Granger Causality Analysis of Baroreflex in Obese Children and Adolescents

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Abstract

Background: Obesity is an important risk factor of arterial hypertension. The impairment of baroreflex – a principal blood pressure (BP) control mechanism – could contribute to the development of hypertension in obese patients. Previous studies have found a decreased baroreflex sensitivity (BRS) measured by transfer function analysis of spontaneous BP and heart rate (HR) oscillations in obese subjects. However, this method ignores the causality and directionality of HR and BP oscillations interactions.

Aim: The aim of the study was to analyse BRS in obese normotensive children and adolescents using causal baroreflex analysis method.

Methods: Continuous noninvasive recordings of BP (volume-clamp method) and R-R intervals (ECG) were obtained from 40 obese subjects (age: 14.7±0.3 yrs, BMI: 32.7±0.6 kg m^{-2}) and gender and age matched non-obese control subjects. Causal close loop model was used to measure classical (noncausal) BRS and causal feedback interaction from BP to HR (causal BRS).

Results: The noncausal BRS did not show any significant difference between groups. On the other hand, causal BRS was lower (p = 0.030) in obese group.

Conclusion: The causal BRS analysis is more sensitive in early detection of baroreflex impairment in obese children and adolescents compared to classical BRS method.

1. Introduction

Obesity is a rapidly growing complex medical problem having a pandemic characteristics nowadays [1]. Obesity increasingly occurs already in early childhood – in the last twenty years the percentage of obese children in developed countries increased three times [2]. Until recently, it was assumed that obesity in childhood brings only the risk of obesity persistence to adulthood [3]. Today, it is proved that the obesity associated complications occuring traditionally only in adults (dyslipidemia, atherosclerotic changes, hypertension, impaired glucose tolerance and diabetes mellitus type 2, depression) occur even in obese children and adolescents [4].

The change in the autonomic nervous system activity is an important factor contributing to initiation and progression of various cardiovascular complications of obesity, including hypertension [5]. From autonomic reflexes, baroreflex is the principal mechanism involved in blood pressure control [6]. It was found that obesity is accompanied by a significant reduction of baroreflex sensitivity (BRS) in adults [7], adolescents [8] and even in children [9].

In human, BRS is most frequently measured from spontaneous beat-to-beat oscillations of blood pressure (BP) and heart rate (HR) assuming the unidirectional influence from BP to HR – the blood pressure drop is sensed by baroreceptors and the response include the increased HR predominantly mediated by parasympathetic withdrawal [10]. However, the interaction of BP and HR is bidirectional – HR also influences BP by changes in diastolic heart filling via Frank-Starling mechanism. The novel method for separate analysis of feedback (baroreflex) and feedforward (mechanical) interactions between HR and BP was recently developed based on Granger causality concept [11].

The aim of our study was to apply the novel causal baroreflex analysis method to analyse BRS in obese normotensive children and adolescents. We aimed to analyse "pure" BRS without the influence of feedforward mechanisms and to compare results with classical noncausal approach.

2. Methods

2.1. Subjects

We examined 40 obese children and adolescents, aged between 9.9 and 18.4 years (26 female, 14 male) and 40 age and gender matched non-obese control subjects. The diagnosis of obesity was based on the body mass index (BMI) values tables for appropriate age and gender according to recommendation of Task Force Obesity [12].

All subjects were normotensive according to a routine clinical examination with repeated measurement of blood pressure on brachial artery by auscultation method. None of the subjects took any medication at the time of the study. The subjects were asked to avoid caffeine and alcohol for 12 hours prior to examination. All subjects were non-smokers.

2.2. Protocol

Subjects were investigated in supine position in a quiet room between 8 and 12*am*. Continuous finger arterial blood pressure was measured noninvasively by the photoplethysmographic volume-clamp method using the Finometer Pro device (FMS, Netherlands) (Figure 1).

Figure 1. Noninvasive recording of beat-to-beat blood pressure values using Finometer device.

ECG signal was recorded from bipolar thoracic lead using Cardiofax ECG-9620 (NihonKohden, Japan). The devices' analog output was transferred into a PC by an analog-digital converter (PCL-711, Advantech, Taiwan) at a sampling frequency of 500 Hz. Custom-made software was used to detect systolic blood pressure (SBP) values from finger blood pressure signal. R-R intervals representing cardiac cycle length were derived from ECG signal. The detection accuracy was visually validated. The *n*-th SBP value in time series corresponded to systolic blood pressure peak within *n*-th R-R interval.

The subjects were resting for 20 min before the actual recording started, allowing the cardiovascular system to reach a quasi-stationary condition. All recordings were obtained under standardized conditions (supine rest) and the subjects were instructed to avoid voluntary movements and speaking.

After the recording of cardiovascular oscillations, the basic anthropometric measures (height, weight, waist and hip circumferences) were taken in each participant. The percentage of body fat was estimated based on bioelectrical impedance analysis (OMRON BF 302, Japan).

2.3. Data analysis

We analyzed 2000 heart beats long time series of R-R intervals and systolic blood pressure values ($rr(t)$ and $sbp(t)$, respectively) starting a stabilization period.

R-R interval and SBP are likely to interact in a closed loop, as a result of the simultaneous presence of the feedback baroreflex mechanism and feedforward mechanism operating in the opposite direction from R-R to SBP. The causal approach [11, 13] offers the possibility to study the effect of both paths of this closed loop system separately. The method is based on a bivariate autoregressive model

$$rr(t) = \sum_{k=1}^{p} a_{11}(k)\, rr(t-k) + \sum_{k=1}^{p} a_{12}(k)\, sbp(t-k) + w_1(t)$$

$$sbp(t) = \sum_{k=0}^{p} a_{21}(k)\, rr(t-k) + \sum_{k=1}^{p} a_{22}(k)\, sbp(t-k) + w_2(t)$$

After transforming these equations into the frequency domain, the auto spectra and cross spectrum can be calculated as follows:

$$P_{rr}(f) = |\Delta(f)|^2(|A_{22}(f)|^2\sigma_1^2 + |A_{12}(f)|^2\sigma_2^2)$$

$$P_{sbp}(f) = |\Delta(f)|^2(|A_{21}(f)|^2\sigma_1^2 + |A_{11}(f)|^2\sigma_2^2)$$

$$P_{rr,sbp}(f) = |\Delta(f)|^2(A_{22}(f)A_{21}^*(f)\sigma_1^2 + A_{12}(f)A_{11}^*(f)\sigma_2^2)$$

where σ_{12} and σ_{22} are variances of zero-mean white noises w_1 and w_2 and a_{11}, a_{12}, a_{12} and a_{22} are the vectors of the regression coefficients. p is the model order chosen based on the Akaike criterion for multivariate processes. Further, $\Delta(f) = [A_{11}(f)A_{22}(f) - A_{12}(f)A_{21}(f)]^{-1}$, where $A_{lm}(f) = \delta_{lm} - \sum_k a_{lm}(k)e^{-j2\pi fk}$ and l, m = 1, 2, $\delta lm = 1$ for $l = m$, $\delta lm = 0$ for $l \neq m$.

Cross-spectral analysis enables to estimate the coherence function which quantifies the strength of the linear coupling between two signals $\gamma^2(f) = \frac{|P_{rr,sbp}(f)|^2}{P_{rr}(f)P_{sbp}(f)}$ and transfer function gain which describes the transfer of power from one series to the other according to the predefined input-output direction – in this case the gain estimates the baroreflex sensitivity: $G_{sbp\rightarrow rr}(f) = \frac{|P_{rr,sbp}(f)|}{P_{sbp}(f)}$.

In the *classical model*, the estimated functions are not able to distinguish whether a detected degree of coupling comes from feedback influences from *sbp* to *rr* or from feedforward interactions from *rr* to *sbp*.

Therefore, in the next step the causal coherences and gains are calculated by switching off separately the feedback or the feedforward path. In this way, the causal direction from *sbp* to *rr* is reached by setting $A_{12}(f) = 0$ and from *rr* to *sbp* by setting $A_{21}(f) = 0$.

We confined analysis to low frequency band only (0.04 – 0.15 Hz) to minimize the effect of other mechanisms on baroreflex assessment. The values of non-causal and causal coherences and gains were calculated as the arithmetic mean of coherence and gain values within this band.

2.4. Statistics

For normally distributed values of analyzed quantitative variables (ascertained by Lilliefors test) two sample *t*-test was applied to test for between groups difference (obese vs. controls). A *p* value < 0.05 (two-tailed) was considered statistically significant and values are presented as arithmetic mean ± standard error of the mean.

3. Results

Basic subjects characteristics are presented in Table 1. According to the design of the study, the obese subjects had significantly higher anthropometric indices.

Table 1. Basic subjects characteristics. Values are mean ± standard error of the mean and *p*-values result from two sample *t*-test.

	Obese	Control	*p*-value
Age (years)	14.7±0.3	14.7±0.3	0.877
Height (cm)	164±1	165±2	0.771
Weight (kg)	89±3	56±2	<0.001
BMI (kg m^{-2})	32.7±0.6	20.4±0.3	<0.001
Waist (cm)	96±2	68±1	<0.001
Hip (cm)	112±1	90±1	<0.001
Waist to hip ratio	0.86±0.01	0.76±0.01	<0.001
Body fat (%)	37.2±0.4	21.4±0.6	<0.001

The coherence calculated by non-causal model was significantly higher in control subjects ($p = 0.002$). Causal coherences were not significantly different between groups (for direction *sbp→rr*: $p = 0.127$, for direction *rr→sbp*: $p = 0.491$).

The transfer function gain (Figure 2) in classical non-causal model of BP – HR interactions was not different between groups ($p = 0.059$). However, causal gain from systolic blood pressure to R-R intervals was significantly lower in obese children and adolescents ($p = 0.012$). No significant between groups difference in causal gain for direction *rr→sbp* was observed ($p = 0.574$).

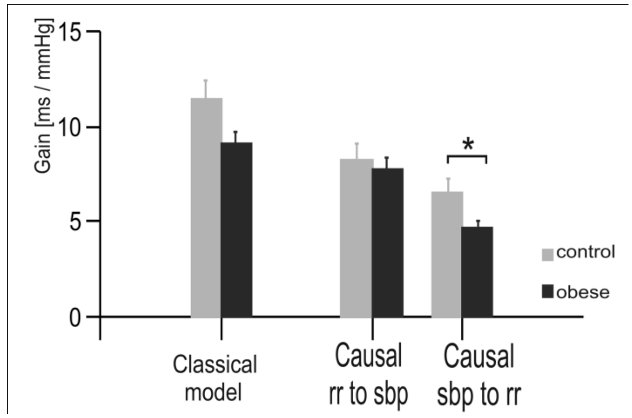

Figure 2. Bar graphs demonstrate the between groups differences in non-causal and causal gain of systolic blood pressure (sbp) and R-R intervals (rr) interactions. Asterisk indicates the significant between groups difference.

4. Discussion

The major findings of our study include increased coherence of SBP and R-R intervals oscillations and the detection of decreased causal gain in the direction from SBP to R-R.

In previous studies, decreased BRS by analysis of spontaneous cardiovascular oscillations was observed in obese subjects, including childhood obesity [8,9]. However, it was shown recently that classical approach to analyse BRS ignored important feedforward influence where the length of cardiac cycle influences blood pressure values in subsequent heart beats. Therefore, new approach based on Granger causality [14] was recently proposed to analyse separately feedback (baroreflex) and feedforward interactions between BP and HR signals and to refine BRS analysis [11,13].

Our results confirmed that the causal analysis as a methodologically more appropriate approach to measure baroreflex sensitivity was also more sensitive to detect impaired BRS in our group of obese children and adolescents. While classical model showed only tendency to lower gain in obese group, causal approach revealed decreased influence of SBP signal on R-R intervals signal indicating early baroreflex impairment.

Lower synchronization between heart rate and blood pressure time series might also be regarded as a marker of baroreflex impairment [15]. Interestingly, highly significant decrease in coherence between SBP and R-R intervals was found in obese subjects. This finding indicate novel aspect of baroreflex impairment in this group of high risk subjects.

Our results based on novel causal approach to analyze baroreflex sensitivity indicate that baroreflex is impaired even in children and adolescents with obesity. Decreased function of baroreflex could predispose them to future cardiovascular complications and could be one of the factors contributing to the future development of hypertension.

5. Conclusion

We conclude that causal approach to analyse baroreflex sensitivity is a sensitive tool to detect baroreflex impairment in obese children and adolescents.

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