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Cardiac Autonomic Dysfunction and Arterial Stiffness among Children and Adolescents with ADHD Treated with Stimulants

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Abstract

Objective—Stimulant medications are used to treat attention deficit hyperactivity disorder (ADHD) but their effects on cardiac autonomic regulation, arterial stiffness, and endothelial function are largely unknown. We compared markers of cardiovascular health in youth diagnosed with ADHD using stimulant medication to healthy controls.

Study Design—Eight-five children and adolescents (mean age 11.2 ± 2.8 years; 66 boys) diagnosed with ADHD using a stimulant and 53 siblings without ADHD (mean age 11.1 ± 3.8 years; 28 boys) were included in this cross-sectional study. Measured variables included blood pressure, heart rate (HR), HR variability: standard deviation of the RR interval (SDRR) and low frequency to high frequency (LF:HF) ratio, carotid-radial pulse wave velocity (PWV), carotid artery augmentation index (AIx), radial artery AIx, brachial artery flow-mediated dilation (FMD), and digital reactive hyperemic index (RHI).

Results—Compared to controls, participants with ADHD had higher resting systolic blood pressure (3.9 mmHg, 95% CI (1.2, 6.7), $P=0.005$), diastolic blood pressure (5.5 mmHg, 95% CI (3.2, 7.8), $P<0.001$), HR (9.2 beats/minute, 95% CI (6.0, 12.3), $P<0.001$), LF:HF ratio (0.55, 95% CI (0.22, 0.89), $P=0.001$), carotid AIx (7.2%, 95% CI (1.9, 12.5), $P=0.008$), and PWV (0.36 meters/second, 95% CI (−0.05, 0.78), $P=0.089$), and lower SDRR (−33.7 milliseconds, 95% CI (−46.1, −21.3), $P<0.001$). Neither FMD nor RHI were significantly different.

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Conclusions—Children and adolescents being treated with a stimulant medication for ADHD exhibited signs of altered cardiac autonomic function, characterized by increased sympathetic tone, and showed evidence of arterial stiffening.

Keywords

Attention Deficit Hyperactivity Disorder; Arterial Stiffness; Heart Rate Variability

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders. Prevalence rates of up to 10% have been observed among children and adolescents in the United States.^{1–3} The rates of ADHD diagnosis have risen over the last decade,⁴ as has the use of medications to treat the condition.^{5–7} Stimulant medications, such as amphetamines and methylphenidates, are among the most commonly used drugs to treat ADHD.^{6–8} These centrally-acting medications activate the sympathetic nervous system by releasing and/or inhibiting the reuptake of catecholamines, primarily nor-epinephrine.⁹ As such, use of stimulant medications are associated with mild-moderate increases in heart rate (HR) and blood pressure in children and adolescents.^{10–14}

The potential for negative cardiovascular outcomes (namely arrhythmia and sudden cardiac death) with ADHD stimulant medication use among children and adolescents has received considerable attention.^{15;16} Despite initial concerns, a number of large studies have reported that stimulant medication use among children and adults was not associated with these types of adverse cardiovascular events.^{17–20} However, little consideration has been given to the potential impact of ADHD stimulant medications on cardiac autonomic function and measures of vascular health, which may have long-term implications for the development of cardiovascular disease later in life. The rationale for exploring a link between stimulant medication use and cardiovascular health is that cardiac autonomic dysfunction (characterized by activation of the sympathetic nervous system) is associated with arterial stiffening and endothelial dysfunction,^{21–25} both of which are independent predictors of cardiovascular disease among adults.^{26–32} Therefore, the aim of the present study was to compare cardiac autonomic function (measured by HR variability), arterial stiffness, and endothelial function among children and adolescents diagnosed with ADHD and currently using a stimulant medication to healthy controls.

Methods

Study Design and Eligibility Criteria

One-hundred thirty-eight children and adolescents (85 diagnosed with ADHD and 53 healthy control participants without ADHD) from a total of 83 families, ages 6–18 years old, were enrolled in this cross-sectional study. Participants with ADHD, primarily recruited from an outpatient general pediatrics clinic, were eligible if they were currently using a stimulant medication (either a methylphenidate or amphetamine preparation) for the treatment of ADHD. All siblings of the participants with ADHD between 6–18 years old were invited to participate as controls. The only exclusion criterion for either group was known/diagnosed cardiovascular disease. The study protocol was approved by the University

of Minnesota Institutional Review Board and consent/assent was obtained from parents/participants.

Measurements of Clinical Variables

All testing was performed in the morning after the participants had been fasting (including no caffeine consumption) for a minimum of eight hours. Participants were asked to refrain from smoking on the morning of study visit. Participants with ADHD were observed (by study staff) taking their respective stimulant medication 90 minutes prior to hemodynamic and vascular testing. Height and weight were determined using a wall-mounted stadiometer and an electronic scale, respectively. Body mass index (BMI) was calculated as the body weight in kilograms divided by the height in meters squared. Seated blood pressure and HR were measured after the participant had been resting quietly without legs crossed for 10 minutes. Blood pressure and HR were measured three consecutive times with an automated blood pressure cuff at approximately 3-minute intervals. The average of the three respective blood pressure and HR measurements was used. Self-reported Tanner stage and physical activity levels were collected.

Measurement of Heart Rate Variability

The SphygmoCor® MM3 system (AtCor Medical, Sydney, Australia) was used to measure supine HR variability after participants had been at rest for approximately 10 minutes. The electrocardiogram signal was continuously recorded throughout the 15-minute data collection period. Only data collected during the last five minutes were used for analysis, and this segment was reviewed for ectopic heart beats or arrhythmias. Any portions of the selected segment with abnormal electrocardiogram signals were excluded from analysis. Automated algorithms were used to calculate the standard deviation of the RR interval (SDRR), low frequency, high frequency, and the low frequency to high frequency (LF:HF) ratio, all of which are metrics of the overall sympathovagal balance of the autonomic nervous system. Low values of the SDRR and high values of LF:HF are suggestive of a state of elevated sympathetic tone and/or reduced parasympathetic tone.³³

Measurements of Arterial Stiffness

Carotid artery and radial artery augmentation index (AIx) (both corrected to a heart rate of 75 beats per minute) and carotid-radial pulse wave velocity (PWV) were measured by the SphygmoCor® MM3 system. Augmentation index is a measure of the relative magnitude of the reflected (or retrograde) pulse wave early in the cardiac cycle. Higher values of AIx represent increased arterial stiffening. Pulse wave velocity was calculated as distance divided by transit time. Since pulse wave transit time increases in stiffer arterial segments, higher values of PWV represent increased arterial stiffness.

Measurements of Endothelial Function

Endothelial function was simultaneously assessed by digital reactive hyperemic index (RHI) (using the EndoPAT 2000, Itamar Medical, Caesarea, Israel), a measure of microvascular function, and brachial artery flow-mediated dilation (FMD) (using a standard ultrasound - Siemens, Sequoia 512, New York, NY), a measure of conduit artery function. Following

baseline measurements in the index fingers and brachial artery, a blood pressure cuff was placed on the forearm (just below the elbow) and inflated to a supra-systolic level for five minutes. RHI was derived from an automated algorithm that calculated the ratio of pulse amplitude for 60 seconds beginning one minute after cuff release (an average of the 60- to 90-second and 90- to 120-second intervals) to the baseline pulse amplitude divided by the corresponding ratio in the control finger. Electronic wall-tracking software (Medical Imaging Applications, Coralville, IA) was used for the measurement FMD as previously described by our group.³⁴

Statistical Analysis

Descriptive statistics were tabulated separately for subjects with ADHD and control subjects. P-values presented in Table 1 were based on t-tests for continuous covariates and chi-squared tests for categorical covariates. General estimating equations (GEE) were used with an exchangeable working correlation structure with clusters defined by families to take into account potential correlation between siblings. Differences between groups were adjusted for sex, race, and Tanner stage, selected a priori for their role as potential confounders or precision variables. Robust variance estimation was used for confidence intervals and P-values. All statistical analyses were performed using R v2.15.2 (R Foundation for Statistical Computing, Vienna, Austria) and the ‘gee’ library v4.13-18.

Results

Mean age and Tanner stage distribution were similar between the groups (Table 1). The percentage of females in the ADHD group was lower compared to the control group (22% vs. 47%, respectively). Although the mean BMI percentile was lower in the ADHD group compared to controls, there was no statistically significant difference in the proportion of obese participants between the groups. In the ADHD group, approximately 44% of the participants were treated with an amphetamine and approximately 56% were treated with methylphenidate preparations. The mean cumulative time treated with a stimulant was approximately 3 years. Physical activity levels were similar between the groups. Within the previous 14 days, 28% in each group reported engaging in vigorous exercise for at least 20 minutes on nine or more days.

Table 2 shows the hemodynamic and vascular results. When adjusted for sex, race, and Tanner stage, compared to controls, participants with ADHD had higher resting systolic blood pressure (3.9 mmHg, 95% CI (1.2, 6.7), $P=0.005$), diastolic blood pressure (5.5 mmHg, 95% CI (3.2, 7.8), $P<0.001$), HR (9.2 beats/minute, 95% CI (6.0, 12.3), $P<0.001$), LF:HF ratio (0.55, 95% CI (0.22, 0.89), $P=0.001$), carotid AIx (7.2%, 95% CI (1.9, 12.5), $P=0.008$), a trend toward higher PWV (0.36 meters/second, 95% CI (−0.05, 0.78), $P=0.089$), and lower SDRR (−33.7 milliseconds, 95% CI (−46.1, −21.3), $P<0.001$). There were no statistically significant differences between groups for radial AIx ($P=0.286$), FMD ($P=0.906$), or RHI ($P=0.627$). The differences between subjects with ADHD and controls were not appreciably different when evaluated by drug class (amphetamines vs. methylphenidates).

A separate analysis was performed with additional adjustment for BMI percentile, and the results were not appreciably different from the results presented above. Further analyses were conducted with adjustment for HR and systolic blood pressure, though these factors may be in a causal pathway of stimulants on HR variability and arterial stiffness. These additional, exploratory analyses demonstrated that the magnitude of effect for SDRR, LF:HF ratio, and carotid AIx was attenuated by 32%, 75%, and 9% respectively, suggesting HR and systolic blood pressure account for some, but not all, of the difference for some of the HR variability and vascular measures.

There was not a meaningful relationship between cumulative time of exposure to stimulant medication and any of the hemodynamic or vascular variables. Similarly, no significant association was observed between stimulant medication dose and any of the hemodynamic or vascular variables.

Discussion

Results of this study demonstrate that children and adolescents diagnosed with ADHD and treated with a stimulant medication have altered cardiac autonomic function and arterial stiffness. The HR variability findings suggest that the balance between the parasympathetic and sympathetic nervous systems is tipped in favor of sympathetic activation by a magnitude of approximately 50% among these youth. In fact, the mean values for many of the HR variability measures among participants with ADHD in the current study were more extreme than the values reported in studies of obese children and adolescents³⁵ and of youth with type 1 diabetes,³⁶ diseases known to be associated with increased cardiovascular risk, albeit likely via additional and/or different pathophysiological mechanisms. Additionally, carotid artery AIx, radial artery AIx, and PWV were higher in those with ADHD compared to controls, indicating elevated arterial stiffness.

The cross-sectional nature of the study and lack of participants with untreated ADHD prevents us from determining whether the disease itself or the treatment (stimulant medication) is the primary cause of cardiac autonomic dysfunction and arterial stiffness. Based on the known mechanisms of action of centrally-acting sympathomimetic drugs such as amphetamines and methylphenidates,⁹ the results could be explained through a physiological construct whereby stimulant medications induce sympathetic activation, which then leads to the clinical manifestation of increased HR, blood pressure, and arterial stiffening. Therefore, one hypothesis posits that stimulant medication may cause cardiac autonomic dysfunction and arterial stiffening among children and adolescents with ADHD. Alternatively, ADHD, in the absence of stimulant treatment, may be associated with altered hemodynamic and vascular parameters.

The results did not demonstrate any meaningful relationship between cumulative months/years of exposure to stimulant medication and any of the hemodynamic or vascular variables. Based upon the mechanism of action of stimulant medications, the hemodynamic and autonomic effects might be fully apparent in the acute setting, as was evaluated in the current study, and may not worsen with continued, chronic use. In fact, these effects may wane in the ensuing hours after administration (particularly evening/overnight hours);

however, our study was not designed to evaluate this possibility. Indeed, a longitudinal study would be necessary to adequately address this question. Interestingly, no significant association was observed between stimulant medication dose and any of the hemodynamic or vascular variables, giving no indication of a dose-response relationship. This may suggest that ADHD, as an underlying condition, could explain the vascular differences or that the use of higher doses of stimulant medication to treat ADHD symptoms may not elicit a higher magnitude of cardiac or vascular dysfunction.

Although many of the measures of cardiac autonomic- and vascular health obtained in this study are used exclusively in the research setting and lack normative pediatric ranges, some discussion of the potential clinical implications and future research directions is warranted. The main objective of this study was to evaluate sub-clinical differences in these measures, which are known to be associated with increased cardiovascular risk. Sympathetic nervous system activation and arterial stiffness are often linked, and the latter is considered to be an independent risk factor for cardiovascular disease among adults.^{21–24;26;27} Therefore, it is reasonable to postulate that the altered cardiac autonomic function, increased arterial stiffness, and unfavorable hemodynamics (higher blood pressure and HR) associated with either ADHD and/or stimulant medication use may place these children and adolescents at increased risk for developing cardiovascular disease later in life if the effects were to persist.

The primary limitation of the current study was its observational and cross-sectional nature, which precludes the determination of whether stimulant medication and/or ADHD explain the negative cardiovascular effects observed in this study. In this way, the results should be considered hypothesis-generating, and caution should be exercised in interpreting the results. The possibility exists that untreated children and adolescents with ADHD may exhibit altered cardiac autonomic function and increased arterial stiffness as a natural consequence of the disorder itself (i.e., it may be related to the underlying pathophysiology of the condition), and that stimulant medications are not responsible for the cardiovascular effects. Two small pilot studies have reported divergent findings regarding cardiac autonomic function among non-medicated children with ADHD,^{37;38} essentially leaving this question unanswered. One longitudinal study demonstrated that childhood hyperactivity predicted carotid artery intima-media thickness in adult women.³⁹ Although ADHD was not specifically addressed in the study, the finding suggests that temperament during childhood may be associated with cardiovascular outcomes later in life. In the current study, co-existing psychiatric conditions (e.g. anxiety, depression) were not evaluated. Strengths of the current study included a relatively large sample size (although precision may have been lacking for some of the measured variables and precluded statistically significant findings) and the comprehensive panel of non-invasive cardiovascular measurements obtained.

In conclusion, the results of the current study demonstrate that children and adolescents diagnosed with ADHD who use a stimulant medication have an unfavorable hemodynamic profile, adverse cardiac autonomic function, and increased arterial stiffness. The long-term health significance of these observations is unclear. However, in light of these findings, the question arises of whether children and adolescents with ADHD who use these drugs may be at increased risk of developing cardiovascular disease later in life if these effects were to persist. Prospective studies will need to investigate the issue of causation in regard to

stimulants and address whether the adverse cardiovascular effects persist into adulthood after cessation, or with continuation, of medication use.

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Table 1

Demographic Characteristics of the ADHD and Control Groups

Covariate	ADHD (N=85)	Control (N=53)	P-value
Age (years)	11.2 (2.8)	11.1 (3.8)	0.844
Height (cm)	144 (16.6)	145 (21.1)	0.772
Weight (kg)	38.6 (16.3)	44.1 (21.6)	0.113
BMI (kg/m ²)	17.8 (4.1)	19.6 (4.9)	0.028
BMI Percentile (%)	42.6 (33.1)	59.6 (30.6)	0.003
BMI 95 th Percentile	7 (8.2%)	6 (11.3%)	0.761
Tanner Stage			0.248
- I	54 (63.5%)	30 (56.6%)	
- II	6 (7.1%)	4 (7.5%)	
- III	5 (5.9%)	5 (9.4%)	
- IV	15 (17.6%)	7 (13.2%)	
- V	3 (3.5%)	7 (13.2%)	
- Missing Tanner	2 (2.4%)	0 (0.0%)	
Female	19 (22.4%)	25 (47.2%)	0.004
Not Latino/Hispanic	79 (92.9%)	50 (94.3%)	>0.999
Race			0.757
- Asian	1 (1.2%)	0 (0.0%)	
- Black	5 (5.9%)	2 (3.8%)	
- White	68 (80.0%)	43 (81.1%)	
- Other/mixed	10 (11.8%)	8 (15.1%)	
- Missing race	1 (1.2%)	0 (0.0%)	
Amphetamine	37 (43.5%)	0 (0.0%)	N/A
Methylphenidate	48 (56.5%)	0 (0.0%)	N/A
Cumulative Stimulant Exposure (years)	2.79 (2.42)	N/A	N/A

Values presented are mean (SD) or N (%) where indicated.

Table 2

Hemodynamic and Vascular Variables in the ADHD and Control Groups

Covariate	ADHD (N=85)	Control (N=53)	Adjusted Diff. (95% CI)	P-Value
SBP (mmHg)	113 (10.4)	109 (11.5)	3.9 (1.2, 6.7)	0.005
SBP Percentile (%)	72.5 (23.0)	60.4 (25.7)	10.3 (3.7, 16.9)	0.002
DBP (mmHg)	61.1 (7.7)	55.9 (7.9)	5.5 (3.2, 7.8)	<0.001
DBP Percentile (%)	48.2 (22.7)	32.3 (19.8)	16.0 (9.5, 22.6)	<0.001
Heart Rate	84.1 (12.5)	73.3 (10.5)	9.2 (6.0, 12.3)	<0.001
SDRR (ms)	65.8 (30.1)	98.8 (43.0)	-33.7 (-46.1, -21.3)	<0.001
LF:HF ratio	1.56 (1.3)	1.03 (0.8)	0.55 (0.22, 0.89)	0.001
Carotid AIx (%)	2.93 (14.9)	-2.29 (16.6)	7.2 (1.9, 12.5)	0.008
Radial AIx (%)	2.03 (14.6)	0.79 (17.8)	2.77 (-2.32, 7.86)	0.286
PWV (m/s)	7.4 (1.24)	7.13 (1.2)	0.36 (-0.05, 0.78)	0.089
FMD (%)	6.2 (3.5)	6.2 (2.8)	-0.07 (-1.27, 1.13)	0.906
RHI	1.44 (0.38)	1.44 (0.31)	0.03 (-0.10, 0.16)	0.627

Values presented are mean (SD) and mean difference (95% CI), adjusted for sex, race (white vs. others), and Tanner stage (stage I vs. others).