Cardiac Autonomic Dysfunction and Arterial Stiffness among Children and Adolescents with Attention Deficit Hyperactivity Disorder Treated with Stimulants

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Objective To compare markers of cardiovascular health in youth diagnosed with attention deficit hyperactivity disorder (ADHD) by the use of stimulant medication with healthy controls.

Study design Children and adolescents (n = 85; 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: SD of the RR interval and low frequency to high frequency ratio, carotid-radial pulse wave velocity, carotid artery augmentation index (AIx), radial artery AIx, brachial artery flow-mediated dilation, and digital reactive hyperemic index.

Results Compared with control patients, participants with ADHD had greater resting systolic blood pressure (3.9 mm Hg, 95% CI [1.2-6.7], $P = .005$), diastolic blood pressure (5.5 mm Hg, 95% CI [3.2-7.8], $P < .001$), HR (9.2 beats/min, 95% CI [6.0-12.3], $P < .001$), low frequency to high frequency ratio (0.55, 95% CI [0.22-0.89], $P = .001$), carotid AIx (7.2%, 95% CI [1.9-12.5], $P = .008$), and pulse wave velocity (0.36 m/s, 95% CI [−0.05, 0.78], $P = .089$), and lower SD of the RR interval (−33.7 milliseconds, 95% CI [−46.1, −21.3], $P < .001$). Neither flow-mediated dilation nor reactive hyperemic index was significantly different.

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. *(J Pediatr 2014;165:755-9)*.

See related article, p 750

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders. A prevalence of up to 10% has been observed among children and adolescents in the US.[1-3] The prevalence of ADHD diagnosis has increased during 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 norepinephrine.[9] The use of stimulant medications is associated with mild-to-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 the use of stimulant medication 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]

ADHD	Attention deficit hyperactivity disorder
AIx	Augmentation index
BMI	Body mass index
FMD	Flow-mediated dilation
HR	Heart rate
LF:HF	Low frequency to high frequency
PWV	Pulse wave velocity
RHI	Reactive hyperemic index
SDRR	Standard deviation of the risk ratio interval

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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 with healthy control patients.

Methods

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, 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 and 18 years of age 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.

All testing was performed in the morning after the participants had been fasting (including no caffeine consumption) for a minimum of 8 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 before 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 3 consecutive times with an automated blood pressure cuff at approximately 3-minute intervals. The average of the 3 respective blood pressure and HR measurements was used. Self-reported Tanner stage and physical activity levels were collected.

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 5 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 risk ratio 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 increased sympathetic tone and/or reduced parasympathetic tone.[33]

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

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—Sequoia 512; Siemens, New York, New York), a measure of conduit artery function. After 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 5 minutes. RHI was derived from an automated algorithm that calculated the ratio of pulse amplitude for 60 seconds beginning 1 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, Iowa) was used for the measurement FMD as previously described by our group.[34]

Statistical Analyses

Descriptive statistics were tabulated separately for subjects with ADHD and control subjects. *P* values presented in **Table I** were based on *t* tests for continuous covariates and χ^2 tests for categorical covariates. General estimating equations 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 and were selected a priori for their role as potential confounders or precision variables. Robust variance estimation was used for CIs and *P* values. All statistical analyses were performed with 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 I**). The percentage of females in the ADHD group was lower compared with the control group (22% vs 47%, respectively). Although the mean BMI percentile was lower in the ADHD group compared with control patients, 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