

Research Article

How to Predict the Impact of Methylphenidate on Cardiovascular Risk in Children with Attention Deficit Disorder: Methylphenidate Improves Autonomic Dysfunction in Children with ADHD

Reiner Buchhorn,¹ Christian Müller,¹ Christian Willaschek,¹ and Kambiz Norozi^{2,3}

¹ Department of Paediatrics, Caritas Hospital, 97980 Bad Mergentheim, Germany

² Department of Paediatrics, The University of Western Ontario, London, ON, Canada N6A 5W9

³ Department of Pediatric Cardiology, Hannover Medical School, 30625 Hannover, Germany

Correspondence should be addressed to Reiner Buchhorn, reiner.buchhorn@ckbm.de

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Background. Although stimulants have long been touted as treatments for attention deficit disorder with or without hyperactivity (ADHD), in recent years, increasing concerns have been raised about the cardiovascular safety of these medications. We aimed to prove if measurements of autonomic function with time domain analysis of heart rate variability (HRV) in 24-hour Holter ECG are useful to predict the risk of sudden cardiac death in ADHD children and adolescents. **Methods.** We analysed HRV obtained from children with the diagnosis of ADHD prior to ($N = 12$) or during medical therapy ($N = 19$) with methylphenidate (MPH), aged 10.8 ± 2.0 years (mean \pm SD), who were referred to our outpatient Paediatric Cardiology Clinic to rule out heart defect. As a control group, we compared the HRV data of 19 age-matched healthy children without heart defect. **Results.** Average HRV parameters from 24-hour ECG in the ADHD children prior to MPH showed significant lower values compared to healthy children with respect to rMSSD (26 ± 4 ms versus 44 ± 10 ms, $P \leq 0.0001$) and pNN50 ($6.5 \pm 2.7\%$ versus $21.5 \pm 9.0\%$, $P \leq 0.0001$). These values improved in MPH-treated children with ADHD (RMSSD: 36 ± 8 ms; pNN50: $14.2 \pm 6.9\%$). **Conclusion.** Children who suffer from ADHD show significant changes in HRV that predominantly reflects diminished vagal tone, a well-known risk factor of sudden cardiac death in adults. In our pilot study, MPH treatment improved HRV.

1. Introduction

Reports of sudden death among children and adolescents receiving stimulant medications for treatment of attention deficit disorder with or without hyperactivity (ADHD) have raised concerns about the safety of these agents. In the last two years, many articles have been published about the cardiovascular safety of stimulant medication [1–6]. There are very few reports about clinically measured cardiovascular data in ADHD children and adolescents [7, 8]. It remains controversial if treatment of ADHD children with stimulants reduces or increases the risk of sudden death (SD) [6]. The assumption that stimulant-treated ADHD patients are at higher risk for SD is based on either (a) the proarrhythmogenic effects of these agents, which are closely

related members of the class of sympathomimetic amines, or (b) complicated statistical models with estimated data from uncertain data bases like the Adverse Event Reporting System. Due to the rarity of SD in pediatric populations, compared to adults, it is extremely difficult to establish a reliable model to predict sudden cardiac arrest in children and adolescents. It is the search for the needle in the haystack [2]. For the assessment of cardiac risk, there is no doubt that an accurate history and physical examination are important, but ambiguities in current screening recommendations with respect to electrocardiogram assessment show the lack of sufficient surrogate measurements [9].

The autonomic nervous system plays an important role in sudden cardiac death [10]. Twenty-four-hour Holter recordings in post myocardial infarction (MI) in adult

patients showed that depressed heart rate variability (HRV) was a significant predictor of mortality after adjusting for clinical and demographic features, including ejection fraction. These studies were further confirmed by others studying post-MI patients, who showed that impaired HRV was an independent predictor of cardiac mortality only within 6 months of MI and seemed to improve over time [10, 11]. HRV is also reduced in survivors of sudden cardiac death not associated with coronary artery disease and may be related to the decrease of parasympathetic tone [12].

Measurement of heart rate variability in 24-hour Holter ECG is completely noninvasive. Normal values are available for children [13] and adults [14].

In our pilot study, we investigate whether measurements of autonomic function with time domain analysis of HRV in 24-hour ECG are useful to determine risk factors for sudden cardiac death in patients with ADHD.

2. Methods

2.1. Subjects. We analysed HRV obtained from children with the diagnosis of ADHD prior to ($N = 12$) or during medical therapy ($N = 19$) with methylphenidate (MPH), aged 10.8 ± 2.0 years. From August 2005 to March 2010, children with the diagnosis of ADHD were referred to our Paediatric Cardiology Outpatient Clinic for cardiology assessment. The mean daily MPH dosage of 19 children on stimulant medication was 0.8 ± 0.4 mg/kg/day (9 children received methylphenidate extended release). All children received a standard 12-lead ECG, an echocardiogram, and 24-hour Holter ECG. As a control group, we compared the HRV data of 19 age-matched healthy children, who were referred to rule out cardiac defects due to heart murmur, palpitation, or chest pain.

2.2. Processing and Analysis of 24-Hour Holter Recordings. Autonomic control of cardiovagal function was assessed by time domain analysis of 24-hour ambulatory digital recordings of the electrocardiogram using a two-channel Holter monitor (Pathfinder, Spacelabs). All Holter recordings were reviewed by the same cardiologist and were edited to validate the system's QRS labelling. Measures of HRV were calculated employing only normal to normal intervals. Numbers of pairs of adjacent normal beat (NN) intervals differing by more than 50 ms were given as the percentage of the total number of all NN intervals during 24 hours (pNN50).

Measurement and physiological interpretation of HRV parameters were performed according to the standards of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [15]. RMSSD, pNN50, and heart rate reflect predominantly a response to changes in vagal tone. SDNN is dually influenced by cholinergic and adrenergic activity, as well as other physiological inputs.

2.3. Exclusion Criteria. The data of 5 children with ADHD and more than 20 premature ventricular contractions per hour were excluded.

2.4. Informed Consent. After adequate explanation of the purpose of the study, informed consent was obtained from the parents. The study protocol was approved by the local ethic committee before the start of the investigation.

2.5. Statistical Analysis. All results are reported as mean \pm standard deviation. Because all variables were normally distributed, a parametric test was used. Differences between the controls and ADHD patients with and without MPH treatment were tested with an unpaired *t*-test with Welch's correction. For all parameters, a value of $P < 0.05$ was considered statistically significant. The data analyses were performed using Excel 2003 (Microsoft, USA) and Prism (GraphPad software Inc., USA).

3. Results

All patients were in sinus rhythm and had a normal echocardiogram. As shown in Table 1, there is no significant statistical difference with respect to age between the ADHD patients (with or without MPH) and the healthy control group. Average HRV parameters from the 24-hour ECG in the ADHD children without MPH show significantly lower heart rate variability compared to the healthy children with respect to rMSSD (26 ± 4 ms versus 44 ± 10 ms, $P \leq 0.0001$) and pNN50 ($6.5 \pm 2.7\%$ versus $21.5 \pm 9.0\%$, $P \leq 0.0001$). These parameters improve significantly after MPH treatment (rMSSD: 36 ± 8 ms; pNN50: $14.2 \pm 6.9\%$). These parameters predominantly reflect changes in vagal tone. Due to these autonomic changes, untreated children with ADHD had a higher mean heart rate compared to healthy children (94 ± 7 /min versus 85 ± 10 /min). Average SDNN in ADHD patients was not significantly different from healthy children.

4. Discussion

In our pilot study, we measured time domain values of heart rate variability in 24-hour Holter ECGs in children with ADHD. Our data demonstrate significantly lower rMSSD and pNN50 values and elevated heart rates in nonpharmacologically treated ADHD children and adolescents. These parameters predominantly reflect diminished parasympathetic activity. If we adjust the data of our 12 untreated children with ADHD in the figure of published rMSSD and pNN50 normal values in children [13] and adults [14] (Figure 1), we notice that these data are not only far away from the mean values for healthy children between 8 and 13 years but also near to the dashed line, which represents cutoff for increased risk of sudden cardiac death in adults. Furthermore, we demonstrate significant improvement and almost normal values of rMSSD and pNN50 after treatment with MPH.

Our data indicate the lack of physiological maturation of autonomic function with low parasympathetic tone in children with ADHD at the average age of 10 years. From a pathophysiological point of view, patients with low parasympathetic activity have an increased risk for sudden cardiac death, independent of other risk factors. This might explain the increased baseline risk in these patients observed

TABLE 1: Heart rate variability in healthy children ($n = 19$), children with ADHD untreated ($n = 12$) and treated with methylphenidate (MPH) ($n = 19$).

| | Mean \pm SD | P 1 versus 2 | P 2 versus 3 | P 1 versus 3 |
|---------------------------|----------------|----------------|----------------|----------------|
| <i>Age (years)</i> | | | | |
| Healthy | 10.8 \pm 3.5 | | | |
| ADHD | 10.8 \pm 2.0 | $P = ns$ | $P = ns$ | $P = ns$ |
| ADHD + MPH | 10.6 \pm 2.8 | | | |
| <i>Heart rate (/min.)</i> | | | | |
| Healthy | 85 \pm 10 | | | |
| ADHD | 94 \pm 7 | $P = 0.003$ | $P = 0.04$ | $P = ns$ |
| ADHD + MPH | 90 \pm 6 | | | |
| <i>SDNN (ms)</i> | | | | |
| Healthy | 146 \pm 30 | | | |
| ADHD | 136 \pm 41 | $P = ns$ | $P = ns$ | $P = ns$ |
| ADHD + MPH | 151 \pm 25 | | | |
| <i>rMSSD (ms)</i> | | | | |
| Healthy | 44 \pm 10 | | | |
| ADHD | 26 \pm 4 | $P < 0.0001$ | $P = 0.0001$ | $P = 0.008$ |
| ADHD + MPH | 36 \pm 8 | | | |
| <i>pNN50 (%)</i> | | | | |
| Healthy | 21.5 \pm 9.0 | | | |
| ADHD | 6.5 \pm 2.7 | $P = 0.0001$ | $P = 0.0002$ | $P = 0.008$ |
| ADHD + MPH | 14.2 \pm 6.9 | | | |

Values are given in mean \pm SD. Probability of difference using student t -test; significant values are in bold; SDNN: standard deviation of all NN intervals; rMSSD: square root of the mean of the squares of differences between adjacent NN intervals; pNN50: number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals.

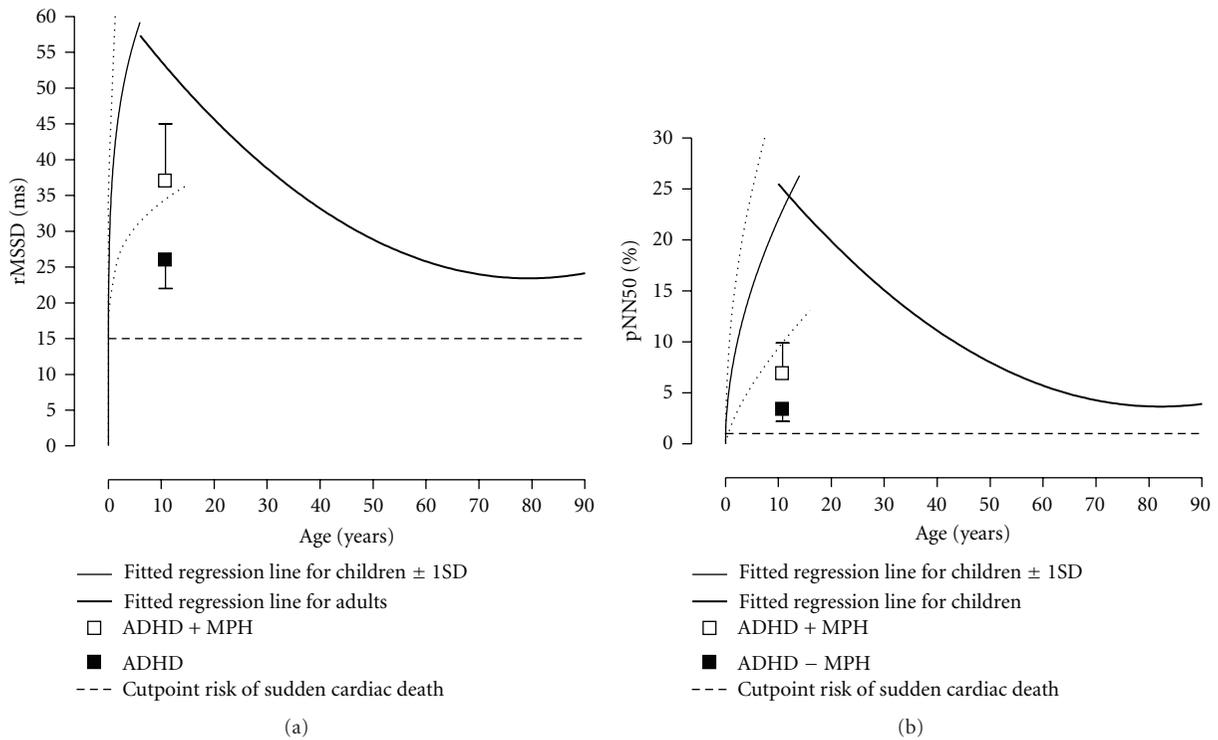


FIGURE 1: Relationship between age and the HRV parameter rMSSD and pNN50 in healthy subjects, published by Massin et al. [13] and Umetani et al. [14]. These parameters reflect parasympathetic activity of the autonomic nervous system. Solid lines: fitted regression lines \pm 1 SD line in childhood. Dashed line: published cutoffs for increased risk of mortality from sudden cardiac death. ■: Values of 12 children with ADHD and □: 19 children with ADHD treated with methylphenidate.

in former studies [3]. However, higher rMSSD and pNN50 values in our children with ADHD who were treated with MPH indicate a higher vagal tone, which is considered as protective for sudden cardiac death [10]. Our data supply the first feasible explanation why recently published population-based cohort studies showed an apparent protective association and not an increased risk of serious cardiovascular events in stimulant users [16–18]. These results need to be proven by randomized prospective studies.

In conclusion, our data provides new information about autonomic dysfunction in children with ADHD and the influence of MPH therapy, which could be important for risk stratification for sudden cardiac death in this patient cohort. In contrast to theoretical speculations that MPH treatment may increase the risk of sudden death in children with ADHD, our data demonstrate improvement of heart rate variability in Holter ECG. This indicates higher parasympathetic activity induced by MPH, which may be beneficial with respect to the risk of sudden cardiac death in ADHD children and adolescents.

Abbreviations

ADHD: Attention deficit disorder with or without hyperactivity

ECG: Electrocardiogram

HRV: Heart rate variability

MPH: Methylphenidate

NN: Normal RR intervals

pNN50: Number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals

SDNN: Standard deviation of all NN intervals

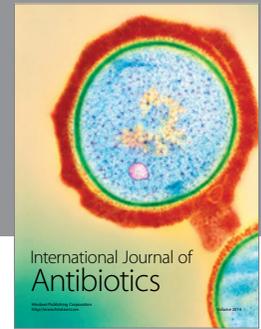
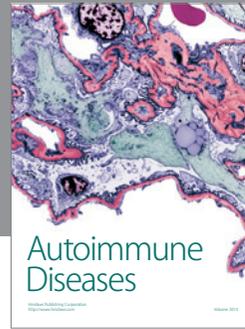
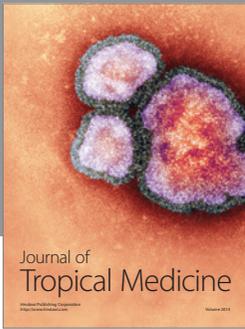
rMSSD: Square root of the mean of the squares of differences between adjacent NN intervals.

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