Changes in the cardiac autonomic regulation in children with attention deficit hyperactivity disorder (ADHD)

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Background & objectives: ADHD is one of the most common mental disorders among children. We hypothesized that ADHD is associated with the impairment of the cardiac autonomic regulation. The aim of this study was to evaluate the cardiac autonomic regulation in children with ADHD at the rest and during orthostasis using short-term heart rate variability (HRV) analysis.

Methods: Eighteen children with ADHD admitted to the Department of Children and Adolescent Psychiatry, Clinic of Psychiatry, University Hospital in Martin, Slovak Republic between January and September 2006 and 18 matched healthy subjects were recruited. HRV analysis was carried out in three positions: supine (S1)-orthostasis (O)-supine (S2). Evaluated parameters were: the mean R-R interval, mean squared successive difference (MSSD), spectral powers in low (LF) and high frequency (HF) bands, total power (TP), coefficients of component variance (CCV LF, CCV HF), LF/HF ratio.

Results: The mean R-R interval was significantly shorter in ADHD group compared to controls in all positions (P<0.05, P<0.001). S1: The parameters MSSD, CCV HF, logHFpower were significantly lower (P<0.05, P<0.05, P<0.01) and ratio LF/HF was significantly higher (P<0.05) in ADHD group compared to controls. O: The parameters MSSD, CCVHF, logHFpower, logTP were significantly lower in ADHD group compared to controls (P<0.01, P<0.05, P<0.01, P<0.01). S2: The parameters MSSD and logHFpower were significantly lower in children with ADHD compared to controls (P<0.05).

Interpretation and conclusions: The children with ADHD had decreased cardiac vagal modulation and tachycardia in supine positions with altered ability of dynamic activation of the autonomic nervous system in response to orthostasis indicating changes in the cardiac autonomic regulation. Further studies need to be done on a larger sample to confirm these findings and to understand the underlying mechanisms.

Key words Attention deficit/hyperactivity disorder (ADHD) - autonomic nervous system - children - heart rate variability -orthostasis

Psychological states and processes are known to profoundly influence the autonomic nervous control of the cardiovascular system with likely contribution to the increased cardiovascular morbidity in patients with mental disorders1,2. During this decade the pathomechanisms by which central nervous system (CNS) modulates changes in autonomic nervous system (ANS) in various mental disorders as well the potential
links between cognitive and emotional processes and changes in ANS have drawn increasing interest\(^3,4\).

Integrative theories that link CNS structures to autonomic function, such as the polyvagal theory\(^5\), have of late emerged. The polyvagal theory has introduced a new perspective relating autonomic function to behaviour but it requires understanding bidirectional communication between the heart and the CNS\(^6\). Porges’ polyvagal theory\(^5,6\) posits that the myelinated vagus, originating in the nucleus ambiguus, is a dynamic contributor to the processes of attention, motion, emotion, and social interactions. Thus, parasympathetic nervous system-linked cardiac activity has been associated with emotion regulation capabilities\(^5\).

Cardiac function is extremely sensitive to autonomic influences. The heart rate variability (HRV), \(i.e.,\) the amount of the heart rate fluctuations around the mean heart rate, is validated indicator of the function of the cardiorespiratory control system. In other words, analysis of heart rate variability provides insights into the autonomic control of the heart and gives important information about cardiac sympathetic and parasympathetic interaction\(^7,8\). Our previous studies revealed that HRV analysis is noninvasive and sensitive method for early detection of asymptomatic changes of cardiovascular neuropathy in various somatic diseases such as hypertension and diabetes mellitus\(^9,10\) as well as for the evaluation of the effect of mental load\(^11\). Moreover, the interplay of sympathetic and parasympathetic (vagal) outputs of the central autonomic network at the sinoatrial node producing this complex beat-to-beat variability is characteristic of a healthy, adaptive organism\(^12\). Thus, the HRV is considered as an index of central-peripheral neural feedback and CNS-ANS integration\(^13\). Consequently, the HRV analysis can be used to study the possible links between mental disorders and cardiac autonomic regulation/dysregulation.

Attention deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed mental disorders among children. ADHD is a developmental disorder characterized by distractibility, hyperactivity, impulsive behaviours, and the inability to remain focused on tasks or activities\(^14\). Evidence from neuropsychological, pharmaceutical, and brain-imaging studies implicates dopamine and norepinephrine neurotransmitter systems in frontostriatal circuit in the pathophysiology of the disorder\(^15\). Although it is generally assumed that the autonomic regulation of the heart is impaired in ADHD, the information about this dysregulation is limited. Some authors propose altered heart rate variability in ADHD children\(^16\) or changes in autonomic profiles in behaviour-disorder in preschool children\(^17\).

The aim of this study was to find differences in the autonomic regulation of the heart at the rest and during orthostasis between children with attention deficit/hyperactivity disorder and healthy subjects using short-term heart rate variability analysis.

Material & Methods

The study was approved by the Ethics Committee of Jessenius Medical Faculty, Comenius University Martin, Slovak Republic. All children/patients/guardian were carefully informed about the study protocol and informed written consent was obtained from them to participate in the study prior to examination.

A total of 36 subjects – 18 patients with ADHD (15 boys, 3 girls) aged 8-12 yr (10.8 ± 0.4 yr) and 18 healthy subjects – control group matched for age (10.9 ± 0.5 yr) and gender (15 boys, 3 girls) were included.

**ADHD group**: Children suffering from ADHD were recruited consecutively from the patients admitted to the Department of Children and Adolescent Psychiatry, Clinic of Psychiatry, University Hospital in Martin, between January and September 2006.

**Inclusion criteria** were - ADHD diagnosis – combined type according to Diagnostic & Statistical Manual of Mental Disorders DSM-IV-TR (Text Revision)\(^18\) without comorbid mental disorders; before psychopharmacological and other treatment; non-smokers; moderate physical activity; and no evidence of hypertension, diabetes mellitus, obesity, underweight or other diseases.

**Control (non-ADHD) group**: The control (non-ADHD) group consisted of healthy pupils of primary school matched for age and gender. The healthy probands were carefully selected according to the same inclusion criteria as ADHD group – non-smokers, not taking drugs and substances influencing cardiovascular system, moderate physical activity, no evidence of cardiovascular, endocrinologic or other diseases. In addition, the children in control (non-ADHD) group have been never treated for any mental disorder (Table I).

**Procedure**: All subjects were examined in a quiet room with standard temperature (23°C) and minimalisation of stimuli in the morning between 0800 and 1200
The cardiac vagal reactivity in response to orthostasis was evaluated as percentual change of logarithmical spectral power in high frequency band (as index of vagal modulation) using mathematical expression: [(logHF power in standing position - logHF power in the 1st supine position) / logHF power in the 1st supine position] x 100 (%).

Statistical analysis: Statistical analyses were performed using the statistical software package SYSTAT 10 for Windows (SSI, Richmond, CA, USA). Because basal spectral absolute values differ greatly among individuals, the spectral powers were then logarithmically transformed for statistical testing. The non-gaussian/gaussian distribution was ascertained using Lilliefors test\textsuperscript{22}. For data with gaussian distribution, two-way ANOVA with one repeated measures factor was used for data analysis. Post-hoc univariate F test was used for between-groups comparison. Mann-Whitney U test\textsuperscript{23} was used for between-groups comparison with non-gaussian distribution. P<0.05 were considered as significant.

Results

The main effect of active posture change (in response to orthostasis and clinostasis) on heart rate variability parameters was significant for the mean R-R interval (P<0.01), logHF power (P<0.01), logLF power (P<0.01), logTP power (P<0.01) and CCV HF (P<0.01). The effect of group (ADHD vs. control) was significant for the mean R-R interval (P<0.01), logHF power (P<0.01), logTP (P<0.05) and CCV HF (P<0.05). No significant interaction between both main factors (posture vs group) was found (Table II).

Table II. The analysis of variance table of repeated measures

<table>
<thead>
<tr>
<th>R-R interval</th>
<th>CCV LF</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>group effect</td>
<td>0.002</td>
<td>group effect</td>
<td>0.640</td>
</tr>
<tr>
<td>posture effect</td>
<td>0.001</td>
<td>posture effect</td>
<td>0.366</td>
</tr>
<tr>
<td>posture x group</td>
<td>0.890</td>
<td>posture x group</td>
<td>0.233</td>
</tr>
<tr>
<td>CCV HF</td>
<td>logLF power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>group effect</td>
<td>0.026</td>
<td>group effect</td>
<td>0.114</td>
</tr>
<tr>
<td>posture effect</td>
<td>0.001</td>
<td>posture effect</td>
<td>0.003</td>
</tr>
<tr>
<td>posture x group</td>
<td>0.760</td>
<td>posture x group</td>
<td>0.098</td>
</tr>
<tr>
<td>logHF power</td>
<td>logTP power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>group effect</td>
<td>0.001</td>
<td>group effect</td>
<td>0.018</td>
</tr>
<tr>
<td>posture effect</td>
<td>0.001</td>
<td>posture effect</td>
<td>0.001</td>
</tr>
<tr>
<td>posture x group</td>
<td>0.132</td>
<td>posture x group</td>
<td>0.069</td>
</tr>
</tbody>
</table>

R-R interval (ms), CCV (%) - coefficients of component variance in low (LF) and high (HF) bands, logarithmic values (log) of spectral powers in low (LF) and high (HF) bands, total power (TP) in ms\textsuperscript{2}.
Post-hoc analysis and Mann-Whitney U test revealed significant changes in the following heart rate variability parameters (Table III):

**The first supine position:** The mean R-R interval was significantly shorter in the ADHD group compared to controls ($P<0.01$). The parameters - MSSD, logHF power, CCV HF - were significantly lower in the ADHD group compared to controls ($P<0.05$, $P<0.01$, $P<0.05$). Ratio LF/HF was significantly higher in the ADHD group compared to controls ($P<0.05$). No significant difference was found in logLF power, logTP, CCV LF.

**The orthostasis:** The mean R-R interval was significantly shorter in the ADHD group compared to controls ($P<0.001$). The parameters - MSSD, logHF power, logTP, CCV HF - were significantly lower in the ADHD group compared to controls ($P<0.01$, $P<0.01$, $P<0.01$, $P<0.05$). No significant difference was found in logLF power, CCV LF and LF/HF.

**The second supine position:** The mean R-R interval was significantly shorter in the ADHD group compared to controls ($P<0.05$). The parameters - MSSD, logHF power - were significantly lower in the ADHD group compared to controls ($P<0.05$). No significant difference was found in the remaining parameters.

The **vagal reactivity:** Percentual change in the high frequency band in response to orthostasis - was significantly higher in the ADHD group compared to controls (-36 vs. -23%, $P<0.05$).

### Table III. The parameters of heart rate variability analysis in ADHD and control groups

<table>
<thead>
<tr>
<th></th>
<th>ADHD (n=18)</th>
<th>Controls (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine 1</td>
<td>Ortho</td>
</tr>
<tr>
<td>R-R</td>
<td>697 ± 24</td>
<td>546 ± 18</td>
</tr>
<tr>
<td>MSSD</td>
<td>3031 ± 877</td>
<td>241 ± 68</td>
</tr>
<tr>
<td>CCV LF</td>
<td>2. 89 ± 0. 18</td>
<td>2. 80 ± 0. 24</td>
</tr>
<tr>
<td></td>
<td>$P&lt;0.01$</td>
<td>$P&lt;0.01$</td>
</tr>
<tr>
<td>CCV HF</td>
<td>3. 82 ± 0. 30</td>
<td>1. 65 ± 0. 17</td>
</tr>
<tr>
<td></td>
<td>$P=0.69$</td>
<td>$P=0.18$</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0. 77 ± 0. 13</td>
<td>3. 95 ± 0. 76</td>
</tr>
<tr>
<td></td>
<td>$P=0.137$</td>
<td>$P=0.52$</td>
</tr>
<tr>
<td>log LF</td>
<td>5. 96 ± 0. 17</td>
<td>5. 32 ± 0. 20</td>
</tr>
<tr>
<td></td>
<td>$P=0.477$</td>
<td>$P=0.052$</td>
</tr>
<tr>
<td>log HF</td>
<td>6. 49 ± 0. 21</td>
<td>4. 16 ± 0. 27</td>
</tr>
<tr>
<td></td>
<td>$P=0.082$</td>
<td>$P=0.384$</td>
</tr>
<tr>
<td>log TP</td>
<td>7. 03 ± 0. 16</td>
<td>5. 67 ± 0. 19</td>
</tr>
<tr>
<td></td>
<td>$P=0.052$</td>
<td>$P=0.384$</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. R-R intervals (ms), mean squared successive differences between R-R intervals in ms$^2$ (MSSD), coefficients of component variance (CCV in %) in low (LF) and high (HF) bands, logarithmic values (log) of spectral powers in low (LF) and high (HF) bands, total power (TP) in ms$^2$. Data in the first supine position (Supine 1), orthostasis (Ortho) and in the following supine position (Supine 2) are given as arithmetic mean ± SEM. Significant difference between ADHD and control groups are presented in the Table alongside data. *$P<0.05$, **$P<0.01$.

**Discussion**

In the last decade, cardiac vagal tone has emerged as a psychophysiological marker of many aspects of behavioural functioning and emotion regulation in both children and adults\(^3\). Several studies have linked changes in cardiac vagal modulation to depression\(^1\) or conduct problems in children and adolescents\(^24,25\).

This study focuses on the changes in autonomic regulation of the heart in children with ADHD. Using short-term heart rate variability analysis autonomic regulation of the heart was compared between the groups of ADHD patients and healthy children under resting conditions and following dynamic activation of the ANS by orthostatic manoeuvre. This orthoclinostatic test measures the dynamic loading of the autonomic nervous system in the progressive increase of the sympathetic activity and concomitant decrease in the vagal activity in the standing position and vice-versa in the diminishing of the sympathetic and in a rise of the vagal activity in the supine position after lying back\(^26,27\).

The consensus of opinion is that HF respiratory component of R-R interval variability primarily reflects respiration-driven vagal modulation of sinus arrhythmia\(^31\). Consequently, other studies found decreased respiratory sinus arrhythmia in children with ADHD\(^28\). However, some authors reported the differences in autonomic activity in dependence on developmental changes\(^25\). Crowell et al\(^17\) compared...
autonomic profiles of preschool children (aged from 4 to 6 yr) with ADHD and oppositional defiant disorder (ODD) with controls. Children with ADHD and ODD were not significantly different in baseline respiratory sinus arrhythmia, but authors referred to autonomic deficiency in later age-period (adolescence) related to emotion dysregulation and lability. In accordance with other studies related to conduct problems29 our results of the HRV analysis indicated decreased cardiac parasympathetic modulation with higher heart rate in both supine positions, as well as during orthostatic manoeuvre, in patients with ADHD in middle childhood.

Moreover, we evaluated the cardiac vagal reactivity in the high frequency band in response to orthostasis. Contrary to the law of initial values29, the vagal reactivity was significantly higher in the ADHD group compared to controls (-36% vs. -23%). As noted by other authors, the excessive vagal withdrawal may be a non specific marker of emotional lability3. Thus, it is questionable whether our findings of lower cardiac vagal modulation associated with higher vagal reactivity are related to the features of the ADHD (i.e., emotional lability due to emotional immaturity) or it is the reflection of subclinical abnormal dynamic activation of the autonomic nervous system in response to posture change in children with ADHD.

The mechanisms underlying these changes in cardiac autonomic regulation in ADHD remain unknown. Thayer and Lane13 emphasized the neural correlates of vagal function and the role of brain in the regulation of the autonomic nervous system. Some studies have identified functional units within central nervous system that are involved in autonomic regulation - the central autonomic network (CAN)30. Functionally, this network is an integrated component of an internal regulation system through which the brain controls visceromotor, neuroendocrinne, and behavioural responses that are critical for goal-directed behaviour and adaptability30. The primary output of the CAN is mediated through the sympathetic and parasympathetic neurons innervated the heart; therefore, it is directly linked to the heart rate variability13. Moreover, the autonomic imbalance - low parasympathetic activity and a relative sympathetic dominance indicated by low heart rate variability - can be a marker for prefrontal hypoactivity4. In ADHD children, the deficit in frontal functioning connected to limbic system and consequent alteration of baroreflex function as well as the modifications in a network of brain regions (e.g., prefrontal cortex, anterior cingulate cortex) are supposed31,32. Therefore, it is not clear whether the alteration of cardiac regulation in ADHD patients is a pure consequence of changes and pathomechanisms in various brain regions related to the modulation in autonomic activity by the central nervous system or it can be an early peripheral autonomic marker of latent asymptomatic and undiagnosed comorbid emotional and psychosomatic disorders due to accumulation of various stressors leading to these disorders.

In addition, the study of the relevant transmitter systems - specially noradrenergic and dopaminergic systems - will be important for a better understanding of ADHD and autonomic dysregulation in children with ADHD, especially linked to effective treatment. Therefore, in the explanation of autonomic nervous system changes the genetic, developmental and others factors should be considered.

Our study included a relatively small homogeneous group of patients with ADHD-combined type. Nonetheless, even with this sample size the potentially important differences in the heart rate variability between ADHD children and healthy probands were identified. The findings of this study need to be independently validated in larger groups of patients.

This study addressed mainly the changes in vagal (parasympathetic) modulation of the heart determined by the method of short-term heart rate variability (HRV) analysis, especially at high frequencies (>0.15 Hz) reflecting respiratory sinus arrhythmia. On other hand, the spectral activity in the low frequency band (0.04-0.15 Hz) is determined by activity of both autonomic - sympathetic and parasympathetic - divisions via barorreftex mechanism21. Since our study did not reveal significant difference between groups in parameters characterizing the low frequency band; conclusions regarding changes in alone sympathetic branch of autonomic nervous system in ADHD could not be drawn from the short-term heart rate variability analysis.

In conclusion, in children with ADHD the cardiovascular dysregulation (decreased cardiac vagal modulation, tachycardia, altered ability of dynamic autonomic nervous system activation during orthostatic load) was discovered using short-term heart rate variability analysis. It is known that lower heart rate variability is associated with increased risk of cardiovascular morbidity and mortality. Therefore, further studies are needed to characterize
and elucidate their mechanisms which may contribute to understanding of complex and sophisticated brain-heart relations.

Acknowledgment

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References


14. Furman L. What is attention-deficit hyperactivity disorder (ADHD)? J Child Neurol 2005; 20: 994-1002.


28. Shibagaki M, Furuya T. Baseline respiratory sinus arrhythmia and heart-rate responses during auditory stimulation of


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