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Reduced Disorder in Heart Rate Variability as an Early Finding of Cardiac Involvement in Steinert's Disease: Evidence Provided by the Estimation of Entropy on the Hourly-Qualified Sinusal R-R Intervals

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The present study tries to compare the disorder in nonlinear variability of electrocardiographic sinusal R-R intervals (SRRI) in clinically healthy subjects (CHS) and patients affected by Steinert's disease (myotonic dystrophy, MD) in its early stage. The aim is to detect whether a reduced disorder in heart rate (HR) variability might represent an early finding of cardiac involvement in MD.

The SRRI were provided by the Holter ECG of 15 MD patients (5 males and 10 females, mean age = 40 ± 7 years) at the early stage of their disease, who were lacking documentable signs of cardiac involvement, including bradycardia. The control data were obtained by the Holter ECG of 10 CHS (5M, 5F, mean age = 38 ± 6 years). The disorder in SRRI nonlinear variability was estimated by measuring the Entropy (E) per each hour of the Holter recording. The hourly-qualified series of SRRI, HR and E were thus analyzed using methods of conventional statistics and chronobiology, the latter ones being used for validating and quantifying the circadian rhythm (CR).

Despite the comparability of the estimates regarding both the SRRI and HR, the E was found to be significantly decreased in its daily, diurnal and nocturnal mean level in MD patients as compared to CHS. Notwithstanding that the E was seen to maintain in its hourly-qualified values a significant CR. The E, however, was found to exhibit a significant reduction in the entity of its circadian oscillatory mean level.

The reduced E in sinusal SRRI is evidence suggesting that a less pronounced disorder is detectable in HR variability of MD patients at the early stage of their disease. Given the fact that the entropic decrease is detectable: 1. in the absence of significant changes for the conventional and rhythmic estimates of SRRI and HR, and 2. in the absence of clinical and instrumental signs of cardiomyopathy, it can be argued that the reduction of the expected disorder in HR variability can be taken as an early finding of cardiac involvement in Steinert's disease. *J Clin Basic Cardiol 2001; 4: 67–72.*

Key words: chaos, chronobiology, circadian rhythms, electrocardiogram, entropy, heart rate, Holter monitoring, nonlinear dynamics, Steinert's disease.

The sinusal R-R intervals (SRRI) of human electrocardiogram (ECG) are known to follow a nonlinear variability (NLV), their interbeat durations changing unpredictably over the 24-h-scale [1–4]. Because of this, human heart rate (HR) is considered to be a dynamic phenomenon which is physiologically characterized by a temporal disorder, namely a temporal "chaos", in its within-day variability.

A consistent body of research demonstrated that human HR shows the properties of a circadian rhythm (CR), its intradaily pattern being mathematically approximable by a waveform profile whose significant oscillation has a period of a day-night cycle [5–9]. Because of this, human HR is regarded as a phenomenon which is additionally characterized by a temporal order, namely a "periodic order", in its physiologic intradiem variability.

Taking into consideration the chaotic and periodic complexity, our research group demonstrated that the disorder in SRRI variability is a phenomenon which is structured in a periodic fashion, being itself the temporal expression of a CR [10]. The demonstration was provided by the chronobiological analysis applied to the estimates of Information Entropy (E) measured on the SRRI, for each hour of the day-night period. As a matter of fact, the E is an index whose entity is positively related to the amount of variation that is present in a given historical (temporal) series of experimental data. Assuming the data show an unpredictable magnitude in their sequence, it can be argued that the estimated E reflects the complexity of the unpredictable variability, say disorder, in that given temporal series. Therefore, the greater the estimated E, the greater the amount of temporal disorder in a given dynamic phenomenon characterized by a NLV in its temporality.

Steinert's disease (myotonic dystrophy, MD) is a neuromuscular disease that is known to be progressively associated with disturbances in HR [11–19]. Notwithstanding that, our research group was able to demonstrate that HR still maintains its CR in MD patients who have not yet developed arrhythmias [20].

Because of this periodic pattern in daily HR, our research group found scientific interest in expanding the investigation on the E of SRRI variability in patients affected by MD at the early stage of its clinical manifestation. The aim is to detect whether or not the amount of disorder in SRRI variability can in advance suggest a cardiac involvement before the occurrence of cardiac conduction defects, cardiac rhythm disturbances (including bradycardia), cardiac muscle impairment, being detectable via electrocardiography and echocardiography.

Materials and Methods

Subjects

The study was carried out on 15 patients affected by MD (5 males and 10 females, mean age: 40 ± 7 years), whose diag-

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nosis was performed via clinical examination and genetic findings with familiarity and CTG trinucleotide repeat expansion positive for Steinert's disease. The severity of their disease was established on the basis of the ability to perform the motor activities that can be limited by the neuromuscular disablement. Importantly, they were all classified as belonging to the "grade 1" of the disease, being affected by a mild neuromuscular deficit. Importantly, none of the investigated MD patients was presenting documentable signs of cardiomyopathy at the Holter ECG and echocardiography. In particular, they were not presenting abnormalities in cardiac function such as conduction defects (ie, atrioventricular and/ or intraventricular conduction delay), rhythm disturbances (ie, supraventricular and/or ventricular arrhythmias), muscle involvement (ie, cardiomyopathy with or without heart failure). In addition to the absence of relevant signs of cardiomyopathy, there were further criteria for exclusion, ie, abnormalities in blood pressure, metabolic disorders, abnormal anxiety, manifest depression, persistent insomnia. Heavy drinkers and smokers were also excluded by the protocol. Institutionalized MD patients were not recruited.

The control group was constituted by 10 sedentary 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. This control group matched with the MD group in age.

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 (see below), which was performed in all the participants on an ordinary day of the week. The ECG Holter was applied to each subject at the same hour of the day, ie at 11:00, and removed twenty-four hours later. All the participants were requested to follow a common protocol concerning the sleep-wake alternation, meal timing schedule and diurnal activity. As a matter of fact, they were requested to wake up from 06:00 to 08:00, to go to sleep from 21:00 to 23:00, to have breakfast, lunch and dinner, respectively, from 06:30 to 08:30, from 12:00 to 14:00, from 19:30 to 21:00. Additionally, they were requested not to do extraordinary physical and mental efforts, not to abuse food, alcohol, coffee, caffeinated beverages, mineral water and dietary salt.

The ECG monitoring was performed by means of a 3-channel Holter recorder, manufactured by Rozinn. The monitored data were transferred and stored in an IBM-compatible microcomputer for their further analysis. The micro-computer was implemented by a computerized analysing system, provided by the manufacturer, for measuring the R-R duration occurring between two normal consecutive QRS

 Table 1. Echocardiographic findings in clinically healthy subjects (CHS)

 and Steinert's patients (SP) investigated in this study

| Estimates | | G | Groups | | | |
|------------------------------------|------------------------------------|--|--|--|--|--|
| | | CHS | SP | | | |
| LAD DLVD SLVD LVM LVFS | (mm) (mm) (mm) (g) (%) | $\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$ | $\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$ | | | |

 \pm : Standard Deviation; LAD: left atrial diameter; DLVD and SLVD: diastolic and systolic left ventricular diaineters; LVM: left ventricular mass, LVFS: left ventricular fractional shortening. *: p > 0.05 for the comparisons via t test between the groups

templates (SRRI), given a minimal "a priori" defined percent difference of duration versus the previous beat. The duration of SRRI was measured in seconds (sec) and averaged for each hour of the day-night time in order to obtain its hourly-qualified mean values in each investigated subject. HR was measured in beats per minute (bpm) and averaged for each hour of the day-night span, in order to obtain the hourly-qualified mean values in each investigated subject. The analysis of the Holter ECG was performed every time by the same person of our staff, in order to avoid the "inter-observer error". This person was, however, not involved in the echocardiographic investigation or data analysis in order to operate in a "double blind" protocol.

Echocardiography

The echocardiographic examination was performed using a Hewlett-Packard Sonos 2000 ultrasound imaging system with a 2.0–2.5 MHz transducer. All MD patients and control subjects were submitted to M-mode and two dimensional echocardiography. Left ventricular mass was calculated by M-mode measurements at end-diastole by Penn conventions. Left ventricular fractional shortening was determined according to Simpson's formula. In order to avoid the "inter-observer error", the echocardiographic examination was performed every time by a given person of our staff. To operate in a "double blind" protocol, this colleague was, however, not involved in Holter ECG or data analysis.

Table 1 displays the comparability of the echocardiographic findings in groups investigated, a prerequisite for validating the hypothesis of the study.

Analysis of the Hourly-Qualified Estimates of Entropy

The SRRI measured in each hour of the day were analysed in the disorder of their NLV, via the estimation of the E, according to Shannon and Weaver [21] (see Appendix). Doing so, it has been possible to obtain the estimate of the hourly-qualified values of E in each subject.

Analysis of the Hourly-Qualified Series

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

Conventional Parametric Biometry

Each individual hourly-qualified series of SRRI, HR and E was conventionally estimated for its within-day variability via the measures 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. The individual estimates were averaged per group.

Rhythm Biometry

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

Results

Conventional Parametric Biometry

The hourly-qualified series of SRRI, HR and E in CHS and MD patients are displayed in Figure 1, as the mean chronograms provided by all the investigated individuals of each group. From the iconography, it can be derived that each 24-h profile, in each group, is characterized by a time-qualified variability.

The conventional parametric biometry for the within-day variability of the hourly-qualified values of SRRI, HR and E in CHS and MD patients is displayed in Table 2.

From the estimates it can be seen that the SRRI, in both the CHS and MD patients, show their highest duration during the night. In addition, it can be realized that both the HR and E, in both the CHS and MD patients, exhibit their highest values during the diurnal part of the day.

Importantly, a *t* test for unpaired data found the daily, diurnal and nocturnal values of E to be significantly decreased in MD patients as compared to CHS. No significant difference was detected in the statistical comparisons for the daily, diurnal and nocturnal mean values of SRRI and HR between MD patients and CHS.

Rhythm Biometry

The three-component harmonic profiles of the above-illustrated chronograms are displayed in Figure 2, as the mean cosinorgrams provided by all the investigated subjects in each group.

From the iconography, it can be derived that each oscillatory curve is effectively a plurimodal waveform profile which shows more than one undulatory component.

The rhythm biometry of the three harmonic components, which modulate each of the plurimodal oscillations, is displayed in Table 3.

From the overall P values, it can be realized that the plurimodal waveform profile fitting the SRRI, HR and E hourlyqualified values is an oscillation which represents a significant CR in both the CHS and MD patients. From the P values of each fitted harmonic wave, it can be derived that the oscillation characterized by a 24-h period is the only harmonic component whose fluctuation is wide enough to reject the



Figure 1. Hourly-qualified values (chronograms) of sinusal R-R intervals, heart rate and entropy in clinically healthy subjects (left panels) and patients affected by early-stage Steinert's disease (right panels).

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Figure 2. Three-component best-fitting harmonic oscillations (cosinograms) for the hourly-qualified values of sinusal R-R intervals, heart rate and entropy in clinically healthy subjects (left panels) and patients affected by early-stage Steinert's disease (right panels).

null-hypothesis of zero-amplitude at a probability of P < 0.05 in both the CHS and MD patients. From the acrophases of these significant circadian components, it can be said that the CR of SRRI shows a nocturnal crest in both the CHS and MD patients. Additionally, it can be seen that the CR of HR and E shows a diurnal crest in both the CHS and MD patients.

Importantly, a *t* test for unpaired data found the circadian mesor of E to be significantly decreased in MD patients as compared to CHS. No significant difference was, however, detected in the statistical contrasts for the circadian mesors of SRRI and HR between MD patients and CHS.

Discussion

The present study documented that the E in NLV of SRRI shows a daily, diurnal and nocturnal mean level which is lower in MD patients as compared to CHS. Such a reduction

occurs even though the daily, diurnal and nocturnal mean levels of both the SRRI and HR are not significantly different in MD patients as compared to CHS.

It is important to realize that the reduction of E in MD patients is not supported by an impairment in the CR of SRRI and HR. As a matter of fact, the within-day variability of SRRI and HR was found to show a significant CR in both the MD patients and CHS. Furthermore, the CR of SRRI and HR in MD patients was found to exhibit rhythmic characteristics that are superimposable on those measured in CHS. Accordingly, it can be said that the reduction of E in NLV of SRRI is a finding which can be detected in early stage MD patients when the dynamic ECG appears not to show disorders in HR.

It is important to remark that the E is an index whose entity increases in direct relation with the complexity in the variability of a given nonlinear dynamic phenomenon. Therefore, the E is an index which can be taken as a measure of the amount of disorder in NLV of such an event. The higher the E, the greater the disorder, and vice versa. Taking such a meaning into consideration, it can be said that the reduced E in NLV of SRRI is evidence showing that the disorder in cardiac pacing is less pronounced in MD patients who are at the early stage of their disease. Therefore, the reduced disorder in SRRI can be taken as an early signal of cardiac involvement in MD patients, considering that a less pronounced complexity in HR variability is regarded as a pathological condition which is associated with an increased risk of sudden death [2, 3, 22, 23].

Accordingly, it can be suggested that the estimation of E on the SRRI of a 24-h dynamic ECG can be taken as a tool for revealing an initial involvement of the heart in MD patients, even though the Holter ECG and echocardiography appear to show physiological patterns. Such a decreased disorder in SRRI variability could be a signal that the neurovegetative control of the cardiac pacing is going to be compromised by the disease. With respect to this, it must be emphasized that some investigations have clearly documented that the sympathetic and parasympathetic regulation of HR may be altered in MD patients [24, 25]. The question is whether or not the initial derangement in the neurovegetative control of cardiac pacing might be itself regarded as an early sign of the cardiomyopathy which develops in Steinert's disease.

Appendix

Information Entropy Determination The Information Entropy (E) of a time data series provides a

Table 2. Conventional parametric biometry of the hourly-qualified values of sinusal R-R intervals, heart rate and entropy in clinically healthy subjects (CHS) and Steinert's patients (SP)

| Fatimataa | Crowno - | Variables | | |
|-----------------------|----------------------|--|--------------------------|---|
| Estimates | Groups | R-R intervals (sec) | Heart Rate (bpm) | Entropy |
| Daily Mean | CHS | $0.7990\ \pm 0.0595$ | 75 ±5 | 1.0726 ±0.0779 |
| | SP | 0.7977 ± 0.0781* | $79 \pm 7*$ | $0.9854 \pm 0.0885^{\dagger\dagger}$ |
| Diumal Mean | CHS SP | $\begin{array}{l} 0.7606 \ \pm \ 0.0205 \\ 0.7503 \ \pm \ 0.0409^{\star} \end{array}$ | $79 \pm 2 \\ 83 \pm 4^*$ | $\begin{array}{c} 1.0733 \pm 0.0734 \\ 1.0025 \pm 0.0906^{\dagger} \end{array}$ |
| Nocturnal Mean | CHS SP | $\begin{array}{l} 0.8586 \ \pm \ 0.0506 \\ 0.8925 \ \pm \ 0\text{-}3833^{*} \end{array}$ | $70 \pm 4 \\ 70 \pm 3^*$ | $\begin{array}{c} 1.0715 \pm 0.0844 \\ 0.9512 \pm 0.0729^{\$} \end{array}$ |
| \pm Standard Deviat | tion; * $p > 0.05$; | †: p < 0.05; †† p = 0.02; 1 | : p < 0.001 for t | he comparisons via |

 Table 3. Rhythmic biometry of the hourly-qualified values of sinusal R-R intervals, heart rate and entropy in clinically healthy subjects (CHS) and Steinert's patients (SP)

| Estimates | Groups | Variables | | | | | |
|---------------------|---------------------------------------|---|---|---|--|--|--|
| | | R-R intervals | Heart Rate | Entropy | | | |
| Overall P | CHS SP | < 0.001 < 0.001^ | < 0.001 < 0.001^ | < 0.001 < 0.001 ^ | | | |
| Mesor | CHS SP | $\begin{array}{c} 0.8011 \ \pm 0.0316 \\ 0.7977 \ \pm 0.0255^{*} \end{array}$ | 75 ±3 79 ±2* | $\begin{array}{c} 1.0709 \pm 0.0316 \\ 0.9854 \pm 0.0425^{\pounds} \end{array}$ | | | |
| First harmonic co | omponent (24-h-pe | eriod) | | | | | |
| Ρ | CHS SP | < 0.001 < 0.001 | < 0.001 < 0.001 ^ | = 0.008 < 0.001 ^ | | | |
| Amplitude | CHS SP | $\begin{array}{r} 0.0727\ \pm\ 0.0297\\ 0.1017\ \pm\ 0.0363^{*} \end{array}$ | 7 ±3 9 ±3* | $\begin{array}{c} 0.0674 \pm 0.0610 \\ 0.1026 \pm 0.0603^{*} \end{array}$ | | | |
| Acrophase | CHS SP | $\begin{array}{r} 03:08\ \pm\ 00:28\\ 03:28\ \pm\ 00:20^{\circ} \end{array}$ | 15:04 ±01:17 15:20 ±00:20 [^] | 07:54 ±02:28 08:24 ±00:36 [^] | | | |
| Second harmoni P | c compounts (12-I CHS SP | n period) = 0.144 = 0.252^ | = 0.070 = 0.318 [°] | = 0.070 = 0.566 [^] | | | |
| Amplitude | CHS SP | $\begin{array}{r} 0.0352 \ \pm \ 0.0537 \\ 0.0386 \ \pm \ 0.0873^{\star} \end{array}$ | 3 ±3 3 ±8* | 0.0522 ±0.0357 0.0287 ±0.1029* | | | |
| Acrophase | CHS SP | $\begin{array}{r} 03:28 \ \pm \ 01:52 \\ 04:16 \ \pm \ 02:12 \\ \end{array}$ | 15:16 ±05:34 16:16 ±02:28 [^] | 17:28 ±04:15 15:25 ±03:24 [^] | | | |
| Third harmonic c | Third harmonic component (8-h-period) | | | | | | |
| Ρ | CHS SP | = 0.621 = 0.957^ | = 0.634 = 0.977^ | = 0.216 = 0.955 [°] | | | |
| Amplitude | CHS SP | $\begin{array}{r} 0.0186 \ \pm \ 0.0278 \\ 0.0071 \ \pm \ 0.0931 \end{array}$ | 2 ±3 1 ±8* | 0.0421 ±0.0304 0.0083 ±0.1025* | | | |
| Acrophase | CHS SP | $\begin{array}{r} 12:04 \ \pm \ 03:40 \\ 16:56 \ \pm \ 12:52^{\circ} \end{array}$ | 00:12 ±11:00 05:09 ±17:48 [^] | 01:52 ±06:23 04:24 ±12:32 [^] | | | |

Mesor and Amplitude gived in seconds, for R-R intervals, in beat minute for heart rare; Acrophase given in hour:minutes; \pm : Standard Deviation. * p > 0.05; [£]: p = 0.002; for the comparisons via *t* test between the groups; *t* test not applicable. quantitative measure of the amount of information contained in a given temporal sequence of values. The amount of information is directly related to the variability of values which constitute the temporal sequence of data. As a matter of fact, the E that equals 0 demonstrates that the time data series is constituted by a value which repeats itself in its entity without showing a temporal variability. Importantly, if the time data series is composed of values whose entity is not predictable in its consecutive occurrences, the E can be regarded as a measure of the NLV existing in that given data series. In other words, the E can be described as a measure of the disorder that characterizes a nonlinear

series of temporal data [26]. Mathematically, the estimation of the E is provided by a function F(*s*) which gives the frequency of occurrence of the values within the data series, being defined by the formula

$$E = -\sum_{s} F(s) \log F(s)$$

where the sum runs over all the values that compose the time data series. The estimation of the E is related to the width of the normalized histogram which represents the repartition of the values in their frequency.

Rhythm Biometry

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

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

in which each parameter represents a rhythmic property, ie, M (mesor) is the rhythm-adjusted mean (mean level of the oscillation); A (amplitude) is the oscillatory extent from M; ω is the angular frequency given by 2π /TAU (TAU = 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 case of a CR (TAU = 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 (cosinorgram), using the least squares method, in order to minimize the sum of the squared residuals [27, 28]. 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 know 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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