), and removed twenty-four hours later. All the participants were requested to follow a protocol regarding the sleep-wake alternation and meal timing schedule. As a matter of fact, they were requested to wake up between 6:00 and 8:00 a. m., to go to sleep between 9:00 and 11:00 p. m., to have breakfast between 6:30 and 8:30 a. m., lunch between 12:00 and 2:00 p. m., and to have dinner between 7:30 and 9:00 p. m. Additionally, they were requested not to do relevant physical and mental efforts, not to abuse in eating and drinking.

The Holter ECG monitoring was performed by means of a 3-channel recorder, manufactured by Rozinn (Glendale,

NY 11385, USA). The monitored data were imported into an IBM-compatible microcomputer for their analysis, which was performed by means of a computerized analysing system, provided by the manufacturer, for measuring the temporal duration intercurring between two normal consecutive QRS templates (SRRI), given a minimal "a priori" defined percent difference of time versus the previous beat. The duration of SRRI, measured in seconds (sec), was averaged per each hour of the day-night time, in order to obtain its hourly-qualified mean values in each investigated subject. HR, estimated in beats per minute (bpm), was averaged per each hour of the day-night span, in order to obtain its hourly-qualified mean values in each investigated subject.

The analysis of the Holter ECG was performed all the times by the same person of our staff, in order to avoid the "inter-observer error". This person, however, was not involved in data analysis in order to operate in a "double blind" protocol.

Importantly, the results obtained by time domain analysis as well as frequency domain analysis of the Holter ECG were not significantly dissimilar in CHS and type 2 DP, with reference to the estimates given by the Task Force of the European Society of Cardiology, and North American Society of Pacing Electrophysiology [22].

Measurement of the hourly-qualified values of entropy

The SRRI measured in each hour of the day were analysed in their chaotic disorder via the measurement of the E according to Shannon and Weaver [23] (see Appendix) and therefore the hourly-qualified values of E were obtained in each subject.

Statistical analysis of the hourly-qualified series

The hourly-qualified mean values of SRRI and HR in each investigated subject were biometrically analyzed in their within-day variability (conventional parametric biometry) as well as in their CR (rhythm biometry). The same statistical procedure was applied to the individual hourly-qualified values of E.

Conventional parametric biometry

Each individual hourly-qualified series of SRRI, HR and E was conventionally analyzed for its within-day variability via the measures of central location (mean) and dispersion (SD) applied to the values from 00:00 to 24:00 (daily mean), from 7:00 a. m. to 11:00 p. m. (diurnal mean), and from 11:00 p. m. to 7:00 a. m. (nocturnal mean). The individual estimates were averaged per group.

Rhythm biometry

Each individual hourly-qualified series of SRRI, HR and E was rhythmometrically analyzed for its CR via a three-component harmonic method of periodic regression (see Appendix). The rhythmic estimates were averaged per group.

Results

Conventional parametric biometry

Figure 1 displays the hourly-qualified mean values (mean chronograms) of SRRI, HR and E estimated in CHS and DP.

The mean chronograms reveal that each 24-h profile, in each group, is characterized by a time-qualified variability.

Table 1 lists the mean estimates obtained by the conventional parametric

Table 1. Measurements of heart rate variability in 10 clinically healthy subjects (CHS) and 10 type 2 diabetic patients (DP)

Measurements	Units	CHS	DP	t test (p)
Time domain analysis				
RRmean	msec	836 \pm 89	811 \pm 69	0.492
SDNN	msec	133 \pm 31	116 \pm 23	0.181
SDANN	msec	114 \pm 30	104 \pm 17	0.371
SDSD	msec	37 \pm 19	40 \pm 15	0.700
cNN50	count	10.088 \pm 9.603	7.591 \pm 5.213	0.479
pNN50	%	10.47 \pm 9.51	7.78 \pm 5.23	0.443
rMSSD	msec	37 \pm 19	44 \pm 18	0.409
Triangular Index	-	36 \pm 11	32 \pm 7	0.345
TINN	msec	282 \pm 128	242 \pm 95	0.438
Log Index	-	-44 \pm 19	-42 \pm 23	0.834
Frequency domain analysis				
Total power	msec ²	4.141 \pm 1,697	2.866 \pm 2.006	0.142
LF power	msec ²	2.086 \pm 847	1.490 \pm 767	0.116
HF power	msec ²	1.309 \pm 485	1.217 \pm 221	0.592
LF power	u.n.	59 \pm 20	47 \pm 14	0.137
HF power	u.n.	37 \pm 11	38 \pm 8	0.819
LF/HF ratio	-	1.59 \pm 0.51	1.22 \pm 0.32	0.068

biometry on the within-day variability of the hourly-qualified values of SRRI, HR and E in CHS and DP.

The estimates show that the SRRI exhibit their highest duration during the night, in both the CHS and DP. Conversely, both the HR and E in CHS and DP exhibit their highest values during the diurnal part of the day. A *t* test for unpaired data found that the daily, diurnal and nocturnal mean values of E were significantly decreased in DP as compared to CHS. Importantly, such a significant difference was not detected in the statistical comparisons between the daily, diurnal and nocturnal mean values of SRRI and HR in CHS and DP.

Rhythm biometry

Figure 2 illustrates the three-component harmonic profiles (mean cosinograms) fitting the hourly-qualified values of SRRI, HR and E estimated in CHS and DP.

The mean cosinograms show that all the oscillatory curves exhibit a plurimodal waveform profile, which is composed by more than one undulatory crest.

Table 2 lists the estimates of the rhythmic properties of the three harmonic components which sustain the within-day variability of the hourly-qualified values of SRRI, HR and E, in both the CHS and DP.

The statistical significance of the overall P value reveals that each plurimodal waveform profile is an oscillation which represents a significant CR. The statistical significance of the P values of each fitted harmonic wave reveals that the oscillation characterized by a 24-h period is the only harmonic component whose fluctuation is wide enough to reject the zero-amplitude assumption at a probability level of $P \leq 0.05$, in both the CHS and DP. The timing of the acrophase of each one of these significant circadian waves reveals that the CR of SRRI exhibits a nocturnal crest, while the CR of HR and E exhibits a diurnal culmen, in both the CHS and DP.

A *t* test for unpaired data found that the circadian mesor, but not the circadian amplitude, of the E is significantly decreased in DP as compared to CHS. Conversely, no significant difference was detected between CHS and DP as far as the circadian mesors of SRRI and HR are concerned.

Discussion

Diabetes mellitus is known as a disease in which the cardiac autonomic activity is going to be progressively compromised. The diabetic cardiac dysautonomia usually shows a presymptomatic stage in which its presence is mainly documentable via measurements of HRV. Therefore, the 24-h Holter ECG

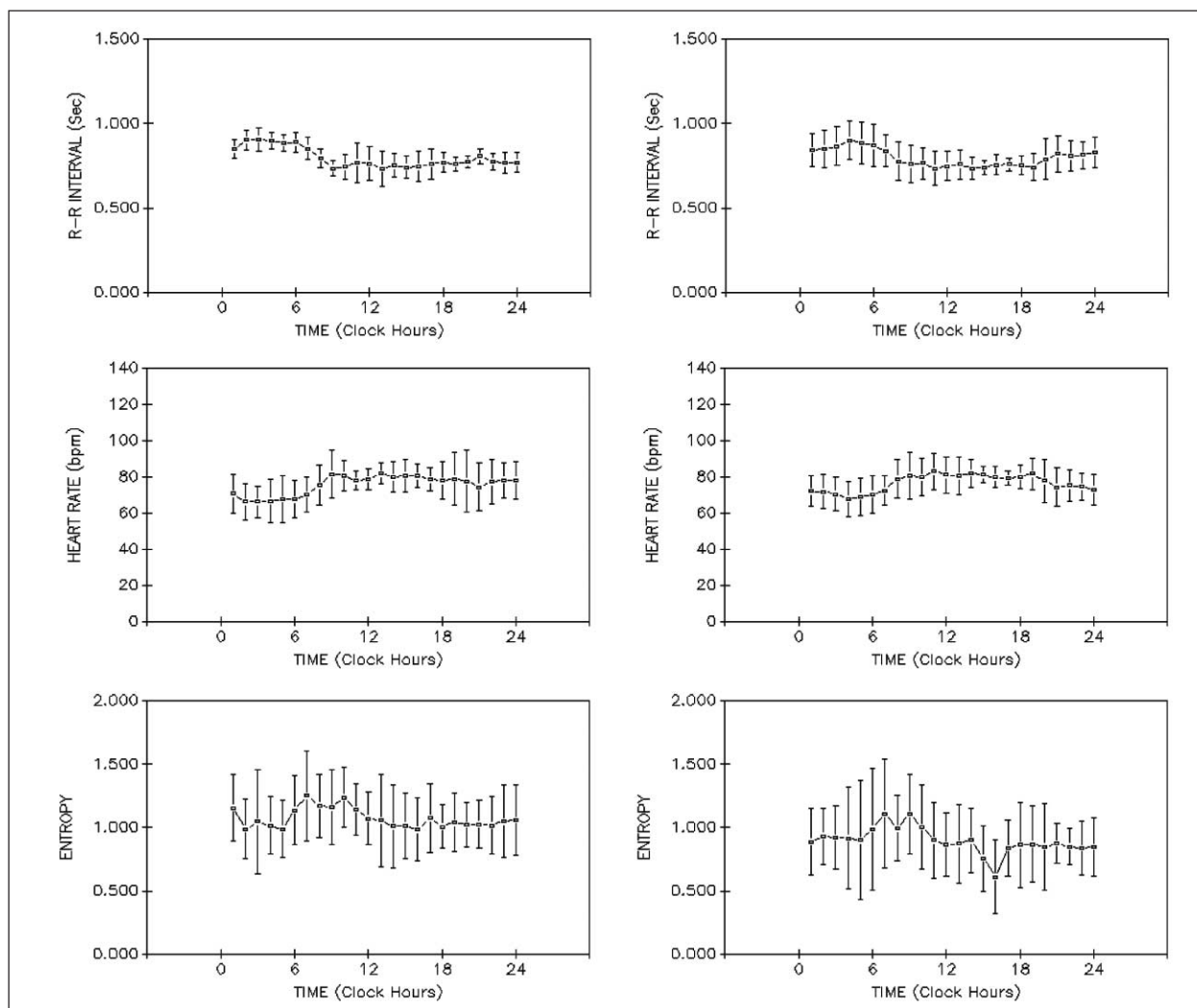


Figure 1. Within-day profiles of the hourly-qualified mean values (\pm SD, mean chronograms) of sinus R-R interval, heart rate and entropy in clinically healthy subjects (left panels) and patients affected by type 2 diabetes mellitus (right panels)

is investigated for this purpose via methods of time domain analysis and frequency domain analysis, which are applied to the SRRI measured over the day-night span (long-term approach) or during a given number of minutes (short-term approach), also to cover the entire period of recording [22]. The estimates repeated by short cycles of time over the 24-h span can be further assessed via chronobiological procedures in order to validate their circadian rhythmicity [7, 8, 11].

Several indices of HRV were found to be altered in presence of a diabetic cardiac neurovegetative involvement, which can be still asymptomatic from a clinical point of view. The mean HR was found to be increased [12, 14, 15]. The SDNN [20, 24–26] and SDANN [27] were found to be reduced. The cNN50 and pNN50 were found to be absolutely and percentually increased [26, 28, 29], as well as lacking of a circadian variation [28]. The rMSSD was found to show a substantial decrease [26], while the LF and HF components were found to be depressed in their power [21, 30–32], and lacking of a circadian variation [12].

It is important to stress that all the above-cited measurements are provided by methods of analysis which are particularly suitable to investigate the HRV as a phenomenon which belongs to the linear dynamics. With this respect, it must be emphasized that the sequence of human SRRI may be regarded as a phenomenon whose unpredictable disorder re-

flects the characteristics of a non-linear process [1–4]. Therefore, it is in principle likely that methods of non-linear dynamics might provide a better information for the physiological as well as clinical interpretation of HRV. In other words, it can be postulated that the methods of non-linear analysis might be more sensitive to detect alterations in the sequence of SRRI.

Methodologically, the methods which have been used for a quantitative description of non-linear processes include the measurement of entropy [11, 33–35]. Accordingly, the present investigation has used the E measurement with the aim of detecting whether or not its estimate is sensitive in detecting disturbances in HRV, when the time domain analysis and the frequency domain analysis both provide results that are not indicative for a silent diabetic cardiac neuropathy.

The present study has documented that the daily, diurnal and nocturnal level of E in NLV of SRRI shows a significant decrease in type 2 DP as compared to CHS. This circumstance is detectable even though the daily, diurnal and nocturnal mean levels of both the SRRI and HR results do not show a significant group-specific difference. Furthermore, the present study has documented that the reduction of E in DP is not attributable to the disappearance of HR CR.

It is convenient to repeat that the measurement of the E provides an index which decreases with the loss of complex-

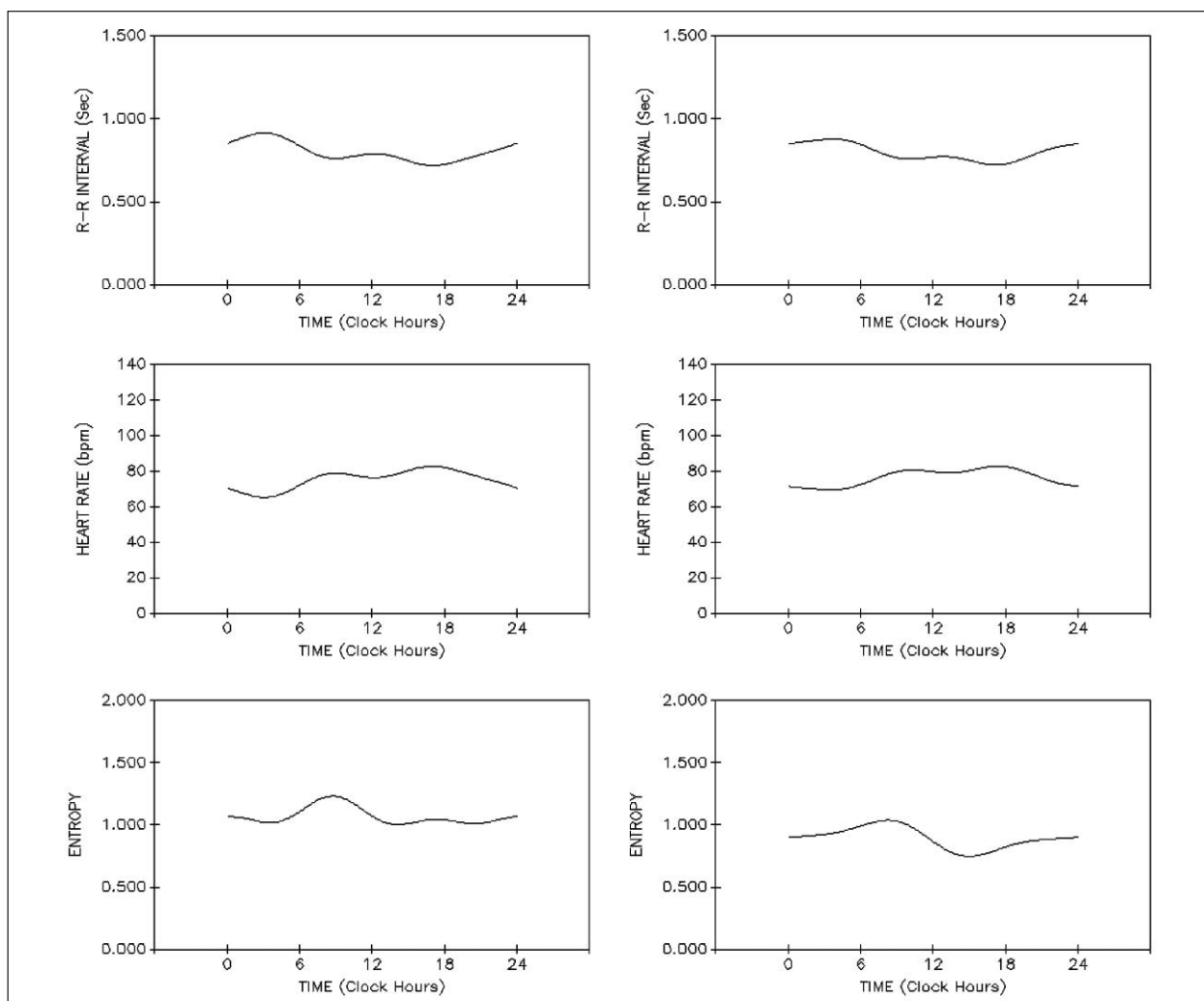


Figure 2. Within-day best-fitting (three-component) harmonic oscillations (mean cosinograms) of the hourly-qualified series of sinus R-R interval, heart rate and entropy in clinically healthy subjects (left panels) and patients affected by type 2 diabetes mellitus (right panels)

ity in NLV of a given dynamic phenomenon. In virtue of this informational meaning, the reduced E in NLV of SRRV can be taken as evidence convincing that the disorder in HRV is less pronounced in type 2 DP. Such a decomplexification of variability may be interpreted as a pathophysiological sign suggesting that the neurovegetative regulation of cardiac activity is disturbed as in the presence of a sympatho-adrenergic system which exerts its prevalence by reducing the amount of disorder that is expected in HRV.

It must be remarked that the linear methods of time domain analysis and frequency domain analysis all failed to detect the circumstance of a cardiac neurovegetative dysfunction

in DP investigated in the present study. Accordingly, it can be argued that a non-linear approach to the HRV via the E measurement may be regarded as a tool which is remarkably sensitive for detecting the beginning of a silent cardiac autonomic dysfunction in Type 2 DP.

Appendix

Information entropy measurement

The information entropy (E) is a method, which provides a quantitative measurement of the amount of information that is contained in a given temporal sequence of values. The amount of information is depending on the variability, which characterizes the values belonging to a given temporal sequence of data. The E measurement is equal to 0 when the time data series is constituted by a value, which repeats itself without showing a variation. If the time data series is constituted by values whose variation is not predictable, the E measurement is an estimate of the unpredictable information, say the disorder, that is contained in the NLV of that given data series.

Mathematically, the E measurement can be performed via a function $F(s)$ which provides the frequency of recurrence of the values within the data series under scrutiny. Therefore, the E measurement can be obtained by the formula

$$E = - \sum_s F(s) \log F(s)$$

the sum which runs over all the values of the time data series. The E measurement is related to the width of the normalized histogram representing the repartition of the values in their frequency.

Rhythm biometry

The three-component harmonic method of regression is based on the formula

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

where the parameters M, A and ϕ represent a given property of the rhythm, ie, M (mesor, acronym of *midline estimating statistic of rhythm*) is the rhythm-adjusted mean (mean oscillatory level); A (amplitude) is the oscillatory extent from M; ϕ (acrophase) is the temporal location of the oscillatory crest with a respect of a local reference time, which in case of a CR is the local midnight. Additionally, ω is the angular frequency given by $2\pi/\tau$, with τ which is the oscillatory period; t is a given temporal instant

Table 2. Conventional parametric biometry of the hourly-qualified values of sinusal R-R interval, heart rate and entropy in clinically healthy subjects (CHS) and diabetic patients affected by type 2 diabetes mellitus (DP)

Estimates	Groups	Variables		
		R-R interval (sec)	Heart rate (bpm)	Entropy
Daily mean	CHS	0.7990 ± 0.0595	75 ± 5	1.0726 ± 0.0779
	DP	0.7979 ± 0.0513*	76 ± 5*	0.8959 ± 0.0999†
Diurnal mean	CHS	0.7606 ± 0.0205	79 ± 2	1.0733 ± 0.0734
	DP	0.7680 ± 0.0530*	79 ± 5*	0.8919 ± 0.1030†
Nocturnal mean	CHS	0.8586 ± 0.0506	70 ± 4	1.0715 ± 0.0844
	DP	0.8578 ± 0.0268*	71 ± 2*	0.9039 ± 0.0448†

± standard deviation; * p > 0.05 † p < 0.001 for the statistical comparisons, via t test, between the two groups

Table 3. Rhythmic biometry of the hourly-qualified values of sinusal R-R interval, heart rate and entropy in clinically healthy subjects (CHS) and diabetic patients affected by type 2 diabetes mellitus (DP)

Estimates	Groups	Variables		
		R-R interval	Heart rate	Entropy
Overall P	CHS	< 0.001	< 0.001	< 0.001
	DP	< 0.001^	< 0.001^	< 0.001^
Mesor	CHS	0.8011 ± 0.0316	75 ± 3	1.0709 ± 0.0316
	DP	0.7977 ± 0.0143*	76 ± 2*	0.8959 ± 0.0483 [£]
<i>First harmonic component (24-h period)</i>				
P	CHS	< 0.001	< 0.001	= 0.008
	DP	< 0.001^	< 0.001^	< 0.001^
Amplitude	CHS	0.0727 ± 0.0297	7 ± 3	0.0674 ± 0.0610
	DP	0.0653 ± 0.0201*	6 ± 2*	0.1009 ± 0.0632*
Acrophase	CHS	03:08 ± 00:28	15:04 ± 01:17	07:54 ± 02:28
	DP	02:44 ± 01:08^	14:32 ± 01:12^	07:36 ± 02:32^
<i>Second harmonic component (12-h period)</i>				
P	CHS	= 0.144	= 0.070	= 0.070
	DP	= 0.486^	= 0.442^	= 0.116^
Amplitude	CHS	0.0352 ± 0.0537	3 ± 3	0.0522 ± 0.0357
	DP	0.0187 ± 0.0485*	2 ± 4*	0.0600 ± 0.0300*
Acrophase	CHS	03:28 ± 01:52	15:16 ± 05:34	17:28 ± 04:15
	DP	02:24 ± 09:52^	14:32 ± 01:12^	17:04 ± 01:44^
<i>Third harmonic component (8-h period)</i>				
P	CHS	= 0.621	= 0.634	= 0.216
	DP	= 0.595^	= 0.651^	= 0.160^
Amplitude	CHS	0.0186 ± 0.0278	2 ± 3	0.0421 ± 0.0304
	DP	0.0160 ± 0.0489*	1 ± 4*	0.0200 ± 0.0300*
Acrophase	CHS	12:04 ± 03:40	00:12 ± 11:00	01:52 ± 06:23
	DP	15:36 ± 11:36^	04:40 ± 12:52^	05:04 ± 07:40^

Mesor and amplitude given in seconds for R-R interval, in beats / minute for heart rate; acrophase given in hours:minutes; ± standard deviation; * p > 0.05 [£] p = 0.002 for the comparisons via t test between the groups; ^ t test not applicable

of the oscillatory period. The acrophase is provided in negative sexagesimal degrees ($^{\circ}$), which can be transformed into hours and minutes considering that 360° correspond to 24 hours, 15° to 1 hour, and 1° to 4 minutes. The periodic regression method computes the rhythmometric parameters by means of the best fitting oscillatory wave (cosinogram), which is found by using the least squares method for minimizing the sum of the squared residuals [36, 37]. The significance of the F ratio, between the variance expressed by the regression and the variance of the raw discrete temporal data, provides the level P of probability with which the oscillation has rejected the null-hypothesis of zero-amplitude. Therefore, a $P \leq 0.05$ demonstrates that the oscillatory curve has fitted data which are arranged in a periodic fashion to indicate a significant CR.

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