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Exercise Training Improves Heart Rate Variability after Methamphetamine Dependency

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¹Exercise Physiology Research Laboratory, Departments of Medicine and Physiology, David Geffen School of Medicine, UCLA, Los Angeles, CA; ²Integrated Substance Abuse Programs, Semel Institute, David Geffen School of Medicine, UCLA, Los Angeles, CA; and ³Department of Integrative Biology and Physiology, UCLA, Los Angeles, CA

ABSTRACT

DOLEZAL, B. A., J. CHUDZYNSKI, D. DICKERSON, L. MOONEY, R. A. RAWSON, A. GARFINKEL, and C. B. COOPER. Exercise Training Improves Heart Rate Variability after Methamphetamine Dependency. *Med. Sci. Sports Exerc.*, Vol. 46, No. 6, pp. 1057–1066, 2014. **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 methamphetamine-dependent participants with age-matched, drug-free controls (DF) and also investigated whether HRV can be improved with exercise training in the methamphetamine-dependent participants. **Methods:** In 50 participants (MD = 28; DF = 22), resting heart rate (HR; 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 wk. Groups were compared using paired and unpaired *t*-tests. Statistical significance was set at $P \leq 0.05$. **Results:** Participant characteristics were matched between groups (mean $\pm$ SD): age = 33 ± 6 yr; body mass = 82.7 ± 12 kg, body mass index = 26.8 ± 4.1 kg·m⁻². Compared with DF, the MD group had significantly higher resting HR ($P < 0.05$), 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 ($+14.7 \pm 2.0$ ms, +34%), RMSSD ($+19.6 \pm 4.2$ ms, +63%), pNN50 ($+22.6\% \pm 2.7\%$, +173%), HFnu ($+14.2 \pm 1.9$, +60%), and decreased HR (-5.2 ± 1.1 bpm, -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. **Conclusions:** HRV, based on several conventional indices, was diminished in recently abstinent, methamphetamine-dependent individuals. Moreover, physical training yielded a marked increase in HRV, representing increased vagal modulation or improved autonomic balance. **Key Words:** HRV, SUBSTANCE USE, AUTONOMIC NERVOUS SYSTEM, PARASYMPATHETIC ACTIVITY

Heart rate variability (HRV) is a reliable, noninvasive measure that reflects the balance of sympathetic and vagal neural influences on heart rate (HR) (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 (9).

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 (1,9,24). 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

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with cardiovascular pathologies such as coronary heart disease, cardiomyopathy, and sudden cardiac death (18,19). 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 (17). Methamphetamine is an illicit psychostimulant used for nonmedical purposes worldwide by an estimated 13.7 to 52.9 million people (37). More potent than its parent compound amphetamine because of 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 (23,30,40).

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 posttreatment relapse (28). Participation in regular physical exercise may be an effective intervention to aid methamphetamine-dependent individuals in reducing relapse to drug use (8). Exercise has proven effective in ameliorating symptoms of depression and anxiety while improving cognition and cognitive deficits found in chronic methamphetamine users (6,32). 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 cardioprotective role (11,22).

In the present study, we investigated recently abstinent methamphetamine-dependent individuals in a residential facility and tested the hypothesis that (i) methamphetamine-dependent participants had impaired (i.e., lower) HRV when compared with age-matched, drug-free, sedentary male controls (DF), and (ii) HRV improved from those methamphetamine-dependent participants randomized into 8 wk of 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.

Methamphetamine-dependent participants age 28–44 yr were recruited into the study within 10 d of admission to the residential facility and met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, criteria for MD as determined via the Mini-International Neuropsychiatric Interview (31). A physician-administered medical history and physical examination along with a 12-lead resting 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 HR between 50 and 99 bpm, (ii) resting blood pressure between 85 and 150 mm Hg systolic and between 45 and 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 angiotensin-converting enzyme 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-wk 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 methamphetamine-dependent participants received incentives to participate in the form of vouchers given out on completion of the study. All participants gave written informed consent to the current study approved by the UCLA Institutional Review Board.

HRV

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 h and all the metabolites at a nondetectable level within 3–4 d of stopping use) would have been washed out before the earliest baseline HRV testing on at least the 14th day of treatment. Participants were also asked to avoid all food intake, caffeine, alcohol, smoking, and heavy physical activity for 12 h before 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 5-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 per minute) 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 (9), 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 s and overlap of 50%. The cleaned signal was then used to provide normal-to-normal (N-N) intervals to compute time and frequency domain HRV parameters.

Time domain analyses included resting 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 (ms^2), 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 (ms^2) 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 wk 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; accuracy ± 0.1 kg), and height was determined using a precision stadiometer (Seca, Hanover, MD; accuracy ± 0.01 m). Body composition was determined using a three-site skinfold method (with a Lange caliper) using standard techniques, whereas 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, $\dot{V}\text{O}_{2\text{max}}$, and the lactate threshold determined by noninvasive gas exchange measurements, $\dot{V}\text{O}_{2\text{E}}$, 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-min intervals of alternate increases in speed (0.5 mph) and grade (2%). Oxygen uptake ($\dot{V}\text{O}_2$), carbon dioxide output ($\dot{V}\text{CO}_2$), and minute ventilation ($\dot{V}_E$) 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 before each measurement. These data were continuously monitored and recorded during 3 min of warm-up and throughout the exercise test. Similarly, HR 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-s average and accepted as maximal in the presence of a plateau in $\dot{V}O_2$ with increasing work rate, or if these criteria were not met, a respiratory exchange ratio, RER_{max} , >1.1 and HR within 12 beats of age-predicted maximal HR (HR_{max}) (28). Gas exchange indices of $\dot{V}O_{2\theta}$, lactate threshold, were ascertained graphically from the point at which $\dot{V}CO_2$ increased more steeply relative to $\dot{V}O_2$ (7). When the lactate threshold was uncertain using this relationship, the ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) were examined for the abrupt increase in $\dot{V}_E/\dot{V}O_2$ without an increase in $\dot{V}_E/\dot{V}CO_2$. Two investigators (B.D. and M.A.) independently selected $\dot{V}O_{2\theta}$. If $\dot{V}O_{2\theta}$ selected by the two investigators agreed within $150\text{ L}\cdot\text{min}^{-1}$, the average was accepted. If the difference was greater than $150\text{ L}\cdot\text{min}^{-1}$, a consensus value was achieved by discussion (7). 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 (13) 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 one to two repetitions at a load estimated to be near maximum. The participant rested for 2 min and then attempted to achieve the 1-RM. For each 1-RM trial, participants attempted two repetitions. If two repetitions were achieved, 2 min of rest was given, and the load was increased. If the attempt at 1-RM failed, a 2-min 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 at 1-RM values.

Exercise Training Intervention

Methamphetamine-dependent participants randomized to ME performed supervised endurance and resistance exercise routines with an experienced exercise trainer for approximately 1 h, 3 d $\cdot$ wk $^{-1}$ for 8 wk in the treatment facility gym. For the first 3 wk, participants walked and/or jogged on a treadmill at a HR (± 6 bpm) that coincided with the $\dot{V}O_2$ at the lactate threshold determined by noninvasive gas exchange measurements during the baseline XT. For the next 5 wk, target HR was increased to midway between the HR

at lactate threshold and HR_{max} 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. After the endurance training session, participants completed a progressive, circuit-type, resistance training program using selectorized machines (Cybex) 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 pull-downs, supine leg press, lateral dumbbell raises, reverse flyes, biceps curl, reverse lunges, triceps pushdown, and standing dumbbell calf raises. For the first 3 wk, 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 5 wk, 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 s for the first 3 wk and under 2 min for the remaining 5 wk.

MC Group

Methamphetamine-dependent 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, acupuncture, and cancer screening.

Statistical Analysis

For analysis, data were exported to statistical software packages (Excel; Microsoft Corporation, Redmond, WA; JMP, SAS Institute, Inc., Cary, NC). Before 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 8 wk with independent *t*-tests. Correlations were determined using Pearson product–moment correlation coefficient. Statistical significance was set at $P \leq 0.05$ 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 33 in-residence methamphetamine addicts, 5 did not

FIGURE 1—Consort diagram showing participant flow through the study.

meet one or more criteria for inclusion so 28 (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 (92%) of 24 training sessions, and during the last month of training (eight sessions), 100% adherence was obtained. Participants in the MC group attended an average of 23 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 among all participants place them well below average (bottom 10%) on a percentile rankings for age- and sex-matched individuals and confirm their sedentary status (2).

Fitness Variables

Body composition and anthropometry. Table 2 highlights baseline and post 8-wk 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 toward increases in the MC group, they were not significant, whereas the differences were significant between groups ($P < 0.001$).

Cardiovascular and perceptual responses. For the ME group, maximal oxygen uptake expressed both in absolute ($L \cdot min^{-1}$) and relative to body mass ($mL \cdot kg^{-1} \cdot min^{-1}$) improved significantly (24% and 27%, respectively; $P < 0.05$), whereas these measures did not change in the MC group. Similarly, lactate threshold, $\dot{V}O_{2\theta}$, expressed both in absolute ($L \cdot min^{-1}$) and relative to body mass ($mL \cdot kg^{-1} \cdot min^{-1}$), improved significantly (64% and 69%, respectively; $P < 0.05$) in the ME group, whereas these measures did not change in the MC group. Moreover, $\dot{V}O_{2\theta} / \dot{V}O_{2max}$ (%) significantly improved in the ME group from baseline (45%) to after training (60%). For all groups, maximal HR, RER, and RPE at maximal exercise did not differ from baseline to the end of study assessments. In all groups, these peak values were 99% of age-predicted HR_{max} with mean $RER_{max} > 1.17$ and mean $RPE_{max} > 18.6$.

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 MD and 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 HR (77 vs 68 bpm) and significantly ($P < 0.001$)

TABLE 1. Baseline participant demographics, fitness variables and drug use history comparing methamphetamine-dependent (MD) and drug-free (DF) groups.

		MD (n = 28)	DF (n = 22)
Age	(yr)	32.3 ± 7	34.4 ± 4
Body mass	(kg)	84.0 ± 14.1	81.0 ± 9.3
BMI	(kg·m ^{−2})	27.3 ± 4.4	26.2 ± 3.6
Body fat	(%)	20.6 ± 6.3	21.1 ± 5.2
$\dot{V}O_{2max}$	(L·min ^{−1})	2.38 ± 0.35	2.45 ± 0.42
	(mL·kg ^{−1} ·min ^{−1})	29.2 ± 6.7	30.3 ± 6.2
$\dot{V}O_{2\theta}$	(L·min ^{−1})	1.06 ± 0.16	1.05 ± 0.14
	(mL·kg ^{−1} ·min ^{−1})	13.0 ± 2.9	13.1 ± 1.7
HR_{max}	(min ^{−1})	186.3 ± 6.4	184.2 ± 4.2
RER_{max}		1.20 ± 0.1	1.21 ± 0.1
RPE_{max}		18.4 ± 0.5	18.4 ± 0.5
Duration of continuous meth use	(yr)	13.0 ± 6.3	—
Meth usage during abuse	(x per 30 d)	16.7 ± 7.5	—

Values are mean ± SD. None of the variables were significantly different between groups at baseline.

BMI = body mass index; $\dot{V}O_{2\theta}$ = lactate threshold; RER = respiratory exchange ratio; RPE = rating of perceived exertion.

TABLE 2. Fitness variables at baseline and 8 wk for the exercise training (ME) and equal-attention (MC) groups.

		ME (n = 14)				MC (n = 14)				
		Baseline	8 wk	Change	P Within	Baseline	8 wk	Change	P Within	P Between
Body mass	(kg)	85.7 ± 3.4	83.2 ± 3.4	-2.5 ± 0.5	<0.05	82.2 ± 4.2	84.3 ± 4.3	2.1 ± 0.7	0.45	<0.001
BMI	(kg·m ⁻²)	28.3 ± 1.1	27.5 ± 1.1	-0.8 ± 1.1	<0.05	26.4 ± 1.3	27.0 ± 1.3	0.7 ± 1.3	0.51	<0.001
Body fat	(%)	21.4 ± 1.6	18.4 ± 1.5	-3.1 ± 0.3	<0.05	19.9 ± 1.8	20.6 ± 1.8	0.8 ± 0.4	0.57	<0.001
VO _{2max}	(L·min ⁻¹)	2.38 ± 0.1	2.96 ± 0.1	0.58 ± 0.1	<0.05	2.38 ± 0.1	2.34 ± 0.1	-0.04 ± 0.02	0.48	<0.001
	(mL·kg ⁻¹ ·min ⁻¹)	28.5 ± 1.7	36.4 ± 1.9	7.9 ± 0.7	<0.05	29.9 ± 1.9	28.5 ± 1.8	-1.3 ± 0.4	0.29	<0.001
VO _{2θ}	(L·min ⁻¹)	1.08 ± 0.1	1.76 ± 0.1	0.69 ± 0.02	<0.05	1.04 ± 0.1	1.03 ± 0.1	-0.01 ± 0.01	0.89	<0.001
	(mL·kg ⁻¹ ·min ⁻¹)	12.9 ± 0.7	21.8 ± 1.3	9.0 ± 0.6	<0.05	13.1 ± 0.9	12.6 ± 0.7	-0.5 ± 0.2	0.78	<0.001
HR _{max}	(bpm)	187 ± 2	187 ± 1	-0.5 ± 0.3	0.97	184 ± 2	185 ± 2	0.4 ± 0.3	0.97	0.96
RER _{max}		1.20 ± 0.0	1.20 ± 0.0	0.01 ± 0.01	0.97	1.20 ± 0.0	1.20 ± 0.0	0.01 ± 0.01	0.97	0.95
RPE _{max}		18.4 ± 0.1	18.6 ± 0.1	0.1 ± 0.1	0.95	18.4 ± 0.1	18.4 ± 0.1	0.0 ± 0.1	0.99	0.94
1-RM chest	(kg)	39.6 ± 3.3	59.7 ± 4.0	20.1 ± 1.6	<0.05	44.5 ± 5.1	45.8 ± 5.4	1.3 ± 0.7	0.67	<0.001
1-RM legs	(kg)	59.1 ± 3.3	83.0 ± 2.7	23.9 ± 1.5	<0.05	63.1 ± 4.1	63.0 ± 4.4	-0.2 ± 0.7	0.53	<0.001
85% 1-RM chest	(reps)	7.4 ± 0.3	14.0 ± 0.6	6.6 ± 0.5	<0.05	6.9 ± 0.4	6.9 ± 0.5	-0.1 ± 0.2	0.49	<0.001
85% 1-RM legs	(reps)	8.3 ± 0.9	17.6 ± 0.9	9.3 ± 0.9	<0.05	8.0 ± 0.9	8.6 ± 1.0	0.6 ± 0.4	0.52	<0.001

Values are mean ± SE.

BMI = body mass index; VO_{2θ} = lactate threshold; RER = respiratory exchange ratio; RPE = rating of perceived exertion.

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 ME and 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_{2max} 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, methamphetamine-dependent individuals; and (ii) 8 wk of exercise training yielded a marked increase in HRV, representing increased vagal modulation and improved sympathovagal balance.

Our data are in agreement with a previous observation from Henry et al. (17) 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 DF controls. Moreover, as evidenced in our study, recent methamphetamine use (i.e., abstinent for <2 wk) was associated with increased resting HR, 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 (12), 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 (20). 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 (23,36).

In addition to direct cardiotoxicity, there are studies suggesting neurotoxicity from chronic methamphetamine use.

TABLE 3. Baseline parameters of heart rate variability between methamphetamine-dependent (MD) and drug-free (DF) groups.

HRV Parameter		MD (n = 28)	DF (n = 22)	P Between
Time domain				
Heart rate	(min ⁻¹)	77.6 ± 0.3	68.1 ± 1.0	<0.05
SDNN	(ms)	43.4 ± 0.5	63.5 ± 2.1	<0.001
RMSSD	(ms)	32.0 ± 0.5	57.0 ± 2.7	<0.001
pNN50	(%)	13.2 ± 0.2	42.4 ± 3.0	<0.001
Frequency domain				
HF	(nu)	23.7 ± 0.2	43.3 ± 1.9	<0.001
LF	(nu)	62.0 ± 0.3	52.9 ± 0.9	<0.001
LF/HF ratio		4.0 ± 0.0	2.3 ± 0.2	<0.001

Values are mean ± SE.

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

TABLE 4. Heart rate variability parameters at Baseline and after 8 wk for the exercise training (ME) and equal-attention (MC) groups.

		ME (n = 14)				MC (n = 14)				P Between
		Baseline	8 wk	Change	P Within	Baseline	8 wk	Change	P Within	
Time domain										
Heart rate	(min ⁻¹)	77.8 ± 0.4	72.6 ± 0.5	-5.2 ± 0.4	<0.05	77.4 ± 0.4	77.4 ± 0.5	0.1 ± 0.2	0.94	<0.001
SDNN	(ms)	43.2 ± 0.7	57.9 ± 0.8	14.7 ± 0.5	<0.05	43.5 ± 0.6	43.7 ± 0.7	0.2 ± 0.5	0.87	<0.001
RMSSD	(ms)	31.3 ± 0.6	50.7 ± 0.9	19.6 ± 1.1	<0.05	32.8 ± 0.7	33.0 ± 0.7	0.2 ± 0.4	0.84	<0.001
pNN50	(%)	13.1 ± 0.3	35.7 ± 0.9	22.6 ± 0.7	<0.05	13.2 ± 0.4	13.2 ± 0.4	0.0 ± 0.2	0.98	<0.001
Frequency domain										
HF	(nu)	23.7 ± 0.3	37.8 ± 0.6	14.2 ± 0.5	<0.05	23.7 ± 0.3	23.7 ± 0.5	0.0 ± 0.3	0.97	<0.001
LF	(nu)	62.0 ± 0.4	52.3 ± 0.5	-9.6 ± 0.4	<0.05	62.1 ± 0.5	61.9 ± 0.5	-0.1 ± 0.3	0.84	<0.001
LF/HF ratio		4.0 ± 0.0	3.2 ± 0.1	-0.7 ± 0.1	<0.05	4.0 ± 0.1	3.9 ± 0.1	-0.1 ± 0.0	0.48	<0.001

Values are mean ± SE.

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

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 (30).

As shown in Figure 2, since HR 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.

FIGURE 2—Interplay between chronic methamphetamine toxicity and exercise training adaptations on parasympathetic and sympathetic components of the autonomic nervous system and heart rate variability (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.

These findings concur with a large body of longitudinal studies that indicate physical activity is a safe, nonpharmacological approach to favorably altering ANS function and thereby providing a cardioprotective role (11,22).

In this study, the impressive gain (24%) in aerobic capacity ($\dot{V}O_{2\max}$) 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 demonstrates 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 (17,23); however, this will have to be further explored in future research.

Because of 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 (22), whereas studies in older individuals remain equivocal (34). This observation is perhaps related to a decrease in HRV with age. A review of HRV in a variety of athletic populations indicated that 3 months of moderate-intensity aerobic training is sufficient to achieve a measurable increase in HRV (3,10). Our results, supported by strong correlations ($r = 0.85$ – 0.88) between changes in $\dot{V}O_{2\max}$ and changes in various HRV indices, confirm several previous longitudinal studies that have demonstrated a significant increase in HRV with aerobic exercise training (21,26,29,33). A cross-sectional study showed that endurance-trained men ($\dot{V}O_{2\max} > 55 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) had higher HRV compared to sedentary controls ($\dot{V}O_{2\max} < 40 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) after training (11). While some research indicates that HRV does not seem 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 8 wk might further increase cardiac vagal modulation.

As a consequence of chronic adaptations to exercise training, there are adjustments in cardiac rhythm that influence HR and HRV. Training induces sinus bradycardia in resting conditions, as demonstrated in the ME group, and a lower HR at any given submaximal level of oxygen uptake because of a shift of the sympathovagal balance toward vagal dominance. The lower HR 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 (22). 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 (15), 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 functions, and research suggests that the effect of psychosocial distress on cardiovascular morbidity and mortality is comparable with the effect 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 (25). Methamphetamine users commonly experience psychiatric symptoms including anxiety and depression (32,41); 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 RMSSD, could have been influenced during the 8 wk by positive psychosocial and behavioral changes in both groups (35). However, no changes, not even nonsignificant 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

group’s parasympathetic and sympathovagal balance through its effect on other health outcomes such as ameliorating negative psychosocial stress (6,15,41).

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. Second, based on the literature, there are confounding factors in the measurement, analysis, and interpretation of HRV, which could obscure results. To minimize known confounding factors influencing HRV, the MD and DF groups were matched for age, body mass index, and fitness measures. In fact, baseline fitness measures ($\dot{V}O_{2\max}$ and percentage body fat) were similar and categorized 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 (19). 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. Third, because nicotine from cigarettes is known to increase sympathetic outflow and to perturb HRV measures (14), participants were asked to refrain from smoking 12 h before measurements. In addition, using a questionnaire, we ascertained that the frequency of cigarette smoking throughout the 8-wk study did not significantly change from baseline in either of the MD groups. Fourth, several of the participants were positive for HIV infection, and recent research has indicated that it is possible that HRV is adversely affected by HIV infection. Fifth, part of intrasubject 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 (16,35). These factors are difficult to control in any study. While 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.

CONCLUSIONS

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 among 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 (2,15). 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.

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