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Time irreversibility of heart rate oscillations in newborns – Does it reflect system nonlinearity?

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ABSTRACT

The aim of our research was to find out if the time irreversibility as a sign of specific class of nonlinear dynamics is present even in the newborn's heart rate oscillations. Multiscale irreversibility indices (Porta's index *P%*, Guzik index *G%* and Ehlers index *E*) of the heart rate signals were computed in 20 healthy neonates. The presence of system nonlinearity was assessed by surrogate data analysis. The results of our analysis revealed asymmetrical nature of heart rate oscillations present in the majority of neonatal heart rate recordings. Moreover, time irreversibility index *P%* was able to detect shift of sympathovagal balance toward sympathetic dominance in newborns. Our findings support the concept of nonlinearity as a universal feature of the biological control system even in the early stage of the system maturation. This finding supports the application of nonlinear methods to heart rate variability analysis.

1. Introduction

Cardiovascular system represents a very precisely and promptly controlled physiological system of the human body. Regulatory mechanisms maintaining the optimal cardiovascular system function are very complex and aimed to adequately react to quickly changing needs of the organism. The instantaneous "beat-to-beat" modulation of cardiovascular parameters is provided mainly by the autonomic nervous system (ANS). Autonomic cardiovascular control is then reflected in the spontaneous fluctuations of the cardiac cycle duration – heart rate variability (HRV) – and its analysis can provide useful information about cardiovascular system autonomic regulation [1–6].

The cardiovascular control of the newborns has its specific features and limits, as the feedback and feedforward mechanisms enabling optimal control of the heart are yet not fully developed. Therefore, HRV analysis can represent a useful tool for the evaluation of the degree of autonomic nervous system maturation in the infants [7–11].

Heart rate variability has been conventionally analyzed by linear methods in time and frequency domains [12]. However, cardiac rhythm originates from sinoatrial node controlled by numerous nonlinear mechanisms operating on the basis of feedback loops with different time delays. The nonlinear nature of these interacting physiological systems, influencing each other, calls for the nonlinear analysis which can be more suitable, precise and potentially more sensitive than linear analysis as it covers complex dynamics of the heart rate regulation more appropriately [13–17].

Time irreversibility or time asymmetry is a recently described phenomenon in adult HRV characterized by faster increase and slower decrease in heart rate signal and it was found to be sensitive to sympathovagal balance changes [2,18]. A signal is said to be time irreversible if its statistical properties change after its time reversal. Time irreversibility is specific for nonequilibrium systems [19] and its extensive presence in cardiovascular signals in adults results from the complexity of the highly adaptable cardiovascular control system. It is not well known whether this phenomenon is present already in young children and even in newborns. The aim of this study was to analyze heart rate time irreversibility in a group of healthy full-term newborns. In addition, we used irreversibility analysis together with surrogate data approach to detect the presence of cardiac rhythm control system nonlinearity in newborns.

2. Methods

2.1. Subjects

Twenty healthy full-term eutrophic infants (11 female, 9 male, gestational age 39 ± 1 weeks, birth weight: 3326 ± 300 g)

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underwent the recording of spontaneous heart rate oscillations 48–72 hours after birth. Into our study, only spontaneously delivered eutrophic newborns with a 1-minute Apgar score >7, and 5-minute Apgar score >8 were included. The newborns with inappropriate postnatal adaptation, perinatal infections, congenital abnormalities and those with hyperbilirubinemia due to hemolytic disease or other disorders were excluded. For the purposes of the study the newborns were placed into the incubator with the temperature within thermoneutral range (29.7–32.7 °C). To prevent movement artifacts, the measurement was performed during quite sleep stage. The stabilization period (30 min) was followed by 40 min of the ECG recording. The neonatal ECG signal was recorded by the bipolar thoracic ECG lead of portable devices for continuous heart rate recording VarCor PF6 and VarCor PF7 (Dimea, Czech Republic) with a sampling frequency of 1000 Hz.

To compare time irreversibility of the heart rate signal in newborns with the adult HRV recordings we have also analyzed heart rate recordings from 28 young adults (21 female, 7 male) aged 20.4 ± 0.2. Adult subjects were examined in supine position and awake. After the stabilization period (15 min), 20 min recording of ECG was obtained. The adult ECG was recorded by the bipolar thoracic lead connected to ECG device Cardiofax ECG-9620 (NihonKohden, Japan) and the analog signal of this device was transmitted to a PC using analog–digital converter (Advantech PCL 711, Taiwan) at a sampling rate of 500 Hz.

The RR interval was defined as the time interval between two consecutive R peaks after its automatic detection. The recordings were visually checked and rarely occurring ectopic beats were interpolated linearly. To avoid movement artifacts, we analyzed the segments lasting 1000 heartbeats where the stationarity of the time series was acceptable for the subsequent offline analysis.

The study was approved by the Ethics Committee of Jessenius Faculty of Medicine, Comenius University. All parents of the infants and adult participants gave their written informed consent prior to the examination.

3. Data analysis

We used three traditionally used indices for the quantification of time irreversibility in the time series: Porta's index *P%* [2,18], Guzik's index *G%* [2,18,20] and Ehler's index *E* [2].

3.1. Porta's index – P%

P% is based on evaluation the percentage of negative ΔRR (i.e. ΔRR^-) with respect to the total number of $\Delta RR \neq 0$:

$$P\% = \frac{N(\Delta RR^-)}{N(\Delta RR \neq 0)} \cdot 100 \quad (1)$$

where ΔRR represents the difference in length of two consecutive RR intervals. Consequently, *P%* ranges from 0 to 100 and time irreversibility is characterized by values of *P%* significantly larger or smaller than 50 [2,18].

3.2. Guzik's index – G%

Contrary to the *P%* index, *G%* considers also the magnitude of the difference between two RR intervals.

G% is defined as the percentage of the sum of the square distances between Δx+ and the main diagonal of the Poincare plot (each point in the plot is constructed with coordinates [RR(i), RR($i+1$)]) with respect to the sum of the squared distances between all Δx and the main diagonal:

$$G\% = \frac{\sum_{i=1}^{N(\Delta RR^+)} \Delta (RR^+)^2(i)}{\sum_{i=1}^{N(\Delta RR)} \Delta RR^2(i)} \cdot 100 \quad (2)$$

G% also ranges from 0 to 100 and irreversible series are characterized by values significantly larger (or smaller) than 50 [2,18,20].

3.3. Ehler's index E

E is based on evaluation of the skewness of the distribution of ΔRR.

$$E = \frac{\sum_{i=1}^{N(\Delta RR)} \Delta RR^3}{\left(\sum_{i=1}^{N(\Delta RR)} \Delta RR^2(i)^{3/2}\right)} \quad (3)$$

E does not have a predefined range, but a significant distance from 0 indicates time irreversibility. If $E > 0$, the distribution of Δx is skewed toward positive values. [2]

In order to increase the information gained from irreversibility analysis, we investigated time irreversibility on 4 different time scales. For the multiscale approach employed in our study the coarse-graining procedure was used (the data inside non-overlapping windows of τ points are averaged). The irreversibility indices were calculated for each coarse-grained time series with the maximal value of τ set to four [21].

3.4. Surrogate data approach

Surrogate data method was used to confirm the presence of time irreversibility in the HRV time series and its dependence on system nonlinearity. In general, surrogate time series are designed to preserve certain statistical properties of the original data in accordance with the given null hypothesis. In order to detect time irreversibility we tested the hypothesis that the time series arise from a linear Gaussian process, possibly distorted by nonlinear static invertible process, which does not alter time reversibility. Iteratively amplitude adjusted Fourier transform surrogates (IAAFT) were generated according to the procedure described by Schreiber and Schmitz [22]. IAAFT method preserves the second order statistical properties (i.e. power spectrum) and distribution and disturbs nonlinearity thus having linear signal with the same properties as the original one.

One hundred realizations of surrogate data were constructed from each original time series to test if *P%* and *G%* are significantly different from 50 and *E* is significantly different from 0. For the given recording, irreversibility indices were calculated for original and corresponding surrogate data. An irreversibility value of an original time series falling within the 2.5th and 97.5th percentile of the index' surrogate data distribution was considered to be consistent with the null hypothesis. Otherwise, the null hypothesis of the presence of a reversible linear process was rejected and the original series was considered to be time irreversible.

4. Statistics

The differences in the calculated parameters between adults (ADT) and neonates (NEO) were analyzed using the nonparametric Mann–Whitney test. The chi-square test was used to assess the between-group differences in the nonlinearity presence analysis in the HRV time series. A p values <0.05 were considered to be statistically significant. All statistical analyses were performed using statistical SYSTAT® version 10 (SPSS, Inc., USA) for Windows®.