Exercise Training Improves Heart Rate Variability after Methamphetamine Dependency

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ABSTRACT

Purpose: Heart rate variability (HRV) reflects a healthy autonomic nervous system and is increased with physical training. Methamphetamine dependence (MD) causes autonomic dysfunction and diminished HRV. We compared recently abstinent MD participants with age-matched, drug free controls (DF) and also investigated whether HRV can be improved with exercise training in the MD participants. Methods: In 50 participants (MD=28; DF=22) resting heart rate (R-R intervals) was recorded over 5 min while seated using a monitor affixed to a chest strap. Previously reported time-domain (SDNN, RMSSD, pNN50) and frequency-domain (LFnu, HFnu, LF/HF) parameters of HRV were calculated with customized software. MD were randomized to thrice weekly exercise training (ME=14) or equal attention without training (MC=14) over 8 weeks. Groups were compared using paired and unpaired t-tests. Statistical significance was set at P≤0.05. Results: Participant characteristics were matched between groups: age 33±6 years; body mass 82.7±12 kg, BMI 26.8±4.1 kg•min^{-2}, mean±SD. Compared with DF, the MD group had significantly higher resting heart rate (P<0.05), LFnu, and LF/HF (P<0.001) as well as lower SDNN, RMSSD, pNN50 and HFnu (all P<0.001). At randomization, HRV indices were similar between ME and MC groups. However, after training, the ME group significantly (all P<0.001) increased SDNN (+14.7±2.0 ms, +34%), RMSSD (+19.6±4.2 ms, +63%), pNN50 (+22.6±2.7%, +173%), HFnu (+14.2±1.9, +60%) and decreased HR (-5.2±1.1 beats•min^{-1}, -7%), LFnu (-9.6±1.5, -16%) and LF/HF (-0.7±0.3, -19%). These measures did not change from baseline in the MC group. Conclusion: HRV, based on several conventional indices, was diminished in recently abstinent, methamphetamine dependent individuals. Moreover, physical training yielded a marked increase of HRV representing increased vagal modulation or improved autonomic balance. Key Words: HRV; substance use; autonomic nervous system; vagal modulation.
INTRODUCTION

Heart rate variability (HRV) is a reliable, non-invasive measure that reflects the balance of sympathetic and vagal neural influences on heart rate (1). It is defined as the changes in the interval between heartbeats (R-R intervals) over time. HRV is thought to reflect the ability of the autonomic nervous system (ANS) to adapt to changing circumstances by detecting and quickly responding to unpredictable stimuli. Generally a healthy ANS is reliant on dominant vagal modulation. By contrast, the effect of chronic, excessive sympathetic stimulation and/or diminished vagal modulation from illness causes ANS dysfunction and sympathovagal imbalance (10).

HRV is recognized as a versatile and promising prognostic marker to detect ANS dysfunction in people with diseases such as diabetes, metabolic syndrome, systemic hypertension, stroke, renal failure and more recently obesity and obstructive sleep apnea (1, 10, 25). Population studies such as the Framingham Heart Study have found that ANS imbalance consisting of hyperactive sympathetic and/or diminished vagal modulation, and reflected by low HRV, is associated with cardiovascular pathologies such as coronary heart disease, cardiomyopathy and sudden cardiac death (19, 20). In addition, HRV is now thought to be a more powerful predictor of sudden death compared to any other cardiovascular disease marker.

Other studies underscore the significance of HRV in assessing cardiac health in vulnerable populations. In particular, studies have shown ANS dysfunction, as determined through diminished HRV, among the deleterious health effects of abused substances such as alcohol (38), sympathomimetics including cocaine (39) and, more recently, methamphetamine (18). Methamphetamine is an illicit psychostimulant used for non-medical purposes worldwide by an
estimated 13.7 to 52.9 million people (8). More potent than its parent compound amphetamine due to its lipophilic nature and increased central nervous system penetration, methamphetamine dependence (MD) is believed to lead to dopaminergic neurotoxicity and cardiovascular toxicity through the release of excess stored catecholamines, resulting in acceleration of acute and chronic cardiovascular diseases such as coronary artery disease, myocardial infarction, aortic dissection, cardiomyopathy and sudden cardiac death (24, 31, 40).

Although behavioral approaches have proven moderately successful in treating MD, problems remain with substantial proportions of individuals dropping out early in treatment. Furthermore, many methamphetamine users are unable to sustain gains from treatment and avoid post-treatment relapse (29). Participation in regular physical exercise may be an effective intervention to aid MD individuals in reducing relapse to drug use (9). Exercise has proven effective in ameliorating symptoms of depression and anxiety while improving cognition and cognitive deficits found in chronic methamphetamine users (6, 33). Furthermore, exercise may have a salutary effect on reducing cardiovascular risk factors, such as hypertension and tachycardia, which are associated with methamphetamine use.

While prior research indicates that healthy, aerobically-trained individuals exhibit a high degree of HRV compared to sedentary individuals (3), to our knowledge it is unknown whether ANS dysfunction and diminished HRV can be improved among individuals with MD. Regular exercise transiently stimulates the sympathetic nervous system, but because it strongly augments background vagal modulation over time, it may be an effective and practical means to restore a healthy balance of autonomic modulation and thereby provide a cardio-protective role (12, 23).
In the present study we investigated recently abstinent MD individuals in a residential facility and tested the hypothesis that: (i) MD participants had impaired (i.e., lower) HRV when compared with age-matched, drug-free, sedentary male controls (DF), and (ii) HRV improved from those MD participants randomized into 8 weeks supervised endurance and resistance training (ME) compared with those randomized to no training (MC). This is believed to be the first study to evaluate the effects of exercise training on HRV in persons in treatment for MD.

METHODS

Participants

Fifty men participated in this study. Twenty-eight were required to be in-residence at a treatment center for substance use and constituted a subset from a larger NIDA-funded study of an exercise intervention for MD. Twenty-two were DF and were recruited from advertisements placed in the Los Angeles community.

MD participants aged 28-44 years were recruited into the study within 10 days of admission to the residential facility and met DSM-IV-TR criteria for MD as determined via the Mini-International Neuropsychiatric Interview (32). A physician-administered medical history and physical examination along with a 12-lead resting electrocardiogram (ECG) were performed to determine study eligibility. In addition, candidates completed clinical laboratory tests including a urine drug screen to assess for drugs of abuse. Additional inclusion criteria were: (i) resting heart rate between 50-99 beats/min, (ii) resting blood pressure between 85-150 mm Hg systolic and 45-90 mm Hg diastolic and, (iii) no clinically significant abnormalities of the resting ECG. Exclusionary criteria included any musculoskeletal conditions and unstable cardiovascular,
pulmonary, metabolic, or other disorders that would preclude exercise training. Moreover, to minimize confounding factors that could impair HRV, participants starting any pharmacologic interventions using β-blockers and ACE-inhibitors as well as behavioral treatments using psychotropic medications were excluded. DF participants had no history of substance use and fulfilled all of the other cardiovascular inclusion and exclusion criteria described above.

During the study, candidates continued to participate in the standard schedule of treatment activities that included group and individual therapy and 12-step meetings, characteristic of residential treatment programs. Candidates who met screening eligibility and successfully completed the 2-week baseline data collection period were randomized to either exercise-training (ME; n=14) or an equal-attention health education program (MC; n=14). To enhance adherence, all MD participants received incentives to participate in the form of vouchers given out upon completion of the study. All participants gave written informed consent to the current study approved by the UCLA Institutional Review Board.

**Heart rate variability**

Participants were abstinent (as measured via urine drug screen) from drug use upon arrival at the residential treatment facility and any residual influence of acute methamphetamine usage (with a known half-life of 10-12 hours and all the metabolites at a non-detectable level within 3-4 days of stopping use) would have been washed out before the earliest baseline HRV testing on at least the fourteenth day of treatment. Participants were also asked to avoid all food intake, caffeine, alcohol, smoking and heavy physical activity for 12 hours prior to testing to control for confounding factors that could alter HRV. Testing was performed between 13:00 and 16:00 in a
comfortable, temperature-controlled (22°C) room with dimmed lighting and absent distraction from noise. The participants were fitted with a physiological status monitor affixed to a chest-strap (BioHarness-3™, Zephyr Technologies, Annapolis, MD). The monitor included a single channel ECG sensor and circuitry (recently validated) at a sampling rate of 250 Hz with the R-R intervals (ms) being calculated on a beat-to-beat basis using the company’s proprietary PC-based software. The electrodes on the strap were moistened and placed on the chest against bare skin to ensure good skin contact. Participants were tested while comfortably seated with the total testing time lasting 20 min. This time was divided into 15 min of rest followed by a five-min measurement where participants were asked to remain motionless and to match their breathing frequency to an auditory metronome set at 0.20 Hz (12 breaths/min) in order to minimize the effects of changes in breathing frequency on HRV. The same conditions were imposed for subsequent measurements.

After recording R-R intervals for a 5-min measurement, the data were exported as a text file to the HRV analysis software (Kubios Heart Rate Variability Software Version 2.0; Biosignal Analysis and Medical Imaging Group, Department of Physics, University of Kuopio, Kuopio, Finland). Before processing, and following standard procedures described in the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (10), raw R-R intervals were edited so that artifacts and non-sinus beats could be replaced by interpolation from adjacent normal R-R intervals. The spectrum for these R-R intervals was calculated with Welch’s periodogram method (Fast Fourier Transform spectrum) with a window width of 256 seconds and overlap of 50%. The cleaned signal was then used to provide normal-to-normal (N-N) intervals in order to compute time and frequency domain HRV parameters.
Time domain analyses included: resting heart rate (HR), standard deviation of normal-to-normal intervals (SDNN), root mean square differences of the standard deviation (RMSSD), and percentage of beats that changed more than 50 ms from the previous beat (pNN50). All time domain indices were expressed in milliseconds (ms). SDNN is a global index and reflects all the long-term components of HRV. RMSSD and pNN50 are short-term HRV measurements reflecting alterations in autonomic modulation that are predominantly vagally mediated.

Frequency domain analysis included: low-frequency (LF) component (frequency range 0.04-0.15 Hz) and high-frequency (HF) component (frequency range 0.15-0.4 Hz), in absolute units (ms²), low-frequency to high-frequency ratio (LF/HF), and the normalized units (nu) were computed by dividing the absolute power of a given LF or HF component (ms²) by the total power (LF+HF) minus very low frequency (0.003-0.04 Hz) power (10). The LF component is modulated by both the sympathetic and parasympathetic nervous system and thus reflects a mixture of both autonomic inputs. The HF component is generally defined as a marker of vagal modulation. Normalization of LF and HF tends to minimize the changes in total power while the LF/HF ratio provides a measure of the global sympathovagal balance, where an increase in the ratio reflects a predominance of sympathetic over vagal modulation.

**Fitness measures**

Fitness measures were obtained before and after 8 weeks of study participation to verify that physiological training effects had occurred as a result of the exercise training regimen and to verify that such changes had not occurred in the education group. Anthropometry, aerobic performance, and muscle strength and endurance assessments were administered by an
experienced investigator (BD) from the UCLA Exercise Physiology Research Laboratory at the residential treatment center. The investigators were blinded to participants’ group assignment.

**Anthropometry:** Body mass was measured on a calibrated digital scale (InBody, Biospace, Cerritos, CA, USA: accuracy ± 0.1kg) and height was determined using a precision stadiometer (Seca, Hanover, MD, USA; accuracy ± 0.01 m). Body composition was determined using a 3-site skinfold method (with a Lange caliper) using standard techniques while body density was estimated from skinfold thickness using sex specific equations. Relative body fat was calculated from these estimates of body density using equations specific for age, sex, and ethnicity (2).

**Aerobic Performance:** Aerobic capacity, VO\(_2\)max, and the lactate threshold determined by non-invasive gas exchange measurements, VO\(_2\)θ, were measured during a symptom-limited maximal exercise test (XT) using standard procedures (2) with an incremental treadmill (StarTrac, Irvine, CA) ramp protocol that started with a 3-min warm up of 3 mph at 0% grade followed by 1 minute intervals of alternate increases in speed (0.5 mph) and grade (2%). Oxygen uptake (VO\(_2\)), carbon dioxide output (VCO\(_2\)), and minute ventilation (V\(_E\)) were measured breath-by-breath with a previously validated portable metabolic measurement system (Oxycon Mobile, CareFusion, Yorba Linda, CA) which incorporated a turbine flow transducer, and discrete oxygen and carbon dioxide analyzers. The Oxycon Mobile was calibrated prior to each measurement. These data were continuously monitored and recorded during 3-minutes of warm-up and throughout the exercise test. Similarly, heart rate was continuously monitored with a portable electrocardiograph (ECG) that was integrated with the metabolic measurement system. All testing was conducted by trained and experienced personnel in accordance with established guidelines for cardiopulmonary exercise testing (2, 7). Maximal oxygen uptake was determined from the highest 15-second average and accepted as maximal in the presence of a plateau in VO\(_2\),
with increasing work rate or if these criteria were not met, a respiratory exchange ratio, Rmax, > 1.1 and HR within 12 beats of age-predicted maximal HR (HRmax) (28). Gas exchange indices of VO₂θ, lactate threshold, were ascertained graphically from the point at which VCO₂ increased more steeply relative to VO₂ (7). When the lactate threshold was uncertain using this relationship, the ventilatory equivalents for oxygen (VE/VO₂) and carbon dioxide (VE/VCO₂) were examined for the abrupt increase in VE/VO₂ without an increase in VE/VCO₂. Two investigators (BD, MA) independently selected VO₂θ. If VO₂θ selected by the two investigators agreed within 150 L·min⁻¹, the average was accepted. If the difference was greater than 150 L·min⁻¹, a consensus value was achieved by discussion (7). Rating of perceived exertion (RPE) was taken periodically during the test and at maximal exercise using the Borg 6-20 scale (5).

Muscular strength and endurance: Muscle strength was assessed using the 1-repetition maximum (1-RM) method (14) for the supine leg press and seated chest press machines (Cybex, Medway, MA). After participants performed a warm-up activity followed by light stretching, they positioned themselves on the leg press or chest press machine with their backs remaining flat against the seat back. Participants were allowed several practice trials of each exercise with minimum resistance to ensure good form, full range of motion, and good breathing technique. Standard procedures for progression toward attempting a 1-RM were followed leading to an attempt to complete 1-2 repetitions at a load estimated to be near maximum. The participant rested for 2 minutes and then attempted to achieve the 1-RM. For each 1-RM trial, participants attempted two repetitions. If two repetitions were achieved, 2-minutes of rest were given and the load was increased. If the attempt at 1-RM failed, 2-minutes rest was provided and the load was decreased to the midpoint between the last successful lift and the failed lift. The 1-RM was defined as the highest weight lifted through a full range of motion one time only. Muscle
endurance was measured as the number of repetitions to failure using 85% of baseline leg press and seated chest press 1-RM values.

Exercise training intervention

MD participants randomized to ME performed supervised endurance and resistance exercise routines with an experienced exercise trainer for approximately one hour, three days per week for eight weeks in the treatment facility gym. For the first three weeks, participants walked and/or jogged on a treadmill at a heart rate (± 6 beats per minute) that coincided with the VO$_2$ at the lactate threshold determined by non-invasive gas exchange measurements during the baseline XT. For the next five weeks, target heart rate was increased to midway between the heart rate at lactate threshold and maximum heart rate measured during the baseline XT. Treadmill speed and grade were adjusted at the trainer’s discretion to maintain these intensities for 30 continuous minutes. In the event a participant was unable to complete 30 continuous minutes, rest periods were given until the participant accumulated a total of 30 minutes at this intensity. Following the endurance training session, participants completed a progressive, circuit-type, resistance training program using selectorized machines (Cybex, Medway, MA) and/or dumbbell resistance that included all the major muscle groups of the upper and lower body. A total of nine exercises were performed in the following order: seated chest press, lat pulldowns, supine leg press, lateral dumbbell raises, reverse flyes, biceps curl, reverse lunges, triceps pushdown and standing dumbbell calf raises. For the first three weeks, participants performed a warm-up set with very light weight then completed one set of 8-15 repetitions for each exercise using resistance that resulted in fatigue (16). During the final five weeks participants added a second set of each
exercise and increased the resistance to a level equal to 8-12 RM. Rest periods between sets were less than 30 sec for the first 3 wks and under 2 min for the remaining 5 wks.

**Equal attention (MC) group**

MD participants randomized to the control group, (equal attention, MC), participated in thrice weekly small-group health and wellness education sessions led by a trained counselor. Sessions consisted of an integrated multimedia program addressing a variety of health, wellness, and lifestyle topics such as healthy eating, dental care, acupressure, and cancer screening.

**Statistical analysis**

For analysis data was exported to statistical software packages (Excel, Microsoft Corporation, Redmond, WA; JMP. SAS Institute, Inc., Cary, NC). Prior to comparative analysis, data were examined using stem-and-leaf plots and found to have normal distribution by Shapiro-Wilk tests. For HRV indices and fitness measures, within group comparisons were evaluated by paired t-tests and between group comparisons for baseline and changes from baseline to eight weeks with independent t-tests. Correlations were determined using Pearson Product-Moment correlation coefficient. Statistical significance was set at P≤0.05 with Bonferroni corrections for multiple comparisons.
RESULTS

Baseline characteristics and adherence

The consort diagram shown in Figure 1 summarizes the flow of participants from eligibility to the end of the study. A total of 55 participants were initially screened. Twenty-two participants made-up the drug-free (DF) group and of the thirty-three in-residence methamphetamine addicts, five did not meet one or more criteria for inclusion so twenty-eight (MD) enrolled. Fourteen methamphetamine participants were randomized into each of the exercise (ME) and education (MC) groups. All of the participants from each group completed the study. In the ME group, all participants finished at least 22 of 24 training sessions (92%), and during the last month of training (eight sessions), 100% adherence was obtained. Participants in the MC group attended an average of 23 out of 24 educational sessions. Mean baseline participant demographics, fitness variables and drug use history for MD and DF are shown in Table 1. The two groups were well balanced without significant differences in any of the demographic and fitness variables. Notably, the low maximal oxygen uptake and lactate thresholds amongst all participants place them well below average (bottom 10%) on a percentile rankings for aged and gender matched individuals and confirm their sedentary status (2).

Fitness variables

Body Composition and Anthropometry

Table 2 highlights baseline and post 8-week fitness training variables for the ME and MC groups. Anthropometric changes observed in the ME group included significant (P<0.05) reductions in body mass (-3%), percent relative body fat (-14%) and body mass index (-4%).
Although anthropometric measures tended towards increases in the MC group, they were not significant while the differences were significant between groups (p<0.001).

*Cardiovascular and Perceptual Responses*

For the ME group, maximal oxygen uptake expressed both in absolute (L·min⁻¹) and relative to body mass (ml·kg⁻¹·min⁻¹) improved significantly (24% and 27%, respectively; P<0.05) while these measures did not change in the MC group. Similarly, lactate threshold, VO₂θ, expressed both in absolute (L·min⁻¹) and relative to body mass (ml·kg⁻¹·min⁻¹) improved significantly (64% and 69%, respectively; P<0.05) in the ME group whereas these measures did not change in the MC group. Moreover, VO₂θ/ VO₂max (%) significantly improved in the ME group from baseline (45%) to post-training (60%). For all groups, maximal heart rate, R and RPE at maximal exercise did not differ from baseline to end of study assessments. In all groups, these peak values were 99% of age-predicted maximum heart rate with mean Rmax>1.17 and mean RPEmax>18.6.

*Muscular Strength and Endurance*

For the ME group, lower body strength significantly (P<0.05) increased by 41% (almost 24 kg) and upper body strength significantly increased by 51% (20 kg). Lower and upper body muscular endurance in this same group significantly improved by nine repetitions (+112%) and seven repetitions (+90%), respectively. These measures did not change in the MC group and the differences were all significantly (P<0.001) greater than those seen in the MC group.
HRV time and frequency domain indices

Baseline between Methamphetamine dependent (MD) and Drug free (DF) groups

Table 3 highlights the mean baseline parameters of HRV between groups. In time domain parameters, when compared with the DF group, the MD group had significantly (P<0.05) higher resting heart rates (77 vs 68 beats•min\(^{-1}\)) and significantly (P<0.001) lower SDNN, RMSSD and pNN50. In frequency domain parameters, the MD group had significantly (P<0.001) lower HF and higher LF and LF/HF ratio when compared with the DF group.

Effect of Training between Exercise training (ME) and Equal-attention (MC) groups

Table 4 highlights baseline to post 8-wk fitness training of HRV parameters for the ME and MC groups. Before training, all HRV parameters were similar between ME and MC groups. However after training, compared with the MC group, the ME group had significantly (P<0.001) increased SDNN (+34%), RMSSD (+63%) and pNN50 (+40%) and decreased HR (-7%) in the time domain parameters. In the frequency domain parameters, the ME group had significantly (P<0.001) increased HF (+60%) and decreased LF (-16%) and LF/HF ratio (-19%) compared with the MC group. Measures in both time and frequency domains did not significantly change from baseline in the MC group. Strong correlations existed between delta-VO\(_2\)max and all delta-HRV indices: SDNN (r=0.85), RMSSD (r=0.85), pNN50 (r=0.85), HFn (r=0.88) and LFn (r=-0.85).
DISCUSSION

The primary findings from the present study are twofold: (i) HRV, based on several conventional indices, was diminished in recently abstinent, MD individuals and (ii) eight-weeks of exercise training yielded a marked increase of HRV representing increased vagal modulation and improved sympathovagal balance.

Our data are in agreement with a previous observation from Henry et al (18) that individuals with a history of MD exhibit a significant increase in LF/HF ratio and LF, along with concomitant reductions in HF, RMSSD and pNN50 when compared with drug-free controls. Moreover, as evidenced in our study, recent methamphetamine use (i.e., abstinent for less than 2 weeks) was associated with increased resting heart rate which reflects either decreased vagal modulation, increased sympathetic modulation or both. Impairments in these time and frequency domain measures of HRV with methamphetamine addiction are consistent with effects observed with other sympathomimetic interventions, such as acute exposure to methamphetamine (13), cocaine (39) and alcohol (38), which resulted in diminished HF, RMSSD and pNN50, all known to be more specific indicators of vagal modulation.

The primary mechanism responsible for the cardiotoxic central and peripheral nervous system effects of methamphetamine is thought to be the release of catecholaminergic neurotransmitters (i.e., norepinephrine and dopamine). Release and/or accumulation of these neurotransmitters causes simultaneous tachycardia and hypertension which increases cardiac oxygen demand coupled with coronary vasoconstriction and vasospasm which decreases cardiac oxygen supply (21). Lack of sufficient oxygen supply to the cardiac muscle causes damage to cardiomyocytes, including hypertrophy tissue necrosis and ultimately fibrosis that impairs cardiac function (40).
Methamphetamine intoxication has therefore been implicated in an assortment of cardiac dysrhythmias as well as congestive heart failure, cardiomyopathy and myocardial infarction (24, 37).

In addition to direct cardiotoxicity, there are studies suggesting neurotoxicity from chronic methamphetamine use. Acute neurotransmitter degradation, alterations in neural circuitry, and cell necrosis in the self-control and pleasure-reward centers (nucleus accumbens) of the brain are proposed mechanisms that may disrupt the ANS and result in sympathovagal imbalance (31).

As shown in Figure 2, since heart rate is regulated predominantly by the ANS, both sympathetic and parasympathetic components play pivotal roles during acute and chronic exercise (i.e., the physiological adaptations that result from exposure to repeated bouts of exercise). Therefore the study of HRV, under conditions of ANS stimulation or inhibition, offers the opportunity to assess the role of the ANS in cardiovascular function. Eight weeks of exercise training during early abstinence from methamphetamines yielded a marked increase of the indices representing vagal modulation. In addition, as evidenced by a lower LF and LF/HF ratio, there was diminished sympathetic modulation in the ME group. These findings concur with a large body of longitudinal studies that indicate physical activity is a safe, non-pharmacological approach to favorably altering ANS function and thereby providing a cardio-protective role (12, 23).

In this study, the impressive gain (24%) in aerobic capacity (VO2max) from the endurance training coupled with increases in muscle strength and endurance for upper (51% and 90%, respectively) and lower body (40% and 112%, respectively) from resistance training demonstrate the potential of exercise to improve health-fitness outcomes in participants obtaining treatment for MD. In the general population, higher aerobic capacity and greater skeletal muscle strength
are both associated with lower prevalence of chronic diseases and lower mortality (4).

Therefore, we speculate that similar improvements might ameliorate some of the deleterious effects associated with chronic methamphetamine exposure, including cardiomyopathy, coronary artery disease, dysrhythmias, myocardial ischemia, hypertension and cerebrovascular dysfunction (18, 24); however this will have to be further explored in future research.

Due to widespread discrepancies in research methodologies (e.g., training duration and intensity) and lack of standardized measurements of HRV during exercise, consensus has yet to be reached regarding the effects of exercise on HRV. Exercise studies in younger adults generally report improvements in HRV (23), whereas studies in older individuals remain equivocal (35). This observation is perhaps related to a decrease in HRV with age. A review of HRV in a variety of athletic populations indicated that three months of moderate intensity aerobic training is sufficient to achieve a measurable increase in HRV (3, 11). Our results, supported by strong correlations (r=0.85 to 0.88) between changes in VO₂max and changes in various HRV indices, confirm several previous longitudinal studies that have demonstrated a significant increase in HRV with aerobic exercise training (22, 27, 30, 34). A cross-sectional study showed that endurance-trained men (VO₂max > 55 ml·kg⁻¹·min⁻¹) had higher HRV compared to sedentary controls (VO₂max < 40 ml·kg⁻¹·min⁻¹) after training (12). While some research indicates that HRV does not appear to increase in a dose-dependent manner with increasing exercise intensity (3), the effect of training program duration on HRV is unknown. It is possible that a study lasting longer than eight weeks might further increase cardiac vagal modulation.

As a consequence of chronic adaptations to exercise training, there are adjustments in cardiac rhythm that influence heart rate and HRV. Training induces sinus bradycardia in resting
conditions, as demonstrated in the ME group, and a lower heart rate at any given submaximal level of oxygen uptake due to a shift of the sympathovagal balance towards vagal dominance. The lower heart rate allows for an increased time for diastolic filling thus enhancing stroke volume through Frank-Starling mechanisms, i.e., increased end-diastolic volume and increased myocardial contractility via increased left ventricular stretch and mass (2). Although differences in individual responses to aerobic exercise training are caused by genetic factors, they may also be due to different adjustments in cardiac autonomic regulation (i.e., sympathovagal balance) or intrinsic adaptations from improved atrioventricular conduction (23). In our study, it could be speculated that the blunting of vagal modulation from catecholamine toxicity in methamphetamine dependent individuals may have subsided under the combined influence of recent abstinence and exercise training, both of which modified the cardiac autonomic balance by increasing vagal modulation and decreasing sympathetic modulation as suggested in Figure 2. In fact comparable to earlier studies with post-myocardial infarction patients (16), exercise training may also accelerate recovery of the physiological sympathovagal interaction.

ANS modulation may influence physical and psychological functioning. HRV is a measure that represents both neurological and cardiovascular function, and research suggests the impact of psychosocial distress on cardiovascular morbidity and mortality is comparable with the impact of traditional cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia and obesity). The link between psychosocial distress and cardiovascular disease is known to relate to sympathetic predominance, as manifested by elevated proinflammatory cytokines, elevated circulating cortisol levels (from the hypothalamic-pituitary-adrenal axis), impaired vagal modulation, and reduced HRV(26). Methamphetamine users commonly experience psychiatric symptoms including anxiety and depression (33, 41); this population may significantly benefit
from interventions such as exercise that may improve cardiovascular symptoms and allay the effects of stress and help individuals to manage stress within their lives.

For this study, both groups at the residential treatment center received ‘usual care’ which included psychological interventions such as behavioral therapy. During our study, some measures of HRV, specifically increased RMSDD, could have been influenced over the 8 weeks by positive psychosocial and behavioral changes in both groups (36). However, no changes, not even non-significant trending, were seen with any parasympathetic indices (RMSSD, pNN50, and HF) in the MC group. Possibly then, exercise mediates some of the changes in ANS as seen by the improvement in the ET groups parasympathetic and sympathovagal balance through its effect on other health outcomes such as ameliorating negative psychosocial stress (6, 16, 41).

The results of this study should be interpreted in light of some limitations. First, the sample in this study was restricted to only those that were admitted to a residential treatment facility. Consequently, it is unclear to what extent the results of this study generalize to treatment in different settings such as outpatient facilities. Secondly, based on the literature, there are confounding factors in the measurement, analysis and interpretation of HRV which could obscure results. In order to minimize known confounding factors influencing HRV, the MD and DF groups were matched for age, BMI and fitness measures. In fact, baseline fitness measures (VO2max and percentage body fat) were similar and categorize both groups of participants as being ‘sedentary’. Moreover, all of the participants were men so as to eliminate the influence of female reproductive hormone levels on HRV (20). Although, it could be argued that our results might not be generalizable to women or more active individuals, we believe our homogenous participant pool ensured more accurate and reliable baseline HRV measures. Thirdly, since nicotine from cigarettes is known to increase sympathetic outflow and perturb HRV measures
participants were asked to refrain from smoking 12 hours prior to measurements. In
addition, using a questionnaire, we ascertained that the frequency of cigarette smoking
throughout the 8-week study did not significantly change from baseline in either of the MD
groups. A fourth limitation was that several of the participants were HIV positive and recent
research has indicated that its possible that HRV is adversely affected by HIV infection. Fifth,
part of intra-subject variability in all participants, particularly methamphetamine addicts, could
have been due to the natural change of HRV parameters that occur under the influence of
temporal factors such as mood, alertness and mental activity (17, 36). These factors are difficult
to control in any study. Whilst it is known that well-being may be impaired in
methamphetamine -dependent individuals, it is hard to ascertain whether the impairment was a
cause, or a consequence, of the drug use. Finally, we acknowledge that this study provides no
direct explanation for the mechanism of improved HRV resulting from the interaction between
drug abstinence and exercise training. However, it does suggest that exercise training is an
effective intervention.

CONCLUSION

Despite the aforementioned limitations, this investigation may represent a strong advance in the
drug addiction literature as a compelling and synergistic approach to the traditional treatment of
methamphetamine addicts in recovery. Vagal or parasympathetic modulation is considered to
offer cardiovascular protection; therefore, ANS dysfunction, particularly reductions in cardiac
vagal modulation from sympathomimetic drugs like methamphetamine, may translate into a
significant increase in risk of cardiovascular morbidity and mortality amongst methamphetamine
-dependent individuals. On the other hand, exercise is widely viewed as a factor that reduces all-causes of mortality and improves a number of health outcomes (2, 16). As evidenced by HRV measures in this study, exercise training in recently abstinent methamphetamine-dependent individuals improved cardiovascular autonomic balance via increased vagal modulation and diminished sympathetic outflow, both of which would predictably contribute to exercise-induced cardioprotection. This study should prompt future investigations into the significance of ANS regulation in drug addiction as measured by HRV.

Acknowledgments

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REFERENCES


17. **Hawkins MA, Stewart JC, Fitzgerald GJ, and Kim S.** Combined effect of depressive symptoms and hostility on autonomic nervous system function. *International journal of


23. **Martins-Pinge MC.** Cardiovascular and autonomic modulation by the central nervous system after aerobic exercise training. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica [et al]* 44: 848-854, 2011.


Figure Legends

FIGURE 1. Consort diagram showing participant flow through the study

FIGURE 2. Interplay between chronic methamphetamine toxicity and exercise training adaptations on parasympathetic and sympathetic components of the ANS and HRV. Methamphetamine dependence increases HRV primarily by suppressing vagal input but also by chronic sympathetic stimulation. Regular exercise also provides short-term sympathetic stimulation together with longer-term augmentation of parasympathetic (vagal) modulation.
FIGURE 1

Assessed for eligibility (n=55)

Methamphetamine Dependent (MD; n=33)

Drug-free Controls (DF; n=22)

Excluded; not meeting inclusion criteria (n=5)

In-Residence MD (n=28)

Exercise (ME; n=14)

Education (MC; n=14)

Exercise (ME; n=14)

Education (MC; n=14)
TABLE 1. Baseline participant demographics, fitness variables and drug use history comparing Methamphetamine dependent (MD) and drug free (DF) Groups

<table>
<thead>
<tr>
<th></th>
<th>MD (n=28)</th>
<th>DF (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>32.3±7</td>
<td>34.4±4</td>
</tr>
<tr>
<td><strong>Body mass (kg)</strong></td>
<td>84.0±14.1</td>
<td>81.0±9.3</td>
</tr>
<tr>
<td><strong>BMI (kg·m⁻²)</strong></td>
<td>27.3±4.4</td>
<td>26.2±3.6</td>
</tr>
<tr>
<td><strong>Body fat (%)</strong></td>
<td>20.6±6.3</td>
<td>21.1±5.2</td>
</tr>
<tr>
<td><strong>VO₂max (L·min⁻¹)</strong></td>
<td>2.38±0.35</td>
<td>2.45±0.42</td>
</tr>
<tr>
<td><strong>VO₂θ (L·min⁻¹)</strong></td>
<td>1.06±0.16</td>
<td>1.05±0.14</td>
</tr>
<tr>
<td><strong>HRmax (min⁻¹)</strong></td>
<td>186.3±6.4</td>
<td>184.2±4.2</td>
</tr>
<tr>
<td><strong>Rmax</strong></td>
<td>1.20±0.1</td>
<td>1.21±0.1</td>
</tr>
<tr>
<td><strong>RPEmax</strong></td>
<td>18.4±0.5</td>
<td>18.4±0.5</td>
</tr>
<tr>
<td><strong>Duration of meth use (years)</strong></td>
<td>13.0±6.3</td>
<td>-</td>
</tr>
<tr>
<td><strong>Meth usage during abuse (x/30 days)</strong></td>
<td>16.7±7.5</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are mean±SD. None of the variables were significantly different between groups at baseline. BMI=Body Mass Index; VO₂θ=Lactate Threshold; R=Respiratory Exchange Ratio; RPE=Rating of Perceived Exertion.
<table>
<thead>
<tr>
<th></th>
<th><strong>ME (n=14)</strong></th>
<th></th>
<th><strong>MC (n=14)</strong></th>
<th></th>
<th><strong>P-between</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>8 weeks</td>
<td>Change</td>
<td>P-within</td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>Body mass (kg)</strong></td>
<td>85.7±3.4</td>
<td>83.2±3.4</td>
<td>-2.5±0.5</td>
<td>&lt;0.05</td>
<td>82.2±4.2</td>
</tr>
<tr>
<td><strong>BMI (kg·m⁻²)</strong></td>
<td>28.3±1.1</td>
<td>27.5±1.1</td>
<td>-0.8±1.1</td>
<td>&lt;0.05</td>
<td>26.4±1.3</td>
</tr>
<tr>
<td><strong>Body fat (%)</strong></td>
<td>21.4±1.6</td>
<td>18.4±1.5</td>
<td>-3.1±0.3</td>
<td>&lt;0.05</td>
<td>19.9±1.8</td>
</tr>
<tr>
<td><strong>VO₂max (L·min⁻¹)</strong></td>
<td>2.38±0.1</td>
<td>2.96±0.1</td>
<td>0.58±0.1</td>
<td>&lt;0.05</td>
<td>2.38±0.1</td>
</tr>
<tr>
<td><strong>(ml·kg⁻¹·min⁻¹)</strong></td>
<td>28.5±1.7</td>
<td>36.4±1.9</td>
<td>7.9±0.7</td>
<td>&lt;0.05</td>
<td>29.9±1.9</td>
</tr>
<tr>
<td><strong>VO₂θ (L·min⁻¹)</strong></td>
<td>1.08±0.1</td>
<td>1.76±0.1</td>
<td>0.69±0.02</td>
<td>&lt;0.05</td>
<td>1.04±0.1</td>
</tr>
<tr>
<td><strong>(ml·kg⁻¹·min⁻¹)</strong></td>
<td>12.9±0.7</td>
<td>21.8±1.3</td>
<td>9.0±0.6</td>
<td>&lt;0.05</td>
<td>13.1±0.9</td>
</tr>
<tr>
<td><strong>HRmax (beats·min⁻¹)</strong></td>
<td>187±2</td>
<td>187±1</td>
<td>-0.5±0.3</td>
<td>0.97</td>
<td>184±2</td>
</tr>
<tr>
<td><strong>Rmax</strong></td>
<td>1.20±0.0</td>
<td>1.20±0.0</td>
<td>0.01±0.01</td>
<td>0.97</td>
<td>1.20±0.0</td>
</tr>
<tr>
<td><strong>RPEmax</strong></td>
<td>18.4±0.1</td>
<td>18.6±0.1</td>
<td>0.1±0.1</td>
<td>0.95</td>
<td>18.4±0.1</td>
</tr>
<tr>
<td><strong>1-RM Chest (kg)</strong></td>
<td>39.6±3.3</td>
<td>59.7±4.0</td>
<td>20.1±1.6</td>
<td>&lt;0.05</td>
<td>44.5±5.1</td>
</tr>
<tr>
<td><strong>1-RM Legs (kg)</strong></td>
<td>59.1±3.3</td>
<td>83.0±2.7</td>
<td>23.9±1.5</td>
<td>&lt;0.05</td>
<td>63.1±4.1</td>
</tr>
<tr>
<td><strong>85% 1-RM Chest (reps)</strong></td>
<td>7.4±0.3</td>
<td>14.0±0.6</td>
<td>6.6±0.5</td>
<td>&lt;0.05</td>
<td>6.9±0.4</td>
</tr>
<tr>
<td><strong>85% 1-RM Legs (reps)</strong></td>
<td>8.3±0.9</td>
<td>17.6±0.9</td>
<td>9.3±0.9</td>
<td>&lt;0.05</td>
<td>8.0±0.9</td>
</tr>
</tbody>
</table>

Values are mean±SE. BMI=Body Mass Index; VO₂θ=Lactate Threshold; R=Respiratory Exchange Ratio; RPE=Rating of Perceived Exertion
TABLE 3. Baseline parameters of heart rate variability between Methamphetamine dependent (MD) and drug free (DF) groups

<table>
<thead>
<tr>
<th>HRV Parameter</th>
<th>MD (n=28)</th>
<th>DF (n=22)</th>
<th>P-between</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time domain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (min(^{-1}))</td>
<td>77.6±0.3</td>
<td>68.1±1.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>43.4±0.5</td>
<td>63.5±2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>32.0±0.5</td>
<td>57.0±2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>13.2±0.2</td>
<td>42.4±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Frequency domain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF (nu)</td>
<td>23.7±0.2</td>
<td>43.3±1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LF (nu)</td>
<td>62.0±0.3</td>
<td>52.9±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>4.0±0.0</td>
<td>2.3±0.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SE. SDNN=standard deviation of normal-to-normal intervals; RMSSD=root mean square differences of the standard deviation; pNN50=percentage of beats that changed more than 50 ms from the previous beat; HF=high-frequency component; LF=low-frequency component; LF/HF=low-frequency to high-frequency ratio.
TABLE 4. Heart rate variability parameters at Baseline and after 8-weeks for the exercise training (ME) and equal-attention (MC) groups

<table>
<thead>
<tr>
<th></th>
<th>ME (n=14)</th>
<th></th>
<th>MC (n=14)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>8 weeks</td>
<td>Change</td>
<td>P-within</td>
<td>Baseline</td>
<td>8 weeks</td>
<td>Change</td>
<td>P-within</td>
</tr>
<tr>
<td><strong>Time domain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (min⁻¹)</td>
<td>77.8±0.4</td>
<td>72.6±0.5</td>
<td>-5.2±0.4</td>
<td>&lt;0.05</td>
<td>77.4±0.4</td>
<td>77.4±0.5</td>
<td>0.1±0.2</td>
<td>0.94</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>43.2±0.7</td>
<td>57.9±0.8</td>
<td>14.7±0.5</td>
<td>&lt;0.05</td>
<td>43.5±0.6</td>
<td>43.7±0.7</td>
<td>0.2±0.5</td>
<td>0.87</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>31.3±0.6</td>
<td>50.7±0.9</td>
<td>19.6±1.1</td>
<td>&lt;0.05</td>
<td>32.8±0.7</td>
<td>33.0±0.7</td>
<td>0.2±0.4</td>
<td>0.84</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>13.1±0.3</td>
<td>35.7±0.9</td>
<td>22.6±0.7</td>
<td>&lt;0.05</td>
<td>13.2±0.4</td>
<td>13.2±0.4</td>
<td>0.0±0.2</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Frequency domain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF (nu)</td>
<td>23.7±0.3</td>
<td>37.8±0.6</td>
<td>14.2±0.5</td>
<td>&lt;0.05</td>
<td>23.7±0.3</td>
<td>23.7±0.5</td>
<td>0.0±0.3</td>
<td>0.97</td>
</tr>
<tr>
<td>LF (nu)</td>
<td>62.0±0.4</td>
<td>52.3±0.5</td>
<td>-9.6±0.4</td>
<td>&lt;0.05</td>
<td>62.1±0.5</td>
<td>61.9±0.5</td>
<td>-0.1±0.3</td>
<td>0.84</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>4.0±0.0</td>
<td>3.2±0.1</td>
<td>-0.7±0.1</td>
<td>&lt;0.05</td>
<td>4.0±0.1</td>
<td>3.9±0.1</td>
<td>-0.1±0.0</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Values are mean±SE. SDNN=standard deviation of normal-to-normal intervals; RMSSD=root mean square differences of the standard deviation; pNN50=percentage of beats that changed more than 50 ms from the previous beat; HF=high-frequency component; LF=low-frequency component; LF/HF=low-frequency to high-frequency ratio.