Heart rate and blood pressure control in obesity – how to detect early dysregulation?
Michal Javorka, Zuzana Turianikova, Ingrid Tonhajzerova, Zuzana Lazarova, Barbora Czippelova and Kamil Javorka
Department of Physiology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia

Summary
Obesity is accompanied by many severe complications including various cardiovascular disorders. An impairment of cardiovascular control by autonomic nervous system could be one of the possible links between obesity and cardiovascular complications development. The aim of this study was to compare spontaneous heart rate and systolic blood pressure oscillations reflecting cardiovascular autonomic control of young obese subjects with normal control subjects by linear and nonlinear methods and to find sensitive markers of early autonomic dysregulation. Continuous recordings of beat-to-beat systolic blood pressure and RR intervals from ECG were obtained from 40 obese subjects (25 female, age 14±2 [13-1–16-1] (median [interquartile range]) years) and gender and age matched non-obese control subjects. In addition to linear measures (time and frequency domain), we performed recurrence quantification analysis (RQA) and multiscale entropy analysis for both signals. While no significant differences in heart rate and systolic blood pressure dynamics were detected by linear measures and MSE, analysis of recurrence plots from RR intervals time series showed significant differences – indices trapping time and maximal length of vertical from RQA were significantly higher in obese compared to control group. We conclude that heart rate and blood pressure control by autonomic nervous system in young obese subjects is relatively well preserved. However, novel RQA-related measures are able to detect early subtle abnormalities in cardiac autonomic control in obese subjects indicating decreased signal complexity.

Introduction
Obesity is a rapidly growing complex medical problem having a pandemic characteristics nowadays (Van Gaal et al., 2006). Obesity increasingly occurs already in childhood – in the last 20 years the percentage of obese children in developed countries increased three times (Lawlor et al., 2006). Until recently, it was assumed that obesity in childhood brings only the risk of its persistence to adulthood (Laederach-Hofmann et al., 2000). Today, it is proved that the obesity-associated complications described traditionally only in adults (dyslipidemia, atherosclerotic changes, hypertension, impaired glucose tolerance and diabetes mellitus type 2, depression) occur even in obese children and adolescents (Vanderlei et al., 2010).

Adult obesity is associated with many cardiovascular complications – obese people are at higher risk of ventricular arrhythmia, sudden cardiac death, coronary heart disease, hypertension, left ventricular hypertrophy, cardiomyopathy and other cardiovascular diseases (Karason et al., 1999; Poirier et al., 2006). The change in the autonomic nervous system (ANS) activity and dysbalance of its main components – parasympathetic and sympathetic nervous systems – are important factors contributing to initiation and progression of various cardiovascular complications of obesity (Ito et al., 2001).

Analysis of spontaneous oscillations of cardiovascular parameters – heart rate and blood pressure variability (HRV and BPV) – provides important information on the autonomic control of circulation (Pagani et al., 1986; Parati et al., 2006). As HRV originates predominantly from oscillations in parasympathetic nervous traffic and blood vessels are predominantly under sympathetic nervous system control, beat-to-beat analysis of simultaneously obtained heart rate, and blood pressure signals may provide information about both branches of cardiovascular control (Laitinen et al., 1999; Eckberg, 2000).

Our study is focused on the assessment of cardiovascular autonomic control in young obese subjects. The obesity in children and adolescents represents an ideal ‘model’ for study of pathogenesis of obesity and its complications because the
prevalence of other potentially confounding factors in these age groups is minimal (Kaufman et al., 2007). The aim of this study was to compare HRV and BPV in young obese subjects with control group and to analyse the performance of various linear and nonlinear HRV and BPV indices in detection of autonomic dysregulation in this future high-risk group. As the obese subjects in our study suffered from the obesity for at least 5 years, we hypothesize that early signs of cardiovascular dysregulation could be detected by novel sensitive methods of cardiovascular signals analysis even in children and adolescents.

Methods

Subjects

A total of 80 subjects divided into two groups participated in this study. The first group (obese) consisted of 40 obese children and adolescents (25 female, 15 male) aged 14-2 [13-1–16-1] years (range: 9-9–18-2 years). The second group (control) consisted of 40 age- and gender-matched subjects 14-5 [13-1–16-2] years (range: 10-7–18-4 years). Body weight, waist and hip circumferences were measured to calculate body mass index (BMI) and waist-to-hip ratio (WHR) values for all the patients. The percentage of body fat was measured using Body Fat Monitor (Omron BF 302, Kyoto, Japan). The study group characteristics are given in Table 1.

All subjects were instructed not to use substances influencing autonomic nervous system activity or cardiovascular system (caffeine, alcohol, energetic beverages) and refrain from smoking for 12 h before examination. All female subjects were examined in the proliferative phase of the menstrual cycle. All subjects gave their written informed consent prior to examination. The study was approved by the Ethics Committee of Jessenius Faculty of Medicine, Comenius University.

Study protocol

All subjects were examined over 60 min under standardized conditions in a quiet room from 8 to 12 AM. The subjects were instructed to lie comfortably in the supine position and not to speak or move unnecessarily. The subjects were rested in the supine position for 20 min before the actual recording of cardiovascular signals started, allowing the cardiovascular system to reach equilibrium, that is quasi-stationary condition.

Throughout the complete study protocol both continuous finger arterial blood pressure measured by photoplethysmographic volume-clamp method (FinometerPro, FMS, Amsterdam, the Netherlands) and ECG signal recorded from bipolar thoracic lead (Cardiofax ECG-9620; NihonKohden, Tokyo, Japan) were transferred simultaneously into PC by analog-to-digital converter PCL-711S (Advantech, Taipei, Taiwan, R.O.C.) at a sampling frequency of 500 Hz. Heart rate variability (HRV) and systolic blood pressure variability (SBPV) analysis were performed offline on 2000-beats long time series segments of beat-to-beat RR intervals and systolic blood pressure values. HRV and SBPV were analysed using standard linear time and frequency domain analysis and by two methods derived from nonlinear dynamics – recurrence quantification analysis (RQA) and multiscale entropy analysis (MSE).

Data analysis

Linear analysis

Time domain analysis. HRV analysis – For traditional time domain analysis of HRV, we computed three most commonly used measures: MeanNN – the mean beat-to-beat interval of normal heart beats, SDNN – standard deviation of NN intervals – reflecting the overall variability magnitude, and RMSSD – the root-mean-square of successive beat-to-beat differences – reflecting the average magnitude of changes in RR intervals length between two consecutive beats that is regarded as a marker of vagal heart rate control (Task Force, 1996).

SBPV analysis – From SBP signals, we computed the following linear measures:

Mean SBP – mean systolic blood pressure value, SD SBP – standard deviation of systolic blood pressure values and RMSSD SBP – root-mean-square of successive differences of SBP values.

SD SBP measure reflects the overall magnitude, whereas RMSSD SBP quantifies the beat-to-beat variability of the SBP oscillations.

Frequency domain analysis. For HRV and SBPV, spectral analysis was performed to obtain spectral powers in low-frequency (LF, 0-04–0-15 Hz) and high-frequency (HF, 0-15–0-5 Hz) bands using the following procedure.

Time series were interpolated at 500 ms to obtain equidistant time series, using cubic splines. As we were interested in oscillations between 0-04 and 0-5 Hz that are thought to be mediated by vagal and sympathetic efferents, we eliminated the slower oscillations and trends using the detrending procedure by Tarvainen (Tarvainen et al., 2002). Subsequently, the power spectrum was repeatedly estimated, using fast Fourier transform (FFT) with the Hanning window length set to 1024

Table 1 Study groups characteristics. Values are presented as median [interquartile range]; P-values were obtained using Kruskal–Wallis test (obese versus controls).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>BMI (kg m⁻²)</th>
<th>WHR</th>
<th>Body fat (%)</th>
</tr>
</thead>
</table>

BMI, Body mass index; WHR, waist-to-hip ratio.

*Significant (P<0.05) between-groups difference.
samples and a shift of 10 samples. The average power spectrum was computed, and the LF and HF powers were calculated for both analysed signals (HRV and SBPV).

**Nonlinear analysis**

Recurrence quantification analysis. First, a multidimensional state space was reconstructed from the one-dimensional time series (RR intervals or SBP oscillations), applying the time delay embedding method (Takens, 1981). Each point in the reconstructed phase space represents the state of the system at a given time and is determined by \( m \) coordinates \( (m \text{ corresponds to the embedding dimension; according to previous studies we chose } m = 10 \text{ (Javorka et al., 2008b; Mestivier et al., 2001)}) \). The coordinates are determined by the original time series’ values delayed by selected time interval \( \tau \). The embedding time delay \( (\tau) \) was set individually for each recording as the first minimum of the mutual information function (Fraser & Swinney, 1986). Next, the distances between individual points (a point in ten-dimensional space corresponds to a state of the system at a given time) at times \( i \) and \( j \) were calculated using the Euclidean norm. When the distance between points was lower than a given threshold (tolerance), a recurrence point was plotted in the recurrence plot (RP) with the coordinates \( [i, j] \) (Fig. 1) (Webber Jr & Zbilut, 1994; Marwan et al., 2007). The tolerance level was selected individually for each recording giving the fixed percentage of recurrence points set to 5\%. This procedure also minimizes the influence of HRV magnitude on RQA parameters and thus renders RP to provide hidden information on control system dynamics (Javorka et al., 2009).

The most important structures for RQA are diagonal and vertical lines in RP. Diagonals reflect the repetitive occurrence of similar sequences of states in the system dynamics and express the similarity of system behaviour in two distinct time sequences. Verticals result from a persistence of one state during some time interval. In our study, we computed the following measures:

- \( \%\text{Det} \) (percentage of determinism) – the percentage of recurrence points forming diagonals from all recurrence points;
- \( l_{\text{max}} \) – maximal length of a diagonal;
- Trapping time (TT) – mean length of the vertical lines;
- Laminarity (Lam) – proportion of recurrence points forming verticals;
- \( V_{\text{max}} \) – maximal length of a vertical.

Low TT, Lam and \( V_{\text{max}} \) values imply high complexity in the system’s dynamics, because the state of the system stays only for a short time in a state similar to the previously occurring state.

Multiscale entropy. Multiscale entropy analysis was performed separately for HRV and SBPV according to a procedure published by Costa (Costa et al., 2002). Given a one-dimensional discrete time series of RR intervals or SBP values, \( \{x_1, \ldots, x_i, \ldots, x_N\} \), we constructed consecutive coarse-grained time series \( \{y(s)\} \) determined by the scale factor \( s \), according to the equation:

\[
y(s)_j = \frac{1}{\tau} \sum_{i=-(j-1)s+1}^{j-1} x_i
\]

where \( \tau \) represents the scale factor and \( 1 \leq j \leq N/\tau \). The length of each coarse-grained time series is \( N/\tau \). For scale 1, the coarse-grained time series is simply the original time series. We calculated sample entropy (SampEn) (Richman & Moorman, 2000) for each one of the coarse-grained time series plotted as a function of the scale factor. SampEn quantifies

![Figure 1](image-url)  

**Figure 1** A representative example of the recurrence plot analysed subsequently by recurrence quantification analysis. Black dot with the coordinates \( [i, j] \) in the plot illustrates the closeness (within tolerance) of states in times \( i \) and \( j \). In other words, the state in time \( i \) recurred later in time \( j \). Recurrence quantification analysis was focused on diagonal lines (recurrent occurrence of the sequence of states in time) and vertical lines (state of the system persisted for some time within system dynamics).
the irregularity of a time series. It reflects the conditional probability that two sequences of $m$ consecutive data points which are similar to each other (within given tolerance $r$) will remain similar when one more consecutive point is included. It is necessary to set parameters within SampEn algorithm before MSE computation. According to previous studies, we have chosen tolerance level $r = 0.15 \times$ standard deviation of an original time series to avoid distortion of SampEn values by changes in signal magnitude. We computed SampEn values for $m = 2$ and for scales $t$ up to 10.

Statistics
Nonparametric tests were used to take into account the non-Gaussian distribution of the HRV and SBPV parameters. Between-groups comparisons (obese versus control group) were performed with Kruskal–Wallis test. Results are presented as median [interquartile range]. A value of $P < 0.05$ was considered statistically significant.

Results
Patient characteristics
Both BMI and WHR were significantly higher in obese patients compared to the control group (Table 1).

Linear measures
Time domain HRV and SBPV analysis
No significant between-groups differences were found in MeanNN (control: 856 [761–973] ms, obese: 812 [756–889] ms; $P = 0.206$) SDNN (control: 73 [61–103] ms, obese: 68 [55–96] ms; $P = 0.427$) and RMSSD (control: 66 [45–102] ms, obese: 57 [41–98] ms; $P = 0.444$). Similarly, for SBPV no significant between-groups differences were found in linear measures reflecting overall (SD SBP; control: 7.0 [6.4–8.7] mmHg, obese: 6.9 [6.0–8.6] mmHg; $P = 0.847$) and beat-to-beat variability (RMSSD SBP; control: 2.7 [2.3–3.2] mmHg, obese: 2.9 [2.5–3.6] mmHg; $P = 0.150$), although MeanSBP tended to be slightly higher in obese group compared to control group (control: 117 [111–124] mmHg, obese: 121.5 [115–128.5] mmHg; $P = 0.051$).

Frequency domain HRV and SBPV analysis
We have found no significant between-groups differences in both frequency bands for HRV (LF HRV – control: 840 [560–1584] ms$^2$, obese: 677 [374–1195] ms$^2$; $P = 0.237$ and HF HRV – control: 1161 [737–2278] ms$^2$, obese: 942 [564–2258] ms$^2$; $P = 0.371$) (Fig. 2). After decomposing the systolic blood pressure time series into spectral components, we have found that the power of high-frequency oscillations was significantly higher in obese patients (HF SBPV; control: 1.67 [1.22–2.23] mmHg$^2$, obese: 2.05 [1.59–3.12] mmHg$^2$; $P = 0.019$). The power of low-frequency oscillations of SBPV (LF SBPV) was not different between obese patients and control group (control: 5.26 [3.17–8.16] mmHg$^2$, obese: 5.03 [3.35–7.03] mmHg$^2$; $P = 0.9$) (Fig. 3).

Recurrence quantification analysis
RQA of heart rate oscillations
No significant between-groups differences were found in RQA measures based on diagonals (%Det; control: 44 [37–52] %, obese: 45 [33–56] %; $P = 0.885$; $L_{\text{max}}$; control: 62 [48–81], obese: 65 [46–84]; $P = 0.806$) (Fig. 4). However, using RQA measures derived from vertical lines, significant differences in $TT$ and $V_{\text{max}}$ were detected. Both $TT$ and $V_{\text{max}}$ were significantly higher in obese patients compared to control group pointing towards complexity loss and simplification of heart rate ($TT$; control: 2.68 [2.38–3.09], obese: 2.96 [2.61–3.26]; $P = 0.028$; $V_{\text{max}}$; control: 36.5 [26.5–47.0], obese: 47.0 [32.0–64.5]; $P = 0.019$). No significant difference in laminarity was found ($P = 0.637$).

RQA of systolic blood pressure oscillations
There were no significant between-groups differences in any RQA measure derived from systolic blood pressure oscillations (%Det: $P = 0.788$; $L_{\text{max}}$: $P = 0.754$; $TT$: $P = 0.897$; $V_{\text{max}}$: $P = 0.413$; Lam: $P = 0.637$).

© 2015 Scandinavian Society of Clinical Physiology and Nuclear Medicine. Published by John Wiley & Sons Ltd 16, 5, 337–345
Multiscale entropy analysis

MSE HRV and SBPV analysis

Computing MSE from both RR intervals and SBP time series, we have found no significant differences in SampEn values on all scales between obese patients and control groups (for HRV: $P = 0.140–0.942$; for SBPV: $P = 0.102–0.814$) (Fig. 5).

Discussion

The major findings of our study include relatively well-preserved heart rate and blood pressure control in young obese subjects, and the higher sensitivity of recurrence plot related measures to detect subtle abnormalities in cardiac autonomic control in obese subjects.

Autonomic nervous system plays an important role in the pathogenesis of cardiovascular complications related to obesity (Alam et al., 2009). ANS is a key mechanism influencing the energy output and metabolic rate, and its activity is controlled by hypothalamic structures that are closely related to centres for food intake. Changes of ANS activity and balance of its components could contribute to the obesity development, but it is assumed that they are rather a consequence of the obesity itself (Karason et al., 1999; Nagai & Moritani, 2004). The shifted balance of the autonomic cardiovascular control towards sympathetic dominance could contribute to the...
progression of severe cardiovascular complications in obese patients and significantly increase the risk of ventricular arrhythmia and sudden cardiac death in this group (Grassi et al., 1995; Muscelli et al., 1998).

In previous studies, a decreased parasympathetic activity in obese adults (Rissanen et al., 2001) and children (Paschoal et al., 2009; Thayer et al., 2010) was demonstrated by a reduced high-frequency power of HRV. The results from the analysis of low-frequency heart rate oscillations are more variable – an increase, no difference or even a decrease in LF power was observed (Rabbia et al., 2003). Although in several studies authors interpreted a relative increase in low-frequency power of HRV (expressed either as LF/HF ratio or LF in normalized units) as an increased cardiac sympathetic activity in obese subjects (Masi et al., 2007; Paschoal et al., 2009), it was found that these measures are not directly related to sympathetic activity (Eckberg, 2000) – LF power in HRV is predominantly under parasympathetic control in supine rest (Martimkki et al., 2006). Accordingly, LF and HF powers were found to be concomitantly decreased in obese (Vanderlei et al., 2010) and increased in physically trained subjects (Nagai & Moritani, 2004).

In contrast to previous studies, we have not found any significant difference in linear HRV measures in time and frequency domains between our groups of 40 obese and 40 age- and gender-matched control children and adolescents. Our findings are in accordance with the studies where no significant effect of obesity on linear HRV measures was observed (Matsumoto et al., 2003; Antelmi et al., 2004; Paschoal et al., 2009; Vanderlei et al., 2010). Several issues could explain the lack of differences in cardiovascular variability magnitude between obese and control groups. Firstly, our two groups of subjects were carefully selected and matched for age and gender and thus were very similar except the obesity state. All subjects were young and without any comorbidity. An attention was given to standardize the menstrual cycle phase in female subjects because menstrual cycle could influence the ANS activity (Bai et al., 2009). In addition, all subjects were not regularly physically trained – a factor that could significantly influence the ANS activity (Routledge et al., 2010). Secondly, study protocol was well standardized and appropriate time interval was allowed for subjects to relax in supine position before the actual recording started. Taken together we could state that in the young age, the obesity alone is not associated with prominent cardiac parasympathetic activity changes.

The effect of obesity on blood pressure variability in humans was analysed only rarely. While preserved LF and HF powers in BPV were found previously in moderately obese subjects, increased overall BPV magnitude was found in massively obese adults (Piccirillo et al., 1998). As the blood vessels are dominantly under sympathetic control and the vascular resistance changes are reflected by blood pressure oscillations, BPV (mostly power in LF band) is commonly regarded as a marker of sympathetic activity (Laitinen et al., 1999). However, causal analysis of heart rate–blood pressure relationship recently showed that the low-frequency blood pressure oscillations are significantly influenced by oscillations in heart rate (Porta et al., 2000) and the influence of vascular sympathetic control to blood pressure oscillations is only partial. Given no significant effect of obesity on magnitude of heart rate oscillations, the lacking effect of obesity on LF power in BPV could be explained by a preserved sympathetic vascular control. We have observed marginally significant increase in HF power in BPV signal in obesity. High-frequency oscillations in BPV result from the mechanical effect of breathing on venous return (Aubert et al., 2009) and from the heart rate–blood pressure interactions (Faes & Nollo, 2010). Our results could indicate increased mechanical effect of ventilation on blood pressure changes in obese subjects. We speculate that it can be the result of the changed magnitude of intrathoracic pressure oscillations caused by increased thoracic mass. Alternatively, a possibly reduced buffering capacity of respiratory sinus arrhythmia could be responsible for the increased BPV seen in obese group (Tan & Taylor, 2010).

Heart rate and BP signals are traditionally analysed by linear data analysis tools (time and frequency domain). However, these methods are not sufficient to characterize the complex dynamics of cardiovascular system. Nonlinear control of heart rate and blood pressure is thought to possess physiological advantages, allowing to adapt faster to changes in physiological needs than linear control mechanisms (Costa et al., 2005).
Analysis methods derived from nonlinear systems theory have opened up a new perspective for studying and understanding the characteristics of cardiovascular dynamics. Nonlinear measures describe qualitative features rather than the magnitude of the signal (Beckers et al., 2006).

We hypothesized that obesity should be accompanied by a decreased complexity of cardiovascular oscillations in accordance with the concept of complexity loss as a generic feature of pathologic dynamics (Goldberger et al., 2002). Multiscale entropy analysis enables to describe complexity of heart rate and blood pressure dynamics on multiple time scales (Costa et al., 2005) and is sensitive to a change in sympathovagal balance evoked by orthostatic stress (Turianikova et al., 2011). MSE analysis revealed that heart rate and blood pressure signals in our study did not reveal any difference in cardiovascular oscillations complexity supporting the concept of well-preserved cardiovascular autonomic control in young obese subjects.

On the other hand, RQA measures trapping time and \( V_{\text{max}} \) calculated from recurrence plot constructed from spontaneous heart rate oscillations were significantly higher in obese group. This finding reflects the longer persistence of the given dynamical system state in obese subjects indicating a mild decrease of control system complexity. Our results suggest the subtle shift in sympathovagal balance–parasympathetic inhibition and/or sympathetic activation in obese group because the qualitatively similar changes in RQA measures – although with markedly higher magnitude – were associated with active orthostasis (Javorka et al., 2009).

The better performance of RQA over MSE analysis could be explained by the methodology of more appropriate high dimensional phase space reconstruction in the process of heart rate dynamics analysis by RQA compared to MSE. Generally, both methods – MSE and RQA with fixed percentage of recurrences – provide completely different information on signal complexity and dynamics. The fixation of the percentage of recurrence points in our study makes the RQA measures independent on the overall presence of recurrent patterns (‘number of recurrences’) – a phenomenon that is principally analysed by MSE method. The fixed percentage of recurrence points makes the results of RQA dependent solely on the structure (prevailing diagonals or verticals) of recurrences within dynamics independently from their number. Therefore, we regard both used nonlinear methods (MSE and RQA) as providing mutually independent and additive information on the cardiovascular dynamics.

The major limitation of our study is in its cross-sectional design. Our conclusions are based on the comparison of two independent groups. The longitudinal changes of cardiovascular system dynamics during the development of cardiovascular complications associated with obesity requires further study. Nevertheless, our results point towards the importance of various signal properties quantification to better describe cardiovascular control. The inherent nonlinearity of analysed system in accordance with our results point towards the application of nonlinear methods to more properly characterize cardiovascular control and its potential impairment associated with obesity. Due to the differences in maturation in analysed age group and inclusion of both genders into our study, the relatively large intersubject variation could be expected. Nevertheless, even with these effects we have found the significant between-groups differences by RQA method of HRV analysis indicating the high sensitivity of this method to detect subtle differences in heart rate dynamics between obese and non-obese subjects.

Our results indicate the higher sensitivity of novel nonlinear methods to detect cardiovascular autonomic control changes as recently demonstrated in several other pathological conditions including diabetes mellitus, post-trauma patients, chronic heart failure patients (Javorka et al., 2008a,b; Norris et al., 2008; Ho et al., 2011). The important contribution of ANS dysbalance to the development of cardiovascular complications of obesity stress the importance of its early detection. Interestingly, several studies have found an improvement of cardiovascular autonomic control in obese subjects associated with lifestyle changes (Nagai & Moritani, 2004). We assume that early detection and grading of high-risk subjects based on HRV and BPV measures could help in administration of proper lifestyle changes to improve the prognosis of obese patients. Longitudinal assessment of sensitive cardiovascular variability measures could quantify the improvement of ANS balance and increase the motivation of the patient.

We conclude that cardiovascular autonomic control is relatively well preserved in obese children and adolescents. Recurrence plot analysis can reveal subtle changes in heart rate dynamics associated with obesity and possibly detect subjects with the higher risk of cardiovascular complications development.

Acknowledgments

The study was supported by project ESF IV ‘The increasing opportunities for career growth in research and development in the medical sciences’, ITMS: 26110230067, grants APVV-0235-12, VEGA no. 1/0059/13 and VEGA no. 1/0223/12.

Conflicts of interest

The authors declare no conflict of interest.

References


Antelmi I, de Paula RS, Shinzato AR, et al. Influence of age, gender, body mass index,
Cardiovascular control in obesity, M. Javorka et al.


Fraser AM, Swinney HL. Independent coordinates for strange attractors from mutual information. *Physiol Rev A* (1986); 33: 1134.


Tarvainen MP, Ranta-aho PO, Karjalainen PA. An advanced detrending method with
application to HRV analysis. IEEE Tran Biomed Eng (2002); 49: 172–175.