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CARDIO-RESPIRATORY INTERACTION AND AUTONOMIC DYSFUNCTION IN OBESITY

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We aimed to test whether the evaluation of the cardio-respiratory interaction using the analysis of heart rate and blood pressure variabilities and respiratory maneuvers can reveal cardiovagal dysfunction in obese adolescents 12-18 years old. The spectral power in high frequency band of the heart rate variability (HRV) reflecting respiratory sinus arrhythmia was used as an index of the cardiac vagal control, and the spectral power in high frequency band of the blood pressure variability (BPV) as an indicator of mechanical effects of respiration. The deep breathing test and Valsalva maneuver were applied. The obese group had a reduction in spectral power in high frequency band of the HRV. Differences in high frequency band spectral power of the BPV between the obese and control groups were not found. The finding of lower respiratory sinus arrhythmia, indicating a cardiovagal dysfunction in obese adolescents, can provide important diagnostic information about early subclinical autonomic dysfunction in obesity.

Key words: *blood pressure variability, heart rate variability, obesity, respiratory sinus arrhythmia, respiratory maneuvers*

INTRODUCTON

Obesity is an excess of adipose tissue accumulation and an important risk factor for developing chronic diseases. Although childhood obesity brings a number of additional problems – such as metabolic, endocrine, cardiovascular, psychological and others – the greatest health problem is seen in the next generation (1). An association between activity of the autonomic nervous system

(ANS) - as a regulatory system for maintenance of the constant energy storage - and obesity in both adults and adolescents has been identified (2). The neural network, mainly the ANS, plays a major role in the interaction of circulation and respiration. Thus, the cardio-respiratory and *vice versa* – respiratory-cardiovascular interaction can be used for the evaluation of autonomic modulation in various diseases.

Respiratory frequency rhythms are translated into changes in a discharge frequency of the sinoatrial node known as respiratory sinus arrhythmia (RSA). RSA is mediated through physiological mechanisms by which the R-R interval in the ECG is shortened during inspiration and prolonged during expiration. These mechanisms include central medullary generator, reflexes from the lungs, baroreflexes, chemoreflexes, and local mechanisms (stretching of the sinoatrial node, etc.). The parasympathetic branch is the main way for phasic beat-to-beat cardiac control, including RSA, and the sympathetic branch plays only a tonic modulatory role. Thus, the assessment of respiratory sinus arrhythmia is accepted as an index of cardiac vagal function (3, 4). RSA can be quantified by spectral analysis of heart rate variability or deep breathing test.

Respiration affects the blood pressure through a number of mechanisms. These mechanisms include the effects of RSA, through changes in cardiac output and timing of diastole, and of respiratory-induced variations in intrathoracic pressure, which modulate arterial blood pressure through a mechanical coupling to the systemic venous and arterial circulations within the thorax (5). Spectral analysis of blood pressure variability can provide an important information about this respiratory-circulatory interaction.

The application of respiratory maneuvers – deep breathing test and Valsalva maneuver as a component of the Ewing battery of cardiovascular tests (6) - is recommended and used for clinical autonomic testing in recent studies (7, 8). These respiratory maneuvers, associated with reflex cardiovascular changes, provide an important information about the appropriate function of ANS and functional capacities of effectors (heart and vessels) and other associated structures.

The aim of the present study was to test whether the evaluation of the cardio-respiratory interaction using different methods - the heart rate and blood pressure variability analysis and respiratory maneuvers - can reveal early subclinical autonomic dysfunction in obese adolescents and to assess which of the method would be the most suitable for the diagnosis.

MATERIAL AND METHODS

The study was approved by the Ethics Committee of the Jessenius Medical Faculty, Comenius University in Martin, Slovakia. All subjects and their parents were carefully instructed about the study protocol and they gave informed consent to participate in the study.

Subjects

We examined 40 children and adolescents - 20 obese patients (12 girls, 8 boys) aged 12-18 years (14.8 ±0.5 years) and 20 healthy subjects – control group matched for age and gender. The obesity was defined using body mass index (BMI) reference cut-off points for overweight and obesity between 2-18 years (9) which are recommended by the Task Force for Obesity (1) and each patient was selected into obese group according to percentile graphs for the Slovak population. All probands were non-smokers, not taking drugs and substances influencing cardiovascular system (i.e., caffeine, alcohol) and they had no evidence of hypertension, metabolic syndrome, mental, or other diseases.

Protocol

All probands were examined under standard conditions (quiet room with minimal arousal stimuli, standard temperature) from 8.00 a.m. to 12.00 p.m. The thoracic belt with ECG electrodes from a telemetric device for R-R intervals recording (Varia Cardio TF4, Sima Media, Olomouc, Czech Republic) was applied after initial 15 min of the rest. Then, the respiratory maneuvers were performed in the following order: deep breathing and Valsalva maneuver.

After this examination, a special thoracic belt with ECG electrodes and a finger cuff of Finapres device were applied for the continuous registration of the cardiovascular parameters. The subjects were instructed to remain in the supine position comfortably and not to speak or move unless neccessary. The heart rate and blood pressure recordings started after 15 min of rest and were continuously recorded during the following 50 min. Anthropometric measurements – weight, height, circumferences of waist and hip, percentage of the fat by the method based on bioelectrical impedance analysis (OMRON BF 302, Japan) – were performed after the respiratory maneuvers and cardiovascular parameters recording had been taken.

Data analysis

The continuous ECG signal was obtained by ECG device Chirastar 60 (CHIRANA, Slovak Republic). The finger blood pressure was continuosly monitored using volume clamp method (10) by Finapres 2300 (Ohmeda, Louisville, CO, USA). The finger cuff of appropriate size was wrapped around middle phalanx of the third finger of the left hand. The finger was passively maintained at the heart level to avoid blood pressure distortion caused by hydrostatic pressure changes. The analog outputs of the ECG device and of the Finapres were transferred into a PC by analog digital conversion at a sampling frequency of 500 Hz by PCL 711 data aquisition card (Advantech Co., Taiwan) for subsequent analysis. The special software for detection of R-R waves to obtain R-R intervals time series, and systolic and diastolic blood pressures (SBP, DBP) was used.

R-R intervals and blood pressure signals were analyzed between 20-25 min of the rest period. Time series were interpolated at 500 ms in order to obtain equidistant time series using cubic spline and slower oscillations and trends were eliminated using the detrending procedure of Tairvanen *et al* (11). Subsequently, mean power spectrum of the analyzed segment was computed and spectral power in the high frequency band (HF:0.15-0.5 Hz) was obtained by integration. We focused on the high frequency spectral power of the HRV (HF-HRV) which reflects mainly respiratory sinus arrhythmia regarded as an index of the cardiac vagal modulation, and on the high frequency spectral power of the BPV (HF-BPV) as a reflection mainly of the mechanical effects of respiration. In addition, the mean R-R interval and the mean systolic and diastolic blood pressures were calculated.

Deep breathing test

The subject lying in the supine position was instructed to breathe deeply four times in twenty seconds. Evaluated parameters: I-E – difference in the mean heart rate during deep inspirations and expirations from 4 cycles, I/E - ratio of these values, CV_{R-R}(%) – coefficient of variation = (SD/MV)x100, SD – standard deviation of R-R intervals, MV- mean value of R-R intervals. Deep breathing test is considered as an index of respiratory sinus arrhythmia.

Valsalva maneuver (VM)

The subject was asked to perform Valsalva maneuver (an expiratory effort to mouthpiece connected to a tonometer and to maintain a pressure of 40 mmHg for 15 s in the sitting position). R-R intervals were recorded during the maneuver and for 25 s following release. Time intervals were indicated by acoustical signal. The Valsalva ratio (VR) - ratio of the maximum heart rate during VM to minimum heart rate after the VM - as a sensitive parameter for the cardiovagal function recommended by the American Association of Neurology (12) - was calculated. Additionaly, the mean heart rate (HRrest) was evaluated before both respiratory maneuvers.

Statistical evaluation

All data are expressed as means ±SE. Distribution of the variables was ascertained using a Lilliefors test. Mann-Whitney U test was used for statistical analysis of the parameters with non-Gaussian distribution and an unpaired *t*-test to assess statistical differences in variables with normal distribution. Since the initial spectral absolute values of HRV differ greatly among individuals, the spectral power of HRV was logarithmically transformed for statistical testing and an unpaired *t*-test was used for between-group comparisons (obese *vs*. nonobese). P≤0.05 was considered as significant.

RESULTS

Anthropometric measurements

Anthropometric characteristics are presented in *Table 1*. The obese subjects had significantly higher BMI, WHR, and the percentage body fat compared with the control group (P=0.001).

Table 1. Anthropometric characteristics of the obese and control groups.

	Obese group (n=20)	Control group (n=20)
Age (years)	14.8 ±0.5	14.9 ± 0.4
BMI (kg/m^2)	32.5 ±0.9	20.7 ± 0.3*
WHR	0.9 ±0.02	0.7 ± 0.01*
Percentage fat (%)	37.2 ±0.7	20.9 ± 0.9*

BMI – body mass index, WHR – waist-to-hip ratio. Values are expressed as means ±SE. *P=0.001 for significant differences were between the obese and control groups.

Mean heart rate and blood pressure

The mean R-R interval was significantly shortened (805 ±17 ms *vs*. 939 ±22 ms, P=0.001) and the mean systolic and diastolic blood pressures were significantly higher in the obese group compared with healthy probands (123 ±3.6 mmHg *vs.* 116 ±3.1 mmHg, P=0.031; 62 ±2.5 mmHg *vs*. 55 ±1.8 mmHg, P=0.042, respectively).

Heart rate and blood pressure variabilities

Differences in the spectral analysis of HRV between a control and an obese subject are illustrated in *Fig. 1* (*Panels A and B*, respectively). High frequency oscillations in HRV were significantly reduced in the obese subjects (P=0.043, *Fig. 2*). Significant differences were not found in the high frequency bands of spectral power of HF-BPV between the obese and control groups.

Respiratory maneuvers

The mean heart rate (HRrest) was significantly higher before a deep breathing test (DB) and the Valsalva maneuver in the obese subjects compared with the controls (85.0 ±3.1 beats/min *vs*. 70.0 ±2.4 beats/min, P=0.001; 89.0 ±2.6 beats/min *vs.* 80 ±2.7 beats/min, P=0.018, respectively). Heart rate differences in the deep breathing test between a control and an obese subject are illustrated in *Fig. 3* (*Panels A and B,* respectively). The coefficient of variation (CV_{R-R}) was lower in the obese group compared with the controls (P=0.052, *Fig. 4*). No

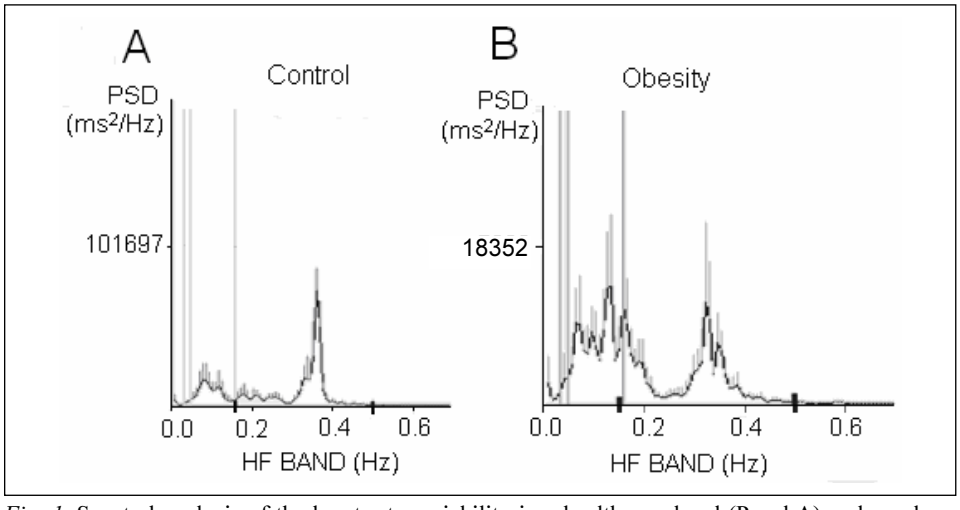

Fig. 1. Spectral analysis of the heart rate variability in a healthy proband (Panel A) and an obese patient (Panel B). A marked reduction in high frequency bands was observed in the obese patient. PSD – power spectral density HF – high frequency.

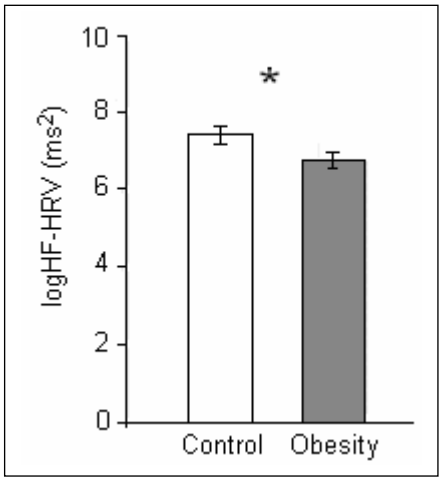

Fig. 2. Mean logarithmic values of the spectral power in high frequency bands of the heart rate variability (HF-HRV) in the control and obese groups. *P=0.043.

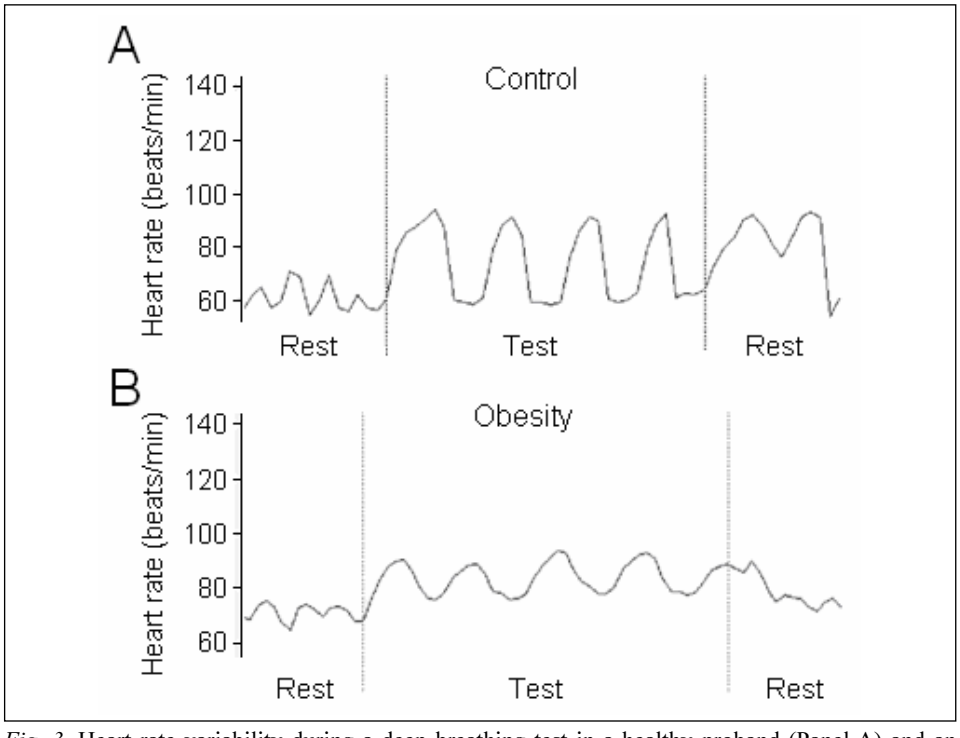

Fig. 3. Heart rate variability during a deep breathing test in a healthy proband (Panel A) and an obese subject (Panel B). The heart rate variations during the test were reduced in the obese subject.

significant differences were found in other parameters of the deep breathing test or the Valsalva ratio.

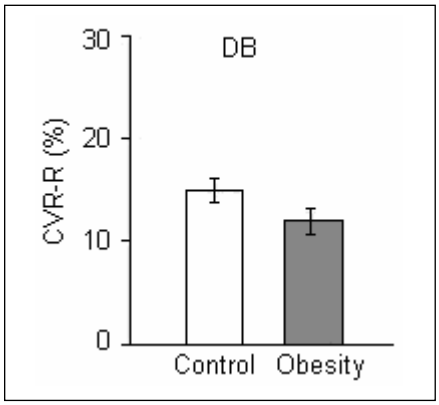

Fig. 4. Mean values of the coefficient of variation (CV_{R-R}) during deep breathing (DB) test in the control and obese groups.

DISCUSSION

Respiratory sinus arrhythmia is an oscillation of the heart rate pattern around the basal mean value at the frequency of spontaneous breathing. The parasympathetic nervous system responds rapidly to rhythmic respiratory discharge; hence the high frequency neuronal oscillations are passed on to the heart *via* the vagus resulting in HF variability (13, 14). Thus, the HRV analysis - especially at respiratory frequencies - provides information about cardiac vagal efferent activity of the autonomic nervous system (15). Reduced HRV is the earliest sign of cardiovascular dysregulation where the heart rate is fixed with autonomic nervous system dysfunction (16). In the obese subjects, a reduction in the HF-HRV spectral power has been found (2). Our results confirmed these findings, as a lower respiratory sinus arrhythmia was shown in obese adolescents, which indicates cardiac parasympathetic dysregulation.

Respiration profoundly influences other cardiovascular parameters (e.g., blood pressure). Direct intraarterial measurement of blood pressure is a precise, but invasive method for continuous monitoring, so the volume-clamp method is the only alternative for non-invasive beat-to-beat blood pressure monitoring (10). Short-term blood pressure changes are mediated mostly by sympathetic nervous system and, therefore, the analysis of short-term blood pressure variability rather than HRV has been taken as more sensitive for detection of sympathetic dysregulation (17, 18). In particular, blood pressure oscillations in the high frequency part of blood pressure variability result predominantly from mechanical changes during respiration *via* changes in venous return transferred into systolic volume fluctuations (18). To our knowledge, spectral analysis of the HF-BPV in obese adolescents has not yet been performed. In the present study, we found no significant differences in the HF-BPV, which suggests similar mechanical changes during respiration in both groups.

Respiratory mediated heart rate changes are small during quiet breathing. It is thus more convenient to evaluate the respiratory sinus arrhythmia during deep breathing (DB). The Valsalva maneuver (VM) increases intrathoracic pressure and consequently induces substantial changes in systemic venous return, potentially having an important effects on the left ventricular output, which is associated with hemodynamic changes.

The evaluation of heart rate responses to the DB VM respiratory maneuvers is suitable for the ascertainment of the cardiovagal modulation (12). However, only a few studies have used these maneuvers for the evaluation of the heart rate reactivity in obese children. Yakinci *et al* (19) referred to the dysfunction in parasympathetic activity in the DB test and hyperactivity in the VM in obese children aged 7-13. In our study, the parameter CV_{R-R} (DB test) was marginally significantly lower in the obese group compared with controls. In addition, no significant differences were found in the VM.

It seems that the HF-HRV spectral analysis is a more sensitive indicator of the autonomic dysfunction than conventional cardiovascular tests in obese adolescents. Likewise, other authors suggest that decreased HRV precedes the overt signs of cardiovascular disease visible in standard clinical examinations (20). Thus, we suppose that an analysis of HRV at respiratory frequencies is the most sensitive method for the diagnosis of cardiovagal dysfunction in obesity.

The mechanisms by which vagal dysregulation relates to obesity are still debatable. Moreover, it is questionable whether cardiac vagal dysregulation results from obesity or facilitates its development. A 10% increase in body weight above the initial weight results in a decline of vagal activity (21). The hypothalamus is a regulatory center of both satiety and the autonomic nervous system. Therefore, central abnormalities might cause both obesity and autonomic dysfunction. Other authors have documented reduced cardiac vagal function associated with modifiable lifestyle factors, including lack of physical activity as a predisposing factor for overweight and obesity (22). It seems that the question of whether alterations in the cardiovagal function play a role in the onset and development of obesity, or whether they are just a consequence of an inadequate life-style, remains incompletely understood. It is worth emphasizing the importance of a non-pharmacological approach (modification of life-style, regular physical activity, psychotherapy) of childhood obesity, which may result in reduced resting heart rate, increased cardiac parasympathetic activity, and improved psychosocial characteristics (23).

In summary, our study revealed lower respiratory sinus arrhythmia, as evaluated by the HF-HRV spectral analysis combined with deep breathing tests, which points to the presence of cardiac vagal dysfunction in obese adolescents. Importantly, autonomic imbalance with decreased parasympathetic activity may be the final common pathway in numerous conditions associated with increased morbidity and mortality (22). We suppose that the evaluation of cardio-

respiratory interactions, in particular the heart rate variability, can provide diagnostic information about early subclinical autonomic dysfunction in obesity.

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