Published in final edited form as:

J Clin Psychopharmacol. 2016 June ; 36(3): 295–297. doi:10.1097/JCP.0000000000000485.

Heart Rate Recovery and Systolic Blood Pressure Recovery after Maximal Exercise in Prevalent Users of Stimulant Medications

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To the Editors

Increasing use of prescribed stimulant medications among adults¹ and a study that linked their use to increased risk of ventricular arrhythmia and sudden death² have increased concerns about their cardiovascular safety. Acute methylphenidate use has been shown to increase heart rate (HR) compared to placebo during exercise.³ However, our recent study found that prevalent use of stimulant medications was associated with *decreased* peak HR during maximal exercise testing.⁴ Additionally, stimulant medication users had an increased risk of chronotropic incompetence (defined as an inappropriately low HR in the face of activity demands) which has been associated with serious cardiovascular events and mortality.⁵ This unexpected finding led us to hypothesize that autonomic adjustment immediately after exercise might be abnormal in stimulant users—heart rate recovery (HRR) and systolic blood pressure (SBP) recovery. Following exercise, HR and BP normally decrease to resting levels via reactivation of vagal tone in healthy persons and withdrawal of sympathetic neural drive. However, the autonomic influence of stimulants during recovery

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Disclosures

Dr. Westover is a consultant for Intra-Cellular Therapies on a research study. Dr. Brown has received research grants from Forest Laboratories and Sunovion. Dr. Vongpatanasin has a research grant from the Forest Research Institute. None of these grants/relationships involve stimulant medications. The remaining authors report no financial relationships with commercial interests.

from exercise has never been adequately assessed. Two prior studies of stimulant medications have demonstrated delayed HRR after exercise testing.^{6,7} Adults with attention deficit hyperactivity disorder (ADHD) on stimulant medications (n=29) had a significant 7 bpm elevation in 1-minute HRR compared to controls (n=27) during symptom-limited treadmill exercise testing (p=0.001). Similarly, in an open-label study of 15 adults who underwent exercise testing before and after 3–6 months of treatment with lisdexamfetamine, the 1-minute HRR increased by 4.3 bpm by study end (p=0.05). The aim of the present study was to determine, in a large sample, whether stimulant medication users compared to matched nonusers have an increased risk of abnormal HRR and abnormal SBP recovery after a maximal exercise test while matching/adjusting for fitness, obesity, smoking and other covariates.

This propensity-score matched cross-sectional design, consisting of persons enrolled in the Cooper Center Longitudinal Study (CCLS) cohort from 1995 to 2013, has been previously described.⁴ Some 42,214 participants were considered for study inclusion. Participants reporting a history of ADHD without use of a stimulant medication were excluded due to concerns about unreported stimulant use and confounding by contraindication (n=976), as were participants who had no available information or response to whether they had been previously diagnosed with ADHD (n=6,264). Participants who used an antihypertensive medication (n=6,072), atomoxetine (n=13), a eugeroic medication (modafinil/armodafinil; n=28), or an over-the-counter drug or supplement possibly containing ephedra (n=81) were excluded. History of myocardial infarction (n=354) or stroke (n=170), no recorded time on the treadmill (n=32), resting SBP ≥ 160 mmHg (n=5), and missing values for covariates (n=8,475) were additional exclusion factors. After exclusions, 19,744 participants were available for propensity score matching. Prior to exercise testing, participants reported all current medications. Participants reporting use of a sympathomimetic-type stimulant medication (described in Appendix A of previous study)⁴ were classified as users (n=245), while participants who did not report stimulant use were classified as nonusers (n=19,499). Dosage and duration of use were unavailable. Participants were instructed to continue taking all prescribed medications prior to exercise testing. Each participant underwent a previously described maximal treadmill exercise test using a modified Balke protocol.⁸ The test ended when the participant reached volitional fatigue or the physician terminated it for medical reasons. Participants were encouraged to give maximal effort. Outcome measures for this study were abnormal HRR and abnormal SBP recovery. Abnormal HRR was defined as the presence of a ≥ 12 beats/minute difference between the HR at peak exercise and 1 minute post-exercise.⁹ SBP recovery was defined as a ratio ≥ 1.0 for 3 minutes post-exercise to 1 minute post-exercise SBP.¹⁰ Baseline covariates were used for propensity score matching and were also included in all of the analytic mixed models. Self-report of current alcohol use, current smoking, family history of heart disease, history of diabetes mellitus, history of high cholesterol, current use of lipid-lowering medication, and history of hypertension were binary indicators. Self-report of physical activity (MET-min) was log transformed to obtain a more normal distribution (because of positive skewness). PAI is an ordinal measure of baseline exercise activity with the following levels: 0 (no organized physical activity), 1 (non-running activities), 2 (0–10 miles/week running), 3 (11–20 miles/week running), and 4 (>20 miles/week running). A propensity score-matched cohort of stimulant users and

nonusers was created using the 18 baseline covariates and has been previously described.⁴ A multiple logistic mixed model analysis, while accounting for blocked matching as a random effect, was used to estimate the odds of HRR and SBP recovery from stimulant exposure, with adjustment for the 18 covariates included in the model. In a logistic mixed model analysis for each outcome, similar to that described above, each individual covariate was tested in subsequent (*post hoc*) models for interaction with stimulant medication exposure status (with adjustment for the other covariates in the model). To assess a moderator effect, the odds of abnormal HRR and SBP recovery were estimated at each level of the categorical moderator. To ascertain the presence of multicollinearity in our multiple logistic regression models, we examined the variance inflation factor for each of the 18 covariates in each model. The estimated variance inflation factors for the covariates ranged from 1.01 to 2.20, suggesting that multicollinearity was not present or problematic. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC). The GMATCH computational SAS macro was used to implement the propensity score matching.¹¹ The level of significance for all tests was set at $\alpha=.05$ (two-tailed). The False Discovery Rate (FDR) procedure was implemented to control for false-positives.

Prior to propensity score matching, stimulant medication users and nonusers differed across many of the 18 observed covariates, but after the propensity score matching procedure, matched users and nonusers were very similar across the 18 observed covariates as previously described.⁴ In the study, 74 (7.6%) of all participants and 27 (11.0%) of the stimulant medication users had abnormal HRR. The covariate-adjusted logistic mixed model revealed that stimulant medication users compared to propensity-score matched nonusers had significantly increased predicted odds of abnormal HRR (adjusted odds ratio [AOR] = 1.87, 95% CI = 1.06 to 3.33, $F[1, 790]=4.60$, raw $p=0.032$, FDR-adjusted $p=0.032$). Similarly, 186 (19.0%) of all study participants and 62 (25.3%) of the stimulant medication users had abnormal SBP recovery. The covariate-adjusted logistic mixed model for abnormal SBP recovery demonstrated increased predicted odds for stimulant medication users compared to matched nonusers (AOR = 1.70, 95% CI = 1.18 to 2.46, $F[1, 735.2]=8.14$, raw $p=0.004$, FDR-adjusted $p=0.008$). In a logistic mixed model analysis for HRR and SBP recovery, each individual covariate was tested in subsequent (*post hoc*) models for interaction with stimulant medication exposure status (with adjustment for the other covariates in the model). A significant interaction effect between stimulant medication use and physical activity index (PAI) for both HRR ($p=0.049$) and SBP recovery ($p=0.038$) outcomes was observed. Stimulant medication users who had a greater level of baseline exercise activity had greater predicted odds of abnormal HRR and SBP recovery compared to nonusers with the same level of baseline exercise activity. At PAI levels 0 and 1, adjusted odds of HRR and SBP recovery in stimulant users compared to nonusers were not significantly elevated. But for PAI levels 2–4, the adjusted odds ratio for stimulant users compared to nonusers was significantly increased at each level in an escalating fashion (data not shown). The AOR for stimulant users compared to nonusers at PAI 4 was 8.92 (CI 1.73 to 45.9, $p=0.009$, FDR-adjusted $p=0.015$) and 4.60 (1.69 to 12.6, $p=0.003$, FDR-adjusted $p=0.005$) for HRR and SBP recovery, respectively.

Discussion

To our knowledge, this is the first study to examine the impact of stimulant medication use on HRR and SBP recovery after maximal exercise testing in a large sample with adjustment for confounders such as fitness, obesity, and smoking. In this cross-sectional study, stimulant medication users had increased odds of both abnormal HRR and abnormal SBP recovery compared to matched nonusers. Increased levels of baseline physical activity moderated the increased odds of abnormal HRR and SBP recovery among stimulant users versus nonusers. This study builds on two prior studies that demonstrated delayed HRR^{6,7} and our prior study of the same participants that showed an increased risk of chronotropic incompetence in stimulant medication users compared to matched nonusers.⁴ Abnormal HRR and SBP recovery, as well as chronotropic incompetence, are risk factors for all-cause mortality.^{5,9,10} In two large pharmacoepidemiological studies of stimulant medication use in adults, one did not find an increased risk of serious cardiovascular events,¹² but the other found an increased risk of both sudden death/ventricular arrhythmia and all-cause death.²

These results suggest that autonomic regulation during maximal exercise is altered in users of stimulant medications. The initial phase of HRR after exercise—especially the first minute—is dominated by parasympathetic activation. Only later does the withdrawal of sympathetic activation play a significant role in HRR.¹³ Increased odds of abnormal HRR (1-minute) among stimulant users suggest that parasympathetic activation is impaired. This is consistent with a “chronic systematic stress syndrome”—congestive heart failure is the best known example and is characterized by “elevated circulating catecholamines, down regulation of beta adrenergic receptors, depletion of myocardial catecholamines, decreased catecholamine turnover rate, and decreased vagal tone as evidenced by decreased heart rate variability [HRV].”¹³ A recent study evidenced significantly decreased HRV in child/adolescent prevalent users of stimulant medications compared to nonuser siblings.¹⁴ Decreased HRV is associated with sudden death.¹⁵ Thus the association between stimulant medication use and increased risk of sudden death previously observed by Schelleman et al.² could be mediated by impaired parasympathetic activation as evidenced by abnormal HRR and SBP recovery, and decreased HRV.

Heart failure patients experience delayed HRR, but athletes experience accelerated HRR.¹³ However, we found that stimulant users who reported higher baseline physical activity were at greatest risk for delayed HRR and SBP recovery. Plasma norepinephrine (NE) increases exponentially at higher levels of exercise effort,¹⁶ and the greater the intensity of exercise the more important the contribution of withdrawal of sympathetic stimulation towards deceleration of HR.¹⁷ From a prior animal study, it is known that when both the sympathetic and parasympathetic nervous systems are activated, the parasympathetic dominates.¹⁸ Thus we may hypothesize in the setting of stimulant-induced impaired parasympathetic activation, higher levels of sympathetic activation (i.e. NE) in fitter stimulant users might manifest as delayed HRR and SBP recovery; whereas in nonusers the parasympathetic activation dominates/overrides sympathetic activation regardless of effort/fitness. Moreover, overtraining (a known cardiac stress) could play a role.

Strengths of this study include its large sample size, rigorous measurement of baseline characteristics (including smoking status, fitness level, and BMI), tight propensity-score matching between stimulant medication users and nonusers, and ascertainment of over-the-counter drug supplement use. A limitation of the study is the inability to determine motivation/effort during the exercise testing. If stimulant users were more motivated than nonusers, we would not have expected to observe decreased peak HR among the users.⁴ If users were less motivated than nonusers, we would not have expected to observe delayed HRR in users, as rapid parasympathetic activation accelerates HRR in the setting of submaximal exercise.¹³ Mitigating concern about this somewhat, however, is that aerobic capacity (estimated VO₂max) was not significantly different between exposure groups during exercise testing.⁴ Stimulant medication users, like all participants, were instructed to take their medications as prescribed prior to exercise, but the timing of such doses were not available. If we assume some users took the medication before exercise testing and some did not, this mixing of effects would tend to bias results to the null. If dosing information were available in CCLS, it would have allowed for testing of a dose response relationship. No dose response relationship between stimulant medication use and decreased HRV was observed in a prior study.¹⁴ Decreased HRV and prior lifetime dosing were not related in the study of currently abstinent adults with methamphetamine dependence.¹⁹ Others have noted the lack of a relationship between stimulant dosing and cardiovascular outcomes.²⁰ Schelleman et al. observed no dose-response relationship between stimulants and ventricular arrhythmia and sudden death.² These prior results suggest a dose-response relationship would not have been observed. Had duration of stimulant use been available, the differential impact of acute and chronic use could have been tested. In this sample of prevalent users, we assume chronic use predominates. Assuming acute use and chronic use have inverse effects, the mixing of acute and chronic users would bias the results to the null.

In summary, abnormal HRR and SBP recovery in stimulant users suggests chronic adaptation of the autonomic nervous system and impairment of parasympathetic activation during exercise recovery. These findings suggest a pathway by which stimulant use may mediate ventricular arrhythmia and sudden death as previously observed.² Exercise outcomes may have the potential to be useful intermediate outcomes in assessing stimulant-associated cardiovascular risk in individuals and subgroups, as well as future studies where ventricular arrhythmia and sudden death are not practical outcomes.

Acknowledgments

Grant Support:

NIH, NIDA 5K08DA031245

NIH, AHRQ R24 HS022418

O'Brien Kidney Center (NIH P30DK079328)

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