INTERDEPENDENCE OF SYMPATHOVAGAL BALANCE AND IRREVERSIBILITY OF HEART RATE OSCILLATIONS

Lenka Chladekova, Zuzana Turianikova, Ingrid Tonhajzerova, Andrea Calkovska, and Michal Javorka
Department of Physiology, Comenius University, Jessenius Faculty of Medicine, Martin, Slovak Republic
Mala Hora 4, 036 01 Martin, Slovak Republic
phone: + (421) 43 4131426, fax: + (421) 43 4131426, email: chladekova@jfmed.uniba.sk

ABSTRACT

Introduction: *Time irreversibility is a characteristic feature of non-equilibrium, complex systems including cardiovascular control mediated by the autonomic nervous system. Its analysis in heart rate variability (HRV) signal represents a new approach to assess cardiovascular regulatory mechanisms.*

Aim: *The purpose of this paper was to assess the changes in time irreversibility during an orthostatic test (a balance shifted towards sympathetic predominance). We also tested the behaviour of the irreversibility indices in relation to different lengths of analysed data and their mutual dependence.*

Methods: *We examined the HRV time series from 28 healthy young subjects recorded during 20 minutes in the supine position followed by 15 minutes in the standing position. We used three different time irreversibility indices – Porta`s, Guzik`s and Costa`s indices (P%, G% and A, respectively). The irreversibility indices were derived from data segments containing 300, 600 and 1000 RR intervals.*

Results: *Indices P% and A were sensitive to the shift in sympathovagal balance during the orthostatic challenge. The indices were relatively insensitive to data length. The indices P% and A are closely mathematically related despite the difference in the calculation and they do not provide mutually independent information.*

Conclusion: *The heart rate irreversibility indices are sensitive to the changes in autonomic tone after the orthostatic challenge even when derived from the 300 interbeat intervals. The Porta`s index seems to be more sensitive to the autonomic nervous balance shift compared to the Guzik`s index. The Costa`s index is closely related to P% and does not provide any additional information.*

1. INTRODUCTION

Heart rate variability (HRV) is a physiological phenomenon and its assessment can provide useful information about the mechanisms involved in the cardiovascular system control. HRV is traditionally quantified in time and frequency domain by linear analysis methods [1]. However, the healthy cardiovascular regulatory system comprises complex interactions of many control loops and manifest nonlinear behaviour [2, 3]. Therefore nonlinear methods measuring complexity and other system dynamic features are more suitable for a detailed description of cardiovascular control system characteristics [3, 4].

From several nonlinear aspects of a cardiovascular signal, time irreversibility has recently gained more attention. A signal is said to be time irreversible if its statistical properties change after its time reversal, i.e. it is characterized by a temporal asymmetry [3, 5, 6]. The phenomenon of irreversibility is specific for nonequilibrium systems [6] and its presence in the heart rate results from the complexity of a cardiovascular control system typical for a healthy human [7].

In the previous papers time irreversibility indices have been applied to HRV analysis to detect the changes in cardiovascular regulation in the pathological groups of chronic heart failure patients [4], patients after acute myocardial infarction [8] and also in healthy subjects after physical activity [7, 8], during passive head-up tilt [2, 5] and active orthostatic challenge [2]. However, there is still a lack of information describing the changes of time irreversibility in HRV during the shift in autonomic nervous system status.

The aim of this study was to determine the effect of the orthostatic test on the time irreversibility of the RR interval time series in healthy young subjects quantified by various time irreversibility indices: Porta`s (P%), Guzik`s (G%) and Costa`s index (A). The postural change from supine to the standing position is a well-known manoeuvre characterized by a shifted balance of the autonomic nervous system towards sympathetic predominance. We also tested the behaviour of the selected irreversibility indices in relation to different lengths of analysed data (300, 600 and 1000 RR intervals).

2. METHODS

2.1 Subjects

We investigated recordings from 28 healthy young volunteers (21 female, 7 male) aged 20.4 ± 0.2 years (SEM) (range: 17.9 – 23.8 years). They were instructed to avoid the substances influencing cardiovascular system activity (caffeine, alcohol) and smoking for 12 hours before the examination. They were normotensive, non-obese (BMI: 21.7 ± 0.5 kg m^{-2}) and were taking no medication for the duration of study. The study was approved by the Ethics Committee of Jessenius Faculty of Medicine, Comenius University and all participants gave their informed consent prior to the examination.

2.2 Protocol

After the stabilization period (15 minutes resting in a supine position) the ECG signal was recorded for 20 minutes in a supine position. Subsequently, the subjects were asked to

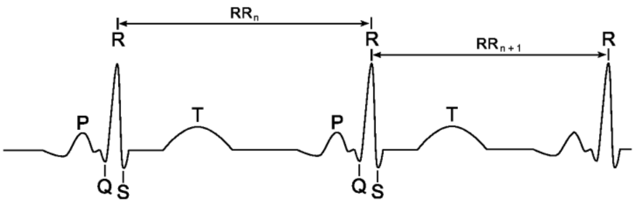

Figure 1 – Heart rate variability is a measure of the beat-to-beat interval changes. On the standard ECG, the duration between two adjacent R wave peaks is termed RR interval. For calculation of irreversibility indices, the differences between consecutive RR intervals (defined as $\Delta RR_n = RR_{n+1} - RR_n$) are used.

stand up slowly (in about 5 seconds) and the recording continued in the standing position for another 15 minutes. Complete study protocol can be found in [3].

2.3 Data recording

The ECG signal (bipolar thoracic ECG lead) from Cardiofax ECG-9620 (NihonKohden, Japan) was transferred into PC by the analog-to-digital converter PCL-711S (Advantech, Taiwan) at a sampling frequency of 500 Hz. After the QRS complex detection, the RR interval was defined as the time interval between two consecutive R peaks (fig. 1). The results were carefully visually checked and the rare ectopic beats were interpolated linearly.

2.4 Time irreversibility analysis

Irreversibility analysis was performed on three time series segments of different lengths (300, 600 and 1000 RR intervals) for each position (lying in a supine position – L, standing position – S) using custom-made software. The following indices were used to measure the time irreversibility of HRV series:

1. *Porta's index P%* [5, 6] based on the evaluation of the percentage of negative *ΔRR* (i.e. ΔRR^-) with respect to the total number of $\Delta RR \neq 0$. ΔRR is defined as a difference of two consecutive RR intervals length.

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

where $N(\Delta RR^-)$ denotes the number of negative ΔRR and $N(\Delta RR \neq 0)$ indicates the number of all non-zero ΔRR.

2. *Guzik's index G%* [5, 6, 9] based on the evaluation of the percentage of the cumulative square values of positive ΔRR (ΔRR^+) to the cumulative square values of all ΔRRs.

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

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

3. *Costa's index A* [10] based on the evaluation of the difference between the percentage of increments and decrements between consecutive RR intervals according to:

$$A = \frac{\sum_{i=1}^{N(\Delta RR)} H[-\Delta RR(i)] - \sum_{i=1}^{N(\Delta RR)} H[\Delta RR(i)]}{N(\Delta RR \neq 0)} \qquad (3)$$

where H is the Heaviside function ($H(a) = 0$ if $a < 0$ and $H(a) = 1$ if $a \geq 0$). The larger departure of *A* from *0*, the more irreversible the corresponding time series is.

2.5 Statistics

The differences between the asymmetry (irreversibility) indices calculated during standing (S) compared to the supine (L) position were analyzed by the nonparametric Wilcoxon signed-rank test. A p value < 0.05 (two-tailed) was considered statistically significant. The Wilcoxon signed-rank test was also used to analyze the differences between the values of single irreversibility index derived from the different number of beats (300, 600 and 1000).

3. RESULTS

We calculated the values of P%, G% and A according to the Eqs. (1) – (3). All irreversibility indices (P%, G% and A) were derived from data segments containing 300, 600 and 1000 beat-to-beat intervals. Statistical analysis showed no significant differences in the indices in relation to data length.

Fig. 2 (on next page) shows the box plots of all investigated irreversibility indices in both experimental conditions – lying ($P_L\%$, $G_L\%$, A_L) and standing ($P_S\%$, $G_S\%$, A_S) and for all analyzed data lengths – 300 RR intervals (on the left), 600 RR intervals (in the middle) and 1000 RR intervals (on the right). Significantly higher values of P% and A were found during standing compared to the supine position for all analysed data lengths. HRV analysis revealed no significant differences in G% during standing compared to the supine position.

Despite the differences in algorithms, the behaviour of P% and A is very similar indicating an evidential mathematical relationship between P% and A (for a detailed description see Appendix).

4. DISCUSSION

The major finding of our study is that indices P% and A are sensitive to the increase in the sympathetic activity during an orthostatic challenge. Interestingly, even very short data series (300 heart beats) provided the information useful to distinguish the time irreversibility of heart rate dynamics. We also demonstrated that all indices are relatively insensitive to data length, as there were no significant differences in relation to the number of RR intervals indicating no systematic differences in their values in relation to data length. Our results suggest that algorithm for calculation of indices P% and A is more sensitive to the autonomic nervous balance shift compared to the index G%. In addition, we showed in the present study that there is a close relationship

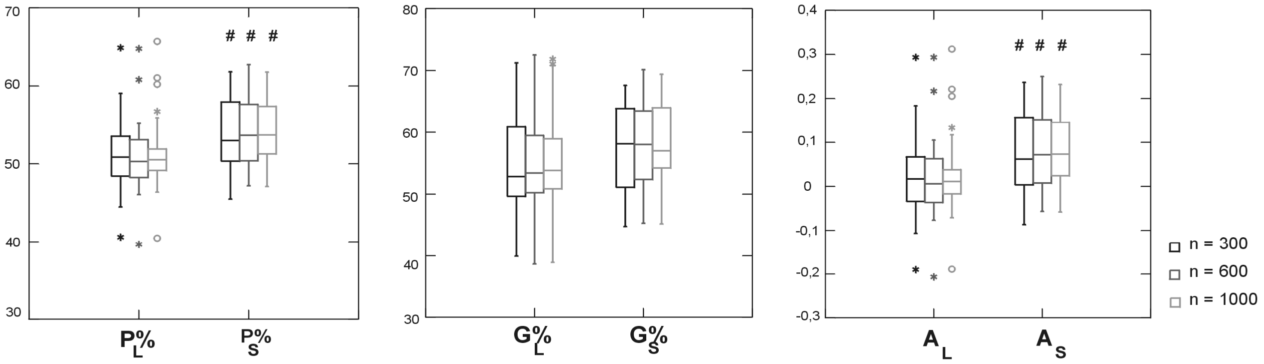

Figure 2 – Box-and-whisker plots representing irreversibility indices calculated from RR interval time series; in the lying position (P_L%, G_L%, A_L) and standing position (P_S%, G_S%, A_S). Indices are derived for both conditions from 300 data points (on the left), 600 data points (in the middle) and 1000 data points (on the right). Asterisks and circles correspond to outlier values, # corresponds to significant difference of the parameter in S with respect to L. #: P_S% ($p_{300} = 0.012$, $p_{600} = 0.002$, $p_{1000} = 0.007$) and A_S ($p_{300} = 0.012$, $p_{600} = 0.003$, $p_{1000} = 0.007$) are significantly larger than P_L%, A_L for all data lengths.

between P% and A (see Appendix). Therefore they do not provide mutually independent information and their simultaneous quantification is redundant.

The increased presence of temporal asymmetries in the HRV signal after the orthostatic challenge might reflect changes in the autonomic tone [2, 5]. The results of previous studies suggest that simple two-dimensional irreversibility tests (Porta's, Guzik`s and Ehler's index) are sensitive to the increase in the sympathetic modulation produced by head-up tilt at the highest inclination angles (i.e. 75° and higher) [2, 5]. However, there is a lack of information about the changes of time irreversibility indices during the active change of posture from supine to standing. Casali et al. [2] performed the two- and five-dimensional irreversibility test during the active orthostatic challenge using the Ehlers' index, which is utilizing the skewness of □RR distribution. But contrary to our results, the Ehlers' index reflected the increase in irreversible dynamics only in the five-dimensional space [2]. Therefore our results suggest that the Porta's and Costa's index might be more sensitive to the change in autonomic control during the active orthostatic challenge.

Although the temporal asymmetries are more likely over short time scales than over longer ones [5], it is well-known that the physiological system is characterized by a complex behaviour over multiple scales. Therefore, it should be more suitable to adjust the irreversibility analysis for different time scales in order to extract more information about the cardiovascular control system [2, 6, 8, 10]. In consequence, further investigations need to focus on time irreversibility methods that are mathematically independent and are able to quantify irreversibility of the HRV series over multiple time scales to improve the performance of the technique.

5. CONCLUSION

Heart rate irreversibility indices are sensitive to the shift in sympathovagal balance induced by a postural change even when derived from 300 interbeat intervals and on a single scale. The Porta's index seems to be more sensitive to autonomic nervous balance shift compared to Guzik`s index. The Costa's index is closely related to the Porta's index and therefore does not provide additional information. We suggest that the irreversibility indices have the potential to provide additional information about cardiovascular control mechanisms, but further investigation on properties, robustness and behaviour of these indices is needed to improve the performance and interpretation of the method.

ACKNOWLEDGEMENT

This study was supported by project of Centre of Excellence for perinatological research no 26220120036.

APPENDIX

According to the original definition of Costa's index (10), Eq. (3) can be expressed as:

$$A = \frac{N(\Delta RR^-) - N(\Delta RR^+)}{N(\Delta RR \neq 0)} \tag{4}$$

The total number of ΔRR ≠ 0, $N(\Delta RR \neq 0)$ is equal to the sum of $N(\Delta RR^+)$ and $N(\Delta RR^-)$. By applying the equation $N(\Delta RR^+) = N(\Delta RR \neq 0) - N(\Delta RR^-)$ to Eq. (4), we obtain the relation of A and P:

$$\begin{aligned} A &= \frac{N(\Delta RR^-) - N(\Delta RR \neq 0) + N(\Delta RR^-)}{N(\Delta RR \neq 0)} = \\ &= 2\frac{N(\Delta RR^-)}{N(\Delta RR \neq 0)} - 1 = 2P - 1 \end{aligned} \tag{5}$$

where $P = \frac{P\%}{100}$.

REFERENCES

[1] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, "Heart rate variability. Standards of measurement,

physiological interpretation, and clinical use," *Circulation*, vol. 93, pp. 1043 – 65, 1996.

[2] K.R. Casali, A.G. Casali, N. Montano, M.C. Irigoyen, F. Macagnan, S. Guzetti, and Porta A, "Multiple testing strategy for the detection of temporal irreversibility in stationary time series," *Physical Review E*, vol. 77, pp. 066204-1-7, 2008.

[3] M. Javorka, Z. Turianikova, I. Tonhajzerova, K. Javorka, and M. Baumert, "The effect of orthostasis on reccurence quantification analysis of heart rate and blood pressure dynamics," *Physiological Measurement*, vol. 30, pp. 29 – 41, 2009.

[4] A. Porta, G. D'addio, T. Bassani, R. Maestri, and G.D. Pinna, "Assessment of cardiovascular regulation through irreversibility analysis of heart period variability: a 24 hours Holter study in healthy and chronic heart failure populations," *Philosophical Transactions. Series A, Mathematical, physical and engineering sciences*, vol. 367, pp. 1359-1375, 2009.

[5] A. Porta, K. R. Casali, A. G. Casali, T. Gnecchi-Ruscone, E. Tobaldini, N. Montano, S. Lange, D. Geue, D. Cysarz, and P. Van Leeuwen, "Temporal assymetries of short-term heart period variability are linked to autonomic regulation," *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, vol. 295, pp. R550-557, 2008.

[6] F. Hou, J. Zhuang, C. Bian, T. Tong, Y. Chen, J. Yin, X. Qiu, and X. Ning, "Analysis of heartbeat asymmetry based on multi-scale time irreversibility test," *Physica A*, vol.389, pp.754-760, 2010.

[7] M. Costa, A.L. Goldberger, and C.K. Peng, "Broken assymetry of the human heartbeat: loss of time irreversibility in aging and disease," *Physical Review Letters*, vol.95, 198102, 2005.

[8] B. De La Cruz Torres, and J. Naranjo Orellana, "Multiscale time irreversibility of heartbeat at rest and during aerobic excercise," *Cardiovascular Engineering*, vol. 10, pp. 1-4, 2010.

[9] P. Guzik, J. Piskorski, T. Krauze, A.Wykretowicz, and A. Wysocki, "Heart rate asymmetry by Poincaré plots of RR intervals," *Biomedizinische Technik*, vol. 51, pp. 272-275, 2006.

[10] M.D. Costa, C.K. Peng, and A.L. Goldberger, "Multiscale analysis of heart rate dynamics: Entropy and time irreversibility measures," *Cardiovascular Engineering*, vol. 8, pp. 88-93, 2008.