



HRV IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) BEFORE AND AFTER METHYLPHENIDATE

Physiology

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ABSTRACT

The present study was conceived with the objective to measure Heart Rate Variability in children with Attention-deficit/hyperactivity disorder (ADHD) before and after treatment with Methylphenidate. ADHD is associated with autonomic dysfunction which gets further modulated with drug therapy. There are few prospective studies to evaluate the changes of HRV parameters before and after methylphenidate treatment in drug naive patients with ADHD. Baseline ADHD Conners rating score, Vanderbilt ADHD score, Clinical Global Impression score and HRV was recorded. The patients then received methylphenidate medication for a period of 12 weeks. The above parameters were repeated at 12 weeks of study period. There was a significant improvement (decrease) in the Conners scores, Vanderbilt ADHD score and Clinical Global Impression score. HRV parameters showed a significant increase in the Low Frequency in normalized units (LF nu) a significant decrease in absolute power and normalized units of High Frequency in (HF) after methylphenidate treatment. The increase in LF indicates an enhanced sympathetic activity whereas the decrease in HF indicates a decrease in the Parasympathetic activity. The LF: HF ratio a marker of sympathovagal balance showed a significant increase after 12 weeks of MPH treatment. On the Time Domain Parameters the RMSSD decreased significantly after methylphenidate treatment. The present study shows that with methylphenidate therapy as the ADHD scores improved the autonomic balance shifted in favour of sympathetic preponderance. Moreover reduction in RMSSD warrants cautious use of methylphenidate in patients vulnerable to cardiac arrhythmias.

KEYWORDS

HRV, ADHD, methylphenidate, autonomic function

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in children and adolescents with estimated worldwide prevalence of 5.29%¹. Although the etiology of ADHD yet has to be determined, there is a growing consensus that the condition involves functional and anatomical dysfunction in the brain's frontal cortex and basal ganglia segments of the cortico-basal ganglia-thalamo-cortical circuitry².

Autonomic function have consistently been found to be impaired/affected in ADHD in various studies. Abnormal catecholaminergic functioning has been thought to be a major pathophysiological mechanism in ADHD. Underarousal of the sympathetic system has been proposed in children with ADHD.³⁻⁷

The heart rate variability (HRV) is the amount of the heart rate fluctuations around the mean heart rate and is validated indicator of the function of the cardiorespiratory control system and autonomic system function including cardiac sympathetic and parasympathetic interaction^{8,9}. Spectral analysis of HRV allows a noninvasive measurement of autonomic modulation of the sinoatrial node¹⁰. HRV is considered as an index of central-peripheral neural feedback and CNS-ANS integration¹¹. HRV analysis can therefore be used to study the possible links between mental disorders and cardiac autonomic function^{12,13}.

AIM

To study in the ADHD children the HRV parameters before and after the methylphenidate therapy.

Methods

The study was carried out in the Department of Physiology in association with the Department of Psychiatry at Lady Hardinge

Medical College and Smt Sucheta Kriplani Hospital, New Delhi and was approved by the institutional ethics committee for human research.

Drug naive cases of Attention-deficit/hyperactivity disorder (ADHD) diagnosed by a Psychiatrist as per DSM - V criteria requiring methylphenidate treatment, 52 in number and were between 6 to 12 years of age were recruited¹⁴. A parent or legal guardian of the patients provided the informed written consent in either Hindi or English. Known patients of hepatic, renal, cardiovascular diseases, diabetes mellitus systemic inflammatory disorders, and mental retardation and patients showing other psychiatric co-morbidities including autism, oppositional defiant disorder, and conduct disorder or receiving medication known to affect autonomic function were excluded from the study.

All the participants were given prerecording instructions as per standard protocol and called to the Physiology department in the morning hours and general physical examination was carried out. Five minutes-segment basal recording of HRV was done after fifteen minutes of supine rest using Autonomic Neuropathy analyzer supplied by Recorders and Medicare System, Chandigarh, India as per the guidelines of Task Force of European society of Cardiology and the North American Society of Electrophysiology (1996)¹⁰. The ambient temperature was maintained at 23-25°C.

The patients were then put on methylphenidate for a period of 12 weeks. Mean dose of methylphenidate at the end point of the study was 20.58 ± 3.52 mg and mean dose per kg of body weight at the end point of the study was 0.70 ± 0.09 mg/Kg. HRV was repeated at 12 weeks of study period.

Data obtained was subjected to statistical evaluation using Graph Pad

Prism Version 7 software. The mean and standard error of mean (Mean \pm SEM) were calculated after testing for normal Gaussian distribution. Wilcoxon matched-pairs signed rank test was used to compare the difference from baseline to 12 weeks after methylphenidate treatment.

Results

Table 1 shows the height, weight, and BMI of the subjects at baseline. In the comparison of HRV measures before and after methylphenidate treatment there was a significant increase in LF nu ($p < 0.0001$) and LF/HF ($p < 0.0001$) and a significant decrease in HF (ms^2) ($p < 0.0001$), HF nu ($p < 0.0001$) and RMSSD ($p < 0.0006$). While no significant difference was obtained in LF and SDNN parameters (table 2).

Discussion

In this study, we found a statistically significant change in HRV parameters in children with ADHD after methylphenidate treatment.

There was a statistically significant increase in LF nu and LF/HF ratio after 12 weeks of methylphenidate treatment indicative of enhanced sympathetic activity. The HF and HF nu parameters which is a measure of parasympathetic activity significantly decreased after the treatment. This implies an enhancement of sympathetic activity, decrease in parasympathetic activity and a shift in sympathovagal balance towards the sympathetic arm with methylphenidate treatment

On the Time Domain Parameters, there was a decrease in the mean value of SDNN after methylphenidate treatment but the decrease was not significant. The mean value of RMSSD, however, decreased significantly ($p < 0.0006$) after 12 weeks of treatment. This indicates that not only there was a reduction in HRV, but also there was a reduction in parasympathetic modulation of cardiac autonomic activity.

Our study is in concordance with studies by several authors. In 2011 Negrao et al¹⁵ reported that stimulant-free children with ADHD showed a sympathetic underarousal and parasympathetic overarousal of the sympathovagal balance relative to control subjects and that methylphenidate shifted the autonomic balance of children with ADHD towards normal levels; however, a normal autonomic balance was not reached. In a recent study by Hayeon Jennifer Kim in 2015¹⁶, it was reported that children with ADHD show parasympathetic dominance and that methylphenidate treatment changes this parasympathetic dominance into an autonomic balance. They also reported a High frequency (HF) and the square RMSSD, which are related to parasympathetic vagal tone, showed significant decreases from baseline to endpoint of 12 weeks of methylphenidate treatment. Thus, there was a shift away from parasympathetic dominance post therapy with methylphenidate.

In our study, the changed autonomic status in patients with ADHD after methylphenidate therapy can be attributed to the decrease in resting parasympathetic activity as shown by a decrease in HF. Thereby depicting an enhancement of the sympathetic activity and a decrease in the parasympathetic activity with a decrease in the severity of illness after methylphenidate treatment.

Thus, in our study ADHD children showed an increase in sympathetic activity with methylphenidate treatment. This increased sympathetic activity was associated with the improvement in the ADHD scores.

In our study, no serious adverse events were reported during the study period. But the increase in sympathetic activity and reduction in HRV warrants a cautious use of Methylphenidate more so in children with cardiac diseases.

This study has a few limitations. No control group was taken in our study to compare the HRV with patients of ADHD. Only male patients were included in our study as no female patient met our inclusion and exclusion criteria. The sample size was small (52 patients) as patients receiving additional psychotropic drugs were excluded from the study.

Table 1: Shows the age, height weight and BMI of the subjects

| Parameters | Mean \pm SEM |
|-------------------------|------------------|
| AGE(yrs) | 8.21 \pm 0.14 |
| Height(m) | 1.34 \pm 0.01 |
| Weight(kg) | 29.44 \pm 0.45 |
| BMI(kg/m ²) | 16.33 \pm 0.22 |

Table 2: Changes in Frequency Domain and Time Domain Parameters of HRV from baseline to 12 weeks after methylphenidate treatment in the study group (Mean \pm S.E.M values)

| Parameters | Baseline | After treatment (N=52) | p value |
|---------------|------------------|------------------------|---------|
| VLF(ms^2) | 83.62 \pm 2.22 | 87.29 \pm 1.83 | 0.0868 |
| LF(ms^2) | 11.84 \pm 1.35 | 9.78 \pm 1.15 | 0.2722 |
| LF nu | 76.38 \pm 1.02 | 79.87 \pm 0.81 | <0.0001 |
| HF(ms^2) | 4.54 \pm 0.98 | 2.94 \pm 0.73 | <0.0001 |
| HF nu | 23.76 \pm 1.01 | 20.31 \pm 0.84 | <0.0001 |
| LF/HF | 3.51 \pm 0.15 | 4.32 \pm 0.20 | <0.0001 |
| SDNN | 62.94 \pm 3.79 | 54.41 \pm 3.27 | 0.1302 |
| RMSSD | 40.71 \pm 1.87 | 34.26 \pm 1.79 | 0.0006 |

p value- > 0.05-Non-Significant (NS), <0.05-Significant, <0.01-Very Significant, <0.001-Highly Significant. Wilcoxon matched-pairs signed rank test

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