

Effect of Moderate Versus High-Intensity Interval Exercise Training on Heart Rate Variability Parameters in Inactive Latin-American Adults: A Randomised Clinical Trial

Running head: Different exercise intensities on heart rate variability

By

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Abstract

We investigated the effect of moderate versus high-intensity interval exercise training on the HRV indices in physically inactive adults. Twenty inactive adults were randomly allocated to receive either moderate intensity training (MCT group) or high-intensity interval training (HIT group). The MCT group performed aerobic training at an intensity of 55-75%, which consisted of walking on a treadmill at 60-80% of the maximum heart rate (HR_{max}) until the expenditure of 300 kcal. The HIT group ran on a treadmill for 4 minutes at 85-95% peak HR_{max} and had a recovery of 4 minutes at 65% peak HR_{max} until the expenditure of 300 kcal. Supine resting HRV indices (time domain: SDNN, standard deviation of normal-to-normal intervals; rMSSD, Root mean square successive difference of RR intervals and frequency domain: HF_{Ln}, high-frequency spectral power; LF, low-frequency spectral power and HF/LF ratio) were measured at baseline and 12 weeks thereafter. The SDNN changes were 3.4 (8.9) ms in the MCT group and 29.1 (7.6) ms in the HIT group (difference between groups 32.6 [95% CI, 24.9 to 40.4 (P = 0.01)]. The LF/HF_{Ln} ratio change 0.19 (0.03) ms in the MCT group and 0.13 (0.01) ms in the HIT group (P between groups = 0.016). No significant group differences were observed for the rMSSD, HF and LF parameters. In inactive adults, this study showed that a 12-week HIT training program could increase short-term HRV, mostly in vagally mediated indices such as SDNN and HF/LF_{Ln} ratio power.

Trial registration. ClinicalTrials.gov NCT02738385, registered on 23 March 2016.

Keywords. Randomized controlled trial; Exercise training; Autonomic nervous system; Cardiac autonomic control; Intensity

Introduction

Disorders of the autonomic nervous system have a key pathophysiological role in the early stages of essential hypertension, myocardial infarction and chronic heart failure by producing coronary vasoconstriction, increasing cardiac oxygen consumption and leading to fatal events [15,56]. Heart rate variability (HRV) is of increasing interest because it is a marker of cardiovascular autonomic function and because reduced HRV is a direct predictor of cardiovascular risk and all-cause mortality [13,58]. Additionally, the parasympathetic withdrawal quantitated by HRV is associated with reduced coronary flow reserve and antedates episodes of dynamic myocardial ischemia [37]. HRV refers to the periodic changes in heart rate and serves as an index of the activity level of the autonomic nervous system [26].

HRV can be evaluated by time and frequency domain indices. Accordingly, it can be represented in a time domain in which R-R intervals (in milliseconds) are plotted against time (in seconds) [53]. Among the most used indices, the standard deviation of normal beat-to-beat (R–R) intervals (SDNN) has been suggested to reflect global variability, and the root-mean-square of successive R–R intervals (rMSSD) and high-frequency (HF) power have been linked to vagal activity [8].

Strong evidence shows that physical inactivity, i.e., <150 min/wk. of moderate activity or 75 min/wk. of vigorous activity, can increase the risk of many adverse health conditions, including major non-communicable diseases such as coronary artery disease (CAD), metabolic syndrome and breast and colon cancers [9,34]. Currently, physical inactivity has a deleterious effect that is comparable to smoking and obesity. It is now recognised as the fourth-leading risk factor for global mortality and accounts for 6% of all deaths [36]. Furthermore, physical inactivity is associated with decreased HRV, particularly HF power, thus reflecting reduced cardiovascular autonomic control [24]. Experimental studies have indicated that sedentary time results in alterations of cardiovascular health and HRV and during prolonged bed-rest [25,28,54].

On the other hand, cross-sectional reports in different population suggest that regular aerobic exercise training is associated with improved HRV [1], however, studies examining the effect of moderate or high intensity on HRV are mixed and incomplete with respect to clinically recommended training paradigms. In the clinical setting, previous systematic reviews have found that inactivity physical adults who participate in supervised interval training can experience improvements in HRV, exercise capacity, quality of life, maximal oxygen consumption ($\text{VO}_{2\text{max}}$) and cardiac remodelling [3,18,50]. Additionally, high-intensity exercise has been shown can positively modify the sympathovagal control of HRV toward facilitating a persistent increase in parasympathetic tone, known to be associated with a better prognosis in non-communicable diseases patients [50].

Interestingly, few studies showed comparable or superior improvements in cardiovascular function using low-volume, high-intensity training (HIT) compared to traditional moderate continuous training (MCT) [18,23,47,50,59]. However, the effects of MCT, HIT or a combination of the two (MCT/HIT) program on HRV indices, which is clinically the current standard in inactive adults, has yet to be established [5,12,21,42].

In the Latin-American population, a region that has undergone a well-documented epidemiologic transition and epidemic of obesity [30,40,52], relatively little research on physical activity [49] and physical fitness exists [17,41,48]. A randomised clinical trial comparing different intensities of exercise training in inactive adults is clinically relevant because it could provide evidence for a precise, prescribed intensity of exercise training for optimal outcomes in this population [20,33,34,59]. Given this knowledge gap, the aim of the current randomised clinical trial was to compare the effect of MCT versus HIT on HRV indices in physically inactive adults.

Materials & Methods

Experimental Approach to the Problem

The HIIT-Heart Study is a substudy of the ‘High Intensity Interval- vs Moderate Training on Biomarkers of Endothelial and Cardiovascular Health in Adults’ study (registered at ClinicalTrials.gov, registration number: NCT02738385) in which the aim was to compare the efficacy of different volumes of HIT and traditional training in reducing risk factors constituting the CAD. In this substudy, we report changes in HVR variables that were only recorded at our local site (Bogotá, Colombia). A participant flow diagram is shown in Figure 1. The overall objective of the substudy “HIIT-Heart” is to quantify the dose-effect of different exercise intensities (i.e. moderate-intensity and low volume vigorous-intensity), on HRV indices (primary outcome), and on physiologic response (heart rate, blood pressure), body composition (BMI, waist circumference, body fat, lean mass) and $\dot{V}O_2$ peak in adults (secondary outcomes).

Participants and recruitment

This randomised clinical trial was conducted at the University of Rosario in Bogota and Santo Tomás University, Colombia, between February 2015 and May 2016. Primary and secondary outcomes were assessed at baseline and 12 weeks thereafter. We provide an overview of the methods as per the Consolidated Standards of Reporting Trials (CONSORT) checklist [11].

Participants were recruited from the Centre of Studies in Physical Activity Measurements (in Spanish, CEMA) by posting study recruitment flyers at community centres, by study recruitment announcements at CEMA and by word-of-mouth. Subjects are eligible to participate if they are located in the metropolitan region with available time (1 hour per day) to support the trial. Additional eligibility criteria include participants were aged 18–45, were inactive (<150 min/wk. of moderate-intensity activity or 75 min/wk. of vigorous-intensity activity), had a body mass index ≥ 18 and ≤ 30 kg/m² and identified as being willing and having almost immediate availability.

Risks were minimised by ruling out contraindications to the testing and training protocols via a health history and a thorough physical examination before the testing sessions. Individuals with a history of a medical condition identified by the American Heart Association (AHA) as an absolute contraindication to exercise testing were excluded from this study [35]. Furthermore, individuals were also excluded if they presented any of the following: systemic infections, weight loss or gain of >10% of body weight in the past 6 months for any reason, currently taking medication that suppresses or stimulates appetite, uncontrolled hypertension (systolic blood pressure 160 mm Hg or diastolic blood pressure 95 mm Hg), gastrointestinal disease (including self-reported chronic hepatitis or cirrhosis, any episode of alcoholic hepatitis or alcoholic pancreatitis within past year, inflammatory bowel disease requiring treatment in the past year, recent or significant abdominal surgery e.g., gastrectomy), asthma, diagnosed diabetes (type 1 or 2), fasting impaired glucose tolerance (blood glucose ≥ 118 mg/dL) or use of any prescribed drugs, any active use of illegal or illicit drugs or inability to participate due to a physical impairment. In addition, we confirmed by two exercise physiologists, subjects if they had alteration in ventricular function and/or cardiomyopathy, through a standard 12-lead ECG at rest and every 3-min of the maximum treadmill exercise test. All subjects remained under usual medical care and clinical follow-up (i.e., regular appointments with a physician) throughout the protocol. Written informed consent was obtained for all subjects, and ethical approval was granted by the local office for Research Ethics Committee at University of Santo Tomás (ID 27-0500-2015). Additionally, each participant completed an informed consent document outlining the experiment that was approved by the Institutional Review Board. The study conforms to the principles outlined in the Declaration of Helsinki.

Blinding and randomisation

Randomisation into the two study arms was performed by the CEMA at University of Rosario, Bogotá, Colombia, using block randomisation with block sizes of four. As each participant consecutively entered this randomised clinical trial, he/she was randomly allocated to either the MCT

or the HIT group according to the computer-generated allocation sequence. The randomisation sequence was not concealed from the investigator who was responsible for assigning participants to groups. All participants and study personnel (including investigators and statisticians) were blinded to treatment allocation throughout the trial protocol. Furthermore, the investigators who performed the statistical analyses were masked from group assignment. The importance of maintaining the blinding and allocation concealment was reinforced by regularly scheduled conference calls at the sites and daily meetings with the field investigators.

Interventions

The participants assigned to the intervention group participated in the cardiometabolic programme as recommended by the Colombian guidelines COLDEPORTES (*in Spanish*, Departamento Administrativo del Deporte, la Recreacion, la Actividad Fisica y el Aprovechamiento del Tiempo Libre) [29], and AHA [35,39] for cardiovascular health promotion and disease reduction. At the beginning of the training protocol, we obtained the participants' weight to determine the weekly energy expenditure necessary to achieve their target of $12\text{-kcal}\cdot\text{kg}^{-1}\cdot\text{week}^{-1}$ (iso-energetic). It was expected that the gradual increase in total energy expenditure would minimise fatigue, soreness, injuries and attrition.

After inclusion, patients performed a maximal cardiopulmonary exercise test on a maximum treadmill exercise test (Precor TRM 885, Italy) following the modified Balke protocol [1] and physiological parameters ($\dot{V}\text{O}_2$, HR and Borg ratings) from the test were used to set exercise intensity. Based on averaged HRmax and $\dot{V}\text{O}_{2\text{peak}}$, the participants were classified according to normative values, referenced to age and sex [1,39]. MCT and HIT interventions lasted 12 weeks, with three sessions per week, consisting in fast walking or running on a treadmill with the deck inclined to reach the desired intensity. HR was recorded each session using a HR monitor (Polar Electro, Kempele, Finland). In addition, rating of perceived exertion (RPE) were also measured in each exercise session. An initial 2-week preparatory phase of training was performed to bring participants up to a $6\text{-kcal}\cdot\text{kg}^{-1}$

$1 \cdot \text{week}^{-1}$ goal (~ 150 kcal per session), which was increased progressively $2 \cdot \text{kcal} \cdot \text{kg}^{-1} \cdot \text{week}^{-1}$ until week 4, and was then maintained at $12 \cdot \text{kcal} \cdot \text{kg}^{-1} \cdot \text{week}^{-1}$ for weeks 5 to 12 (~ 300 kcal per session).

Moderate-continuous training (MCT) group

Exercise training sessions were designed to elicit a response in the acceptable moderate-to-vigorous range, i.e., 55–75% HRmax/RPE of 11–15 on Borg scale. Sessions consisted of a warm-up (5 min), followed by 15–55 min of treadmill walking/running (15–35 min during the 2-week preparatory phase), and a final relaxation/cool-down period (10 min).

High-intensity training (HIT) group

We calculated the training energy expenditure for participants' age ranges associated with meeting the consensus public health recommendations from the Cardiometabolic HIIT-RT Study [47]. A complete description of the design and methods has been published elsewhere [47]. During the 2-week preparatory phase subjects warmed up at 65% HRmax (5 min), then perform 4×4 min intervals at 60–80% HRmax/RPE of 13–15 on Borg scale, interspersed with 4 min of recovery at 55% HRmax/RPE of 11–13 on the Borg scale. During weeks 3–12 subjects perform 4×4 min intervals at 85–95% HRmax/RPE of 15–17 on Borg scale (with the target zone maintained for at least two minutes), interspersed with 4 min recovery at 65% HRmax, and a cool-down (5 min), with a range total exercise time of 35 to 55 min (with warm-up and cool-down).

Both groups were required to attend two supervised sessions with an exercise physiologist at the University of Rosario at a fitness centre “CEMA”, which contained the treadmills needed to complete the prescribed exercise programmes. Each participant was instructed to immediately inform the supervisor if he or she experienced any unusual symptoms while exercise training and to consult a physician if needed. Participants were instructed to refrain from exercise training and to avoid changing their physical activity levels outside this study. All participants reported adhering to these instructions.

We estimated the energy expenditure during the exercise sessions by calibrating the energy expenditure to the HR during the maximal oxygen uptake tests performed at the baseline and post-intervention time points. The regression of the energy expenditure was calculated for each participant according to both the HR and the minutes spent exercising during the training sessions. Trainers were physical therapists and physical educators with experience developing and monitoring exercise programmes among clinical populations. Adherence to the exercise programme was encouraged by the exercise professional who supervised each of the group sessions. To maximise adherence to the training programme, a maximum of 3–5 participants were trained simultaneously. Each participant met with the study dietician for nutrition assessment and counselling. An individualised nutrition intervention plan was developed from the baseline food intake assessment according to participant preferences [47]. This plan consisted of a standardised meal consisting of 1300 to 1500 kcal (50–55% carbohydrates, 30–35% total fat, <7% saturated fat and 15–22% protein).

Experimental procedure

Prior to the procedure, participants were instructed to refrain from strenuous activities for at least 48 h, and caffeine and alcohol for at least 24 h before all tests. Subsequently, participants reported for testing following an overnight fast, consuming only water, and refraining supplement intake that morning. All measurements were tested on two different days in climate controlled room between the hours of 07:00 and 10:00 h.

Primary outcome measures

The primary outcome measure was HRV measured between 07:00 and 08:00 h for 25 minutes in a semi-dark room (22–23°C) following a 12-hour fast. HRV measurements were conducted at the same time (± 1 hour) of day for each assessment period. We used a two-channel ECG signal detected by a Heart Rate Monitor (Polar Electro, Kempele, Finland) and transmitted online to a PC through Polar Advantage Interface receiver. We quantified HRV from the last 5 minutes of R–R interval recording. First, we examined the parasympathetic nervous system by calculating the square root of the mean of

the sum of the squares of differences between adjacent R–R intervals (rMSSD). rMSSD is considered to be a stable measure of parasympathetic modulations of heart rate [14]. Mean R-R intervals were recorded at a rate of 250 Hz. Second, SDNN was measured, reflecting the cyclic components responsible for variability in the period of recording and reflective of both sympathetic and parasympathetic tone. Third, frequency domain was analysed in three absolute and log normalized frequency bands define as: HF and LF. In the frequency domain, oscillations of RR intervals were examined within the low-frequency (LF: 0.04–0.15 Hz) and high-frequency bands (HF: .0.15–0.40 Hz). The sympatho-vagal balance was obtained by the ratio of the power LF to HF (LF/HF) bands. All index are described and used in previous reports [14,45,53]. The resulting R-R intervals were analysed in the time domain, in the frequency domain using spectral analysis (Fast Fourier Transform), and nonlinearly through the Poincare' plot (Kubios HRV Analysis v 2.0, Biosignal Analysis and Medical Imaging Group at the Department of Applied Physics, University of Kuopio, Kuopio, Finland). In-house testing revealed near perfect ($r = 0.99$) correlations between these methods and electrocardiographs. These differences were also similar to what was reported by other applications that assess HRV via heart rate monitors. The reproducibility of 24-hour derived HRV indices was ICC = 0.86 to frequency domain parameters and ICC = 0.95 to time domain parameters.

Secondary outcomes

Anthropometric and body composition measurements: Body weight was measured using electronic scales (Tanita® BC544, Tokyo, Japan) with a low technical error of measurement (TEM = 0.510%). Height was measured using a mechanical stadiometer platform (Seca® 274, Hamburg, Germany; TEM = 0.01%). Body mass index (BMI) was calculated as the body weight in kilogrammes divided by the square of height in meters (kg/m^2). The waist circumference (WC) was measured at the narrowest point between the lower costal border and the iliac crest using a tape measure (Ohaus® 8004-MA, New Jersey, USA; TEM = 0.05%). In cases where this point was not evident, it was measured at the midpoint between the last rib and the iliac crest. We measured each variable twice and

used the average measure obtained unless the first and second measures varied by more than 1%, in which case we used the median of three measurements. The percentages of body fat mass and mass muscle were obtained using the Tetrapolar Bioelectrical Impedance Analysis (BIA) system (BF-350, Tanita Corp, Tokyo, Japan). Before testing, participants were required to adhere to these BIA manufacturer's instructions: 1) to not eat or drink within 4 h of the test; 2) to not consume caffeine or alcohol within 12 h of the test, 3) to not take diuretics within 7 days of the test; 4) to not do physical exercise within 12 h of the test, and; 5) to urinate within 30 min of the test. An electrical current of 50 kHz was passed through the participant and resistance and reactance were measured. To ensure data quality, the equipment was calibrated daily using a known calibration standard, in accordance with the manufacturer's instructions [6]. Subjects stood on the metal contacts in bare feet, and body fat mass was determined. This measurement was repeated twice and the average value was obtained. The reproducibility of our data was $R=0.98$.

Cardiorespiratory fitness: $\dot{V}O_{2peak}$ was determined using a maximum treadmill exercise test (Precor TRM 885, Italy) following the modified Balke protocol, which has been extensively used [47] in people inactive. The treadmill test used a ramp protocol where the inclination is constant (5.5%) and the speed increases by 0.5 km/h every minute, starting at 4 km/h [47]. Each session began with a 5 to 10 min warm-up at 50 W. We asked participants to refrain from smoking two hours before the test, and from drinking alcohol or doing any vigorous or moderate intensity activities 48 h before the test. HRmax was used to determine the training intensity for each participant. We measured blood pressure prior to and during the test. Exercise was terminated if participants were fatigued, or earlier if they fulfilled the AHA guidelines for 'Indications for Terminating Exercise Testing' [35]. Maximal oxygen uptake was defined as the highest recorded $\dot{V}O_{2peak}$ after two of three criteria were met: 1) a plateau in $\dot{V}O_2$ after increase in workload; 2) a respiratory exchange ratio >1.10 , and (3) a maximal heart rate within 10 bpm of their age-predicted maximum. Exercise capacity was defined as the total duration (minutes) of the graded exercise test. The findings of previous research suggest that graded exercise

testing as described in this study is reliable and is a standard for measuring exercise capacity [4,49]. The reproducibility of our data was $R=0.92$.

Resting blood pressure: Blood pressure was measured using an electronic oscillometric device (Riester Ri-Champion model, Jungingen, Germany) after being seated in a quiet room for 10 min with their back supported and feet on the ground according to the International Protocol of the European Society of Hypertension [55]. Two blood pressure readings were taken separated by a 10-min interval. Inter-observer variability was $R=0.96$.

Additional outcomes of this study were participant adherence and adverse events. The investigator or research assistant, who supervised each group, recorded the date of each completed exercise training session and the length of time spent during each exercise training session. These data were used to assess each group's adherence to the exercise program. Total exercise time was defined as total time spent on exercise training during the study. Interim monitoring focused on patient intake, adherence to the protocol, baseline comparability of treatment groups, completeness of data retrieval and adverse events. Data about participant adherence to the prescribed exercise training variables are presented in the interventions section. However, self-reported physical activity was measured using the recent physical activity questionnaire. This questionnaire assesses physical activity across four domains (domestic, recreational, work and commuting) over the previous 7 days. It has shown moderate-to-high reliability for physical activity energy expenditure and good validity for ranking individuals according to their time spent in vigorous intensity physical activity and overall physical activity energy expenditure [4]. The outcome was assessed in METs (units of metabolic equivalence) per week. This questionnaire was administered immediately before and after the training period and at 12 weeks following the completion of the exercise intervention.

Statistical Analysis

To retain data of all randomly allocated participants, an intention-to-treat analysis population (all randomly assigned patients) was performed. Before the planned statistical analyses, a preliminary analysis was conducted (*Shapiro–Wilk test*) to confirm data distribution normality. Primary and secondary outcomes values are reported as mean (\pm) standard deviation (SD) or 95% confidence interval (CI 95%) unless otherwise specified. Due to their skewed distribution, the following variables were log-transformed before analyses: SDNN, rMSSD, HF, LF and LF/HF ratio. To aid interpretation, data were back-transformed from the log scale for presentation in the results.

Adherence to the exercise program for both groups was expressed as the total number of training days that each participant completed of the prescribed number of training days and total exercise time during the 12-week supervised exercise program. Once it was confirmed that the sample data satisfied the normality assumption, statistical analyses relevant to our main research interest were conducted. A *t*-test was used to investigate any possible differences in baseline characteristics and adherence between the groups. We used a generalised linear model (GLM) to analyse the influence of the differing doses of exercise training on HRV characteristics. The Dunnett-Hsu test allows for specific multiple pair-wise comparisons while still protecting against type I statistical errors. Change between the pre- and post-measures was calculated for each outcome variable of interest. For normal data, effect sizes (ES) were calculated using Cohen's *d* (between group: $d = (M_1 - M_2) / \text{spooled}$, where M_1 and M_2 are the mean changes ($M_{\text{post}} - M_{\text{pre}}$) for each group, and spooled is the pooled standard deviation of changes from each group; within group: $d = M_d / S_d$, where M_d is the mean difference from pre-to-post and S_d is the standard deviation of differences between subjects), which was defined as small, medium, and large for 0.20, 0.50, and 0.80, respectively. Finally, we used a subgroup analysis to compare dose-response effects across predefined baseline groups. Significance of interaction relationships between variables was tested using a Spearman correlation analysis and denoted as r_s . All reported P values are two-

sided ($P < 0.05$). In order to determine TEM for HRV indices, blood pressure and cardiorespiratory fitness, a experiment trial involving six recreationally active participants (Four males; two females, age, 29 ± 1 yrs; BMI, 26 ± 9 kg/m²; VO₂peak, 38 ± 7 ml·kg·min⁻¹) reported to the lab on two separate occasions separated by at least a week and the resulting values were utilized to calculate TEM (*data no shown*). The body composition variables were used as the indicator of precision by TEM. It is based on at least two measurements taken of the same subject by the same observer (intraobserver variability). The TEM was estimated from the results of an ANOVA as the square root of the within-subject mean square. The coefficient of reliability (R) and ICC estimates the proportion of between-subject variance in a measured population that is free from measurement error to HRV indices, blood pressure and cardiorespiratory fitness. Measures of 'R' can be used to match the relative reliability of different anthropometric measurements, as well as of the same measurements in different age groups and to estimate sample size requirements in anthropometric studies. 'R' as a percentage (R%) was calculated using the following equation: $R \% = 1 - (\text{total TEM}^2 / \text{SD}^2)$. Intraclass correlation coefficients (ICC) were also determined from the mean square values of the ANOVA. In order to establish criteria to categorize participants as 'responders' or 'non-responders', the biological variability (i.e. ICC and R) were established to determine the TEM. In this study, non-responses were determined using two times the TEM of measurement for SDNN (0.007 ms), rMSSD (0.003 ms), and rr interval length (0.005 ms). Statistical analyses were conducted using SPSS version 22 (IBM, Armonk, New York, USA).

Results

A total of 28 potential physically inactive subjects were assessed for eligibility, seven of whom were excluded for not meeting inclusion criteria. Ten participants were randomly allocated

to the MCT group and 11 participants were randomly allocated to the HIT group. After allocation, one participant in the MCT group withdrew from this investigation for reasons unrelated to this study (lack of time due to work schedule).

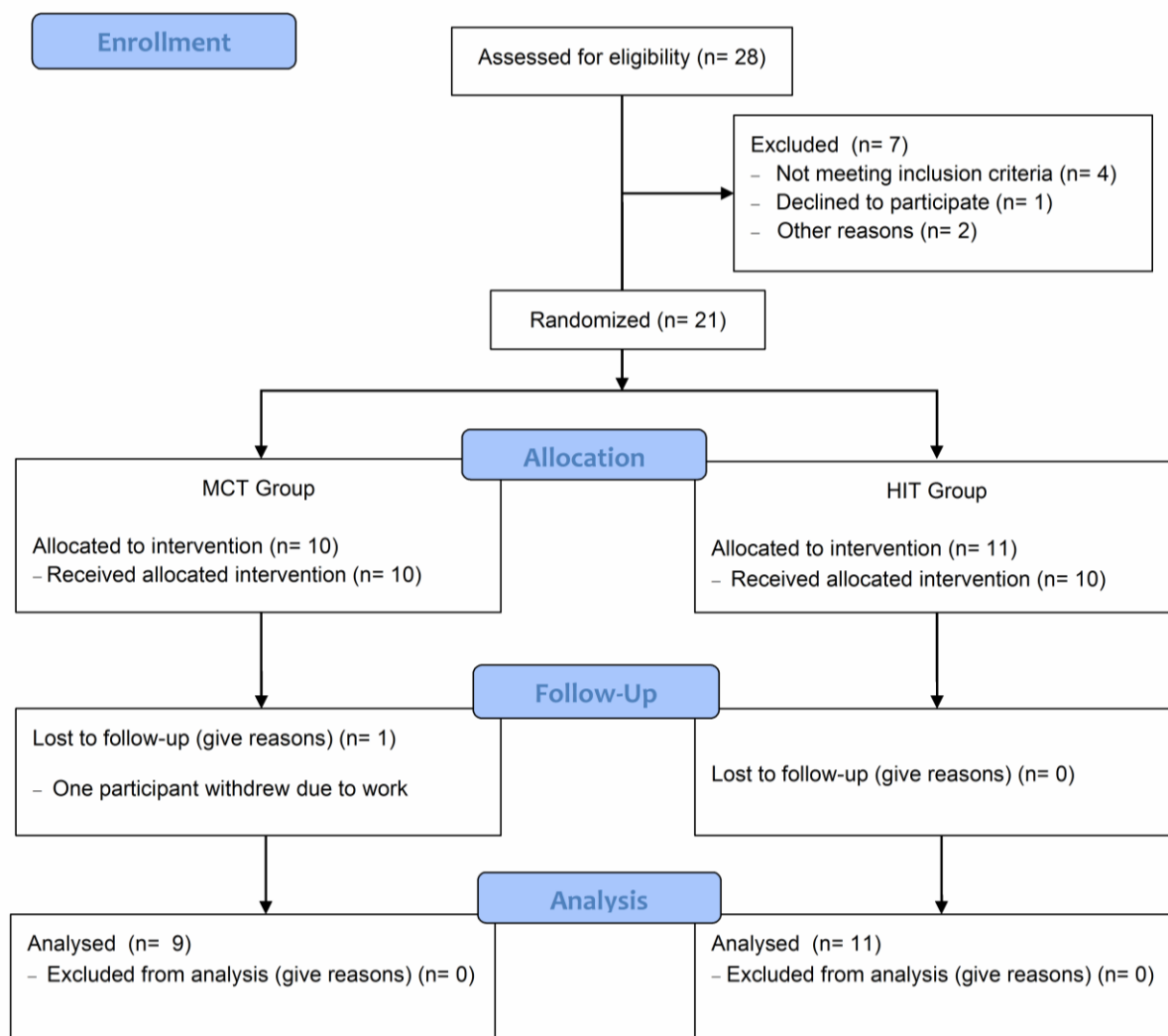


Figure 1. CONSORT guidelines flow diagram for enrolment and randomization HIIT-Heart Study.

Baseline characteristics of the MCT group, HIT group and the total sample are outlined in Table 1. The t-test indicated no statistically significant differences ($p > 0.05$) in baseline characteristics between the groups.

Table 1. Baseline participant characteristics

	Total sample (n = 20)	MCT (n = 9)	HIT (n = 11)
Sex, n (%)			
Male	8 (40.0)	5 (55.6)	3 (27.3)
Female	12 (60.0)	4 (44.4)	8 (72.7)
Age, mean (SD), y	31.8 (7.8)	31.4 (6.4)	32.1 (9.0)
Race/ethnicity, n (%)			
Black or Afro-Colombian	18 (90.0)	7 (77.7)	11 (100)
Others (Indigenous)	2 (10.0)	2 (22.3)	0 (0.0)
Socioeconomic level, n (%)			
Low-mid	11 (55.0)	5 (55.5)	6 (54.5)
Mid-high	9 (45.0)	4 (45.5)	5 (45.4)
Education, n (%)			
Secondary	1 (5.0)	0 (0.0)	1 (9.1)
Technical	1 (5.0)	1 (11.1)	0 (0.0)
University	18 (90.0)	8 (88.9)	10 (90.9)
Occupation, n (%)			
Student/work	20 (80.0)	7 (77.7)	9 (81.8)
Housewife	5 (20.0)	2 (22.3)	3 (18.2)
Marital status			
Single	4 (20.0)	3 (33.3)	1 (10.0)
Married/de facto	16 (80.0)	6 (66.3)	10 (90.0)
Weight, mean (SD), kg	68.2 (11.3)	69.3 (15.3)	66.8 (10.9)
Height, mean (SD), m	1.67 (0.06)	1.69 (0.05)	1.68 (0.09)
BMI, mean (SD), kg/m ²	24.9 (3.7)	23.6 (3.6)	25.5 (4.2)

BMI, body mass index; HIT, high-intensity interval training; MCT, moderate-intensity continuous training; SD, standard deviation

Table 2 and Figure 2, lists the effects of the exercise interventions on HRV and physiological parameters. Difference between groups were observed on SDNN change, with 3.4 (8.9) ms in the MCT group and 29.1 (7.6) ms in the HIT group (difference between groups 32.6 [95% CI, 24.9 to 40.4; $p = 0.01$]; $d = 1.14$ [95% CI, 0.19 to 2.00]) and in the LF/HF ratio, with a change of 0.5 (0.9) ms in the MCT group and 0.5 (0.4) ms in HIT group (P between groups = 0.016; $d = 0.01$ [95% CI, -0.88 to 0.88]). Additionally, the percentage of body fat did not change in the MCT group (0.8); $d = 0.01$ [95% CI, -0.92 to 0.92], whereas it decreased by 1.1 percent in the HIT group -1.1 (1.5); $d = 0.10$ [95% CI, -0.73 to 0.93], (difference between groups 1.2 [95% CI, 0.1 to 2.4 $P = 0.04$]; $d = -0.88$ [95% CI, -1.81 to 0.03]). There were no significant treatment effects on other parameters.

Table 2. Intent-to-Treat Analysis of indices of heart rate variability and physiologic characteristics at baseline and changes after 12 weeks

10	Groups				From Baseline to 12-week, Mean (95% CI)			MCT effect (p value)	HIT effect (p value)	Time x group (p value)
	Baseline		Follow-up		Whiting-Group Change		Between- Group Difference in Change			
	MCT	HIT	MCT	HIT	MCT	HIT				
	(n = 9)	(n = 11)	(n = 9)	(n = 11)	(n = 9)	(n = 11)				
Time domain										
SDNN (ms)	65.2 (21.6)	74.9 (35.5)	61.7 (12.6)	104.1 (43.1)	3.4 (8.9)	29.1 (7.6)	32.6 (24.9 to 40.4)	0.838	0.097	0.013
rMSSD (ms)	58.3 (30.9)	68.8 (39.9)	59.5 (22.1)	80.2 (51.5)	1.2 (8.8)	11.4 (11.5)	10.2 (0.3 to 20.1)	0.724	0.721	0.576
Frequency domain										
HF (ms)	1673.2 (2074.7)	1547.8 (1399.7)	1020.4 (725.5)	1654.8 (1857.1)	652.7 (1349.2)	107.0 (457.3)	759.8 (-148.6 to 1668.1)	0.832	0.842	0.897
LF (ms)	1422.0 (1141.2)	954.0 (903.5)	1624.4 (964.5)	1138.3 (946.8)	184.3 (43.3)	202.3 (176.6)	18.0 (-109.3 to 145.3)	0.697	0.543	0.245
LF/HF (ms)	1.1 (0.9)	1.5 (1.5)	1.7 (1.8)	2.1 (1.9)	0.5 (0.9)	0.5 (0.4)	0.05 (-0.61 to 0.71)	0.612	0.407	0.016
Physiologic characteristics										
Heart rate (bpm)	62.0 (7.6)	58.6 (9.6)	59.3 (9.1)	52.7 (8.7)	-2.6 (-1.5)	-5.9 (0.8)	-3.2 (-4.4 to -2.1)	0.512	0.150	0.118
Systolic blood pressure (mmHg)	116.8 (5.1)	116.2 (6.5)	113.0 (7.6)	112.5 (9.1)	-3.8 (7.6)	-3.7 (6.5)	-0.2 (-6.8 to 6.5)	0.222	0.283	0.906
Diastolic blood pressure (mmHg)	72.3 (7.0)	71.0 (8.7)	67.8 (9.4)	67.0 (10.3)	-4.4 (8.5)	-4.0 (6.8)	-0.4 (-7.7 to 6.8)	0.274	0.339	0.960
Anthropometric and body composition										
Weight (kg)	69.3 (15.3)	66.8 (10.9)	68.6 (13.5)	66.7 (10.5)	-0.6 (1.9)	-0.1 (1.6)	-0.5 (-2.2 to 1.2)	0.179	0.353	0.451
BMI (kg/m ²)	23.6 (3.6)	25.5 (4.2)	23.4 (3.0)	24.4 (4.2)	0.2 (0.7)	1.1 (3.2)	-0.9 (-1.4 to 3.3)	0.190	0.130	0.879
Waist circumference (cm)	81.9 (12.2)	75.4 (7.6)	79.5 (10.6)	75.7 (8.3)	-1.7 (3.0)	0.3 (2.6)	-2.1 (-4.7 to 0.5)	0.070	0.357	0.672
Body fat (%)	27.4 (7.2)	31.2 (12.1)	27.4 (6.5)	30.0 (11.5)	0.0 (0.8)	-1.1 (1.5)	1.2 (0.1 to 2.4)	0.500	0.010	0.048
Lean mass (kg)	24.0 (5.9)	21.1 (3.5)	24.2 (5.1)	22.0 (3.6)	0.1 (0.8)	0.9 (0.0)	0.8 (0.3 to 1.3)	0.363	0.032	0.292
Cardiorespiratory fitness										
VO ₂ peak (ml·kg·min ⁻¹)	37.1 (9.7)	36.1 (7.6)	43.6 (9.0)	40.7 (7.9)	6.5 (9.3)	6.0 (4.5)	0.5 (-7.2 to 6.2)	0.035	0.012	0.731

Data in Mean (SD). BMI, body mass index; HIT, high-intensity interval training; SDNN, standard deviation of RR intervals; MCT, moderate-intensity continuous training; rMSSD, root mean square successive difference of R-R intervals; HF, high frequency spectral power; LF, low frequency spectral power

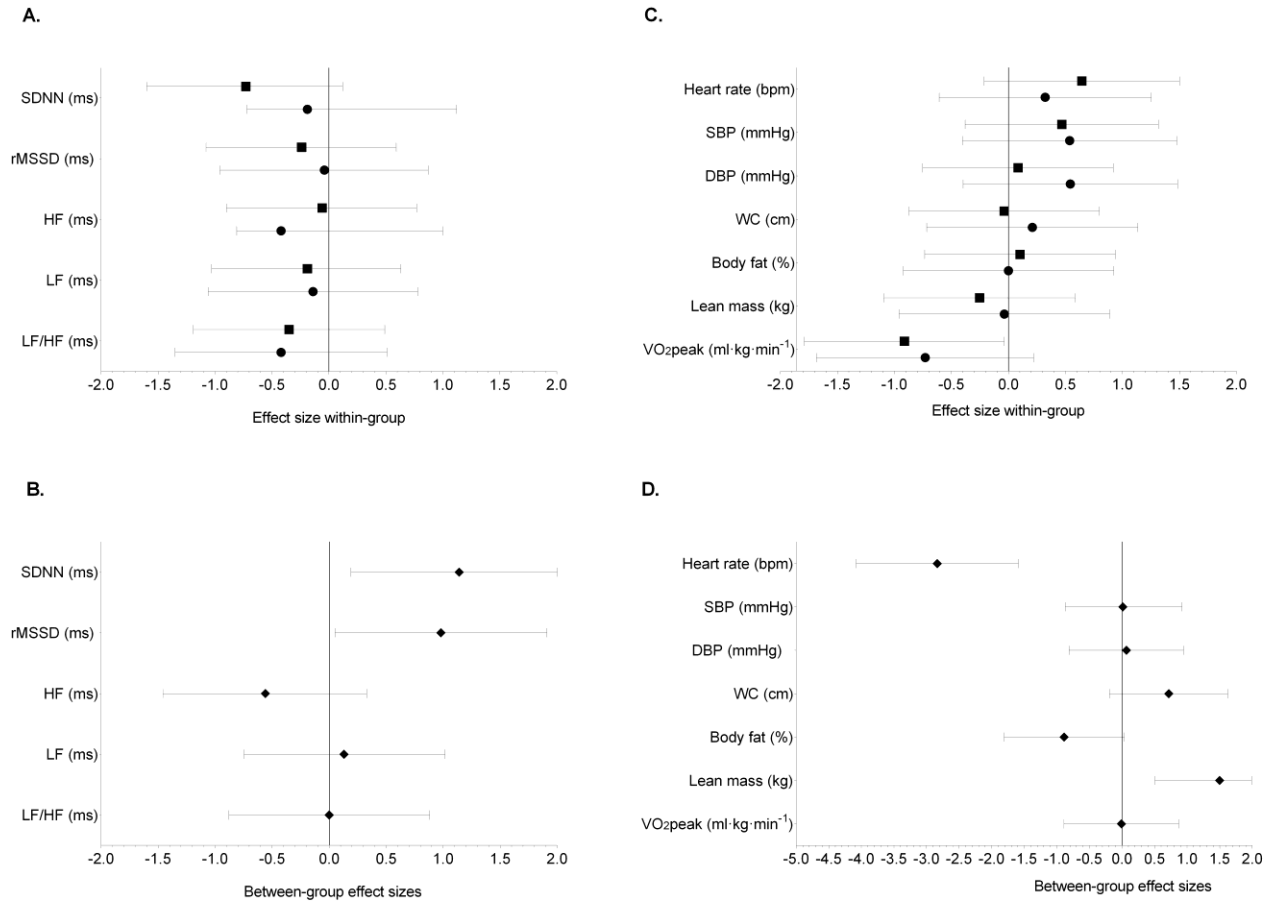


Figure 2. The relationship between the R-R interval length and the natural logarithm of the square of the mean sum of the squared differences between R-R intervals (rMSSD) after 12 weeks of program training by groups.

Spearman correlation (r_s) characteristics for various physiologic variables and HRV indices after 12 weeks of program training are presented in Table 3. We observed a moderate negative correlation between BMI and rMSSD in the MCT group ($r_s = -0.667$; $p < 0.05$). When analysing the HRV change from baseline to 12-week follow-up, we observed negative correlations between rMSSD and waist circumference ($r_s = -0.747$; $p < 0.001$), changes in SDNN ($r_s = -0.720$; $p < 0.05$) and HF_{Ln} ($r_s = -0.700$; $p < 0.05$), in the HIT group. Finally, we observed a stronger correlation between Ln rMSSD and R-R interval in the HIT group ($r_s = 0.834$; $p < 0.05$) Figure 3A. We also observed a non-significant correlation between Ln rMSSD and R-R interval in the MCT group ($r_s = 0.396$; $p = 0.290$), Figure 3B.

Table 3. Partial correlation between physiologic characteristics and indices of heart rate variability after 12 weeks of exercise training.

	MCT					HIT				
	Time Domain		Frequency Domain			Time Domain		Frequency Domain		
	rMSSD	SDNN	HF	LF	LF/HF	rMSSD	SDNN	HF	LF	LF/HF
Physiologic characteristics										
Weight (kg)	-0.619	-0.268	-0.611	-0.159	0.326	-0.464	-0.455	-0.391	-0.200	0.273
BMI (kg/m ²)	-0.667*	-0.267	-0.633	-0.167	0.333	-0.601	-0.569	-0.601	-0.374	0.405
Waist circumference (cm)	-0.385	-0.452	-0.418	-0.435	-0.050	-0.747**	-0.720*	-0.702*	-0.469	0.474
Body fat (%)	-0.567	-0.517	-0.583	-0.650	-0.167	-0.365	-0.397	-0.384	-0.356	0.242
Lean mass (kg)	-0.433	0.050	-0.467	0.183	0.500	-0.082	-0.073	0.045	0.427	0.045
Cardiorespiratory fitness										
VO ₂ peak (ml·kg·min ⁻¹)	0.323	0.349	0.264	0.162	0.017	-0.101	0.183	-0.156	0.119	0.178

Data represent *Spearman* correlation coefficients. * P<0.05 ** P<0.001

BMI, body mass index; SDNN, standard deviation of RR intervals; rMSSD, root mean square successive difference of RR intervals; HF, high frequency spectral power; LF, low frequency spectral power

No adverse events were reported during this investigation. The average exercise-training days and total exercise time during the programme were 35.5 days (standard deviation 1.3) and 1100 minutes (standard deviation 258) in MCT group; and 35.4 days (standard deviation 0.9) and 1031 minutes (standard deviation 147) in HIT group ($p = 0.043$). As expected self-reported physical activity increased as a result of training ($F [1.65, 135.03] = 4.37$; $p < 0.001$). Pairwise comparison analyses showed that the participants sustained levels of vigorous or moderate physical activity at the 12-weeks follow-up (data not shown).

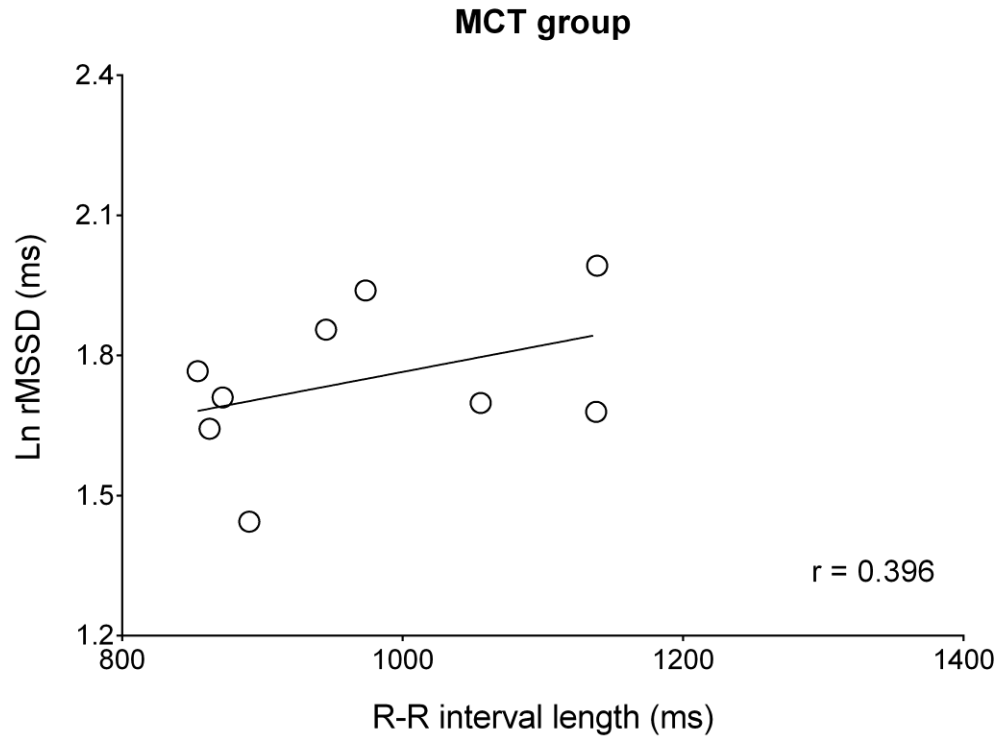
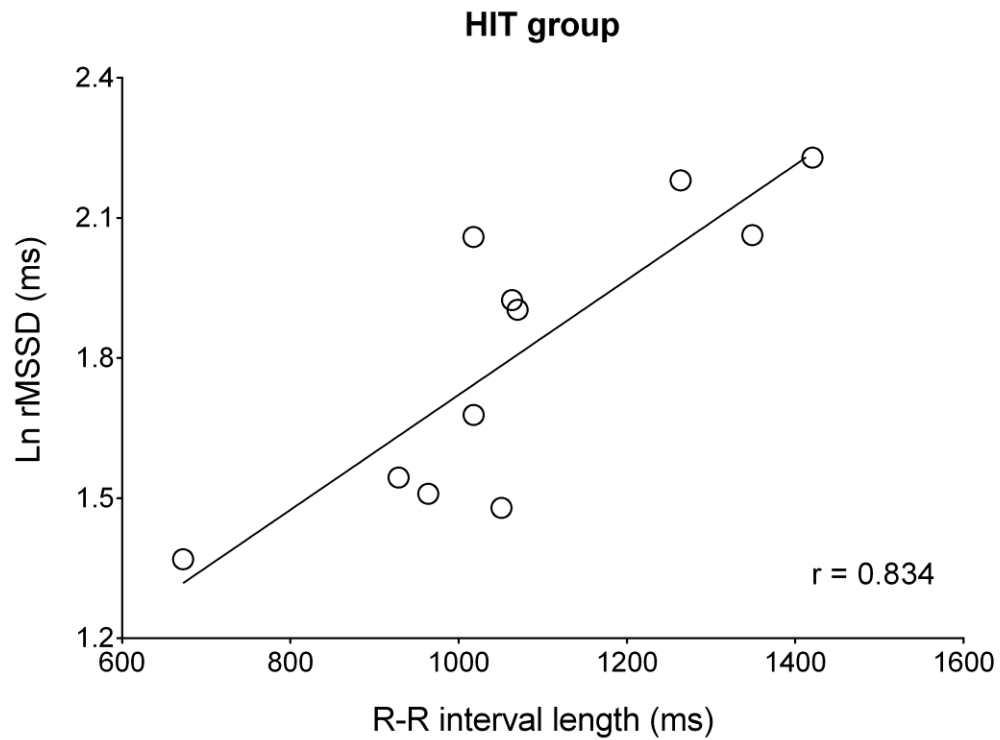
A**B**

Figure 3. A and C, within-subject effect sizes (Cohen's $d \pm 95\%$ CI) following 12 weeks of program training by groups. B and D, magnitude-based effect sizes ($ES \pm 95\%$ CI) between-group difference in change. ■ HIT group; ● MCT group.

Figure 4. Individual patterns of response following 12 weeks of program training by groups.

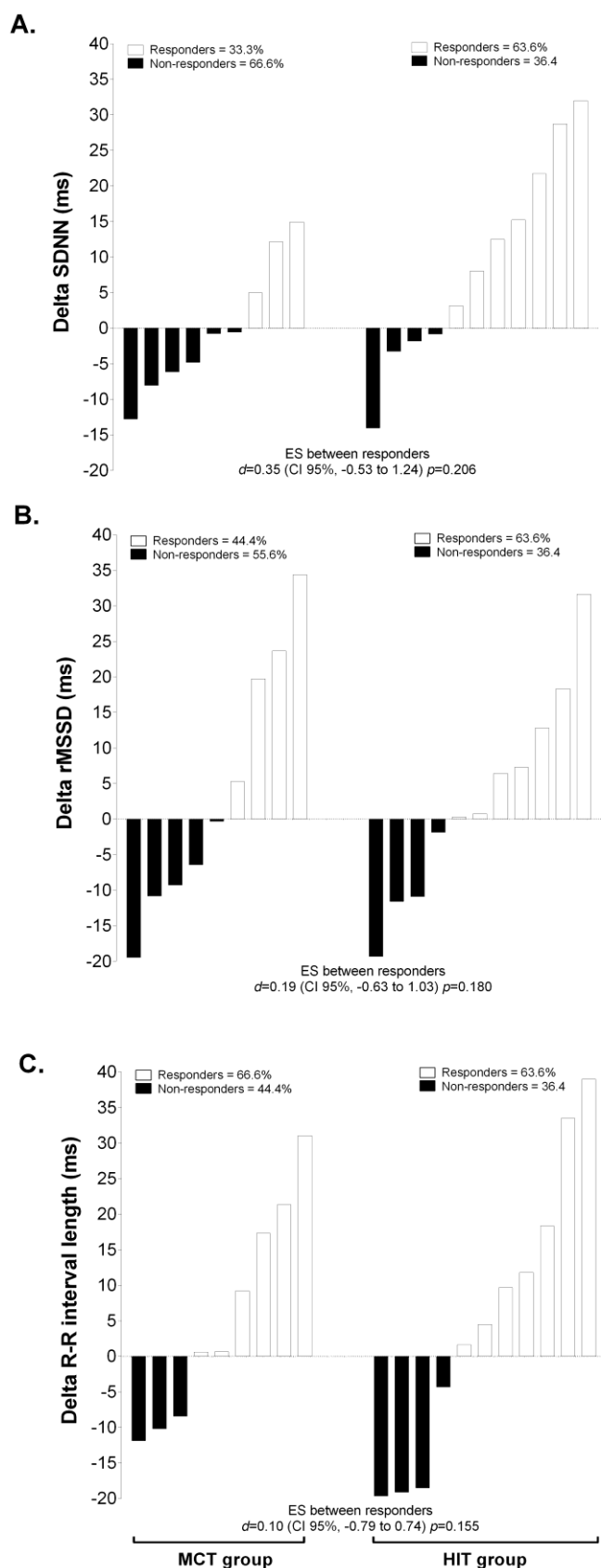


Figure 4 shows differences on prevalence of ‘responders’ and ‘non-responders’ based on relevant HRV indices after the 12-week supervised exercise. However, no significant effect size difference was found between ‘responders’ and ‘non-responders’ prevalence for the HRV variables: Δ SDNN (ms) 33.3% versus 63.6% ($d = 0.35$ (CI 95%, -0.53 to 1.24) $p = 0.206$), Δ rMSSD (ms) 44.4% versus 63.6% ($d = 0.19$ (CI 95%, -0.63 to 1.03) $p = 0.180$), and Δ rr interval length (ms) 66.6% versus 63.6% ($d = 0.10$ (CI 95%, -0.79 to 0.74) $p=0.155$) in the MCT and HIT groups, respectively.

Discussion

To our knowledge, this is the first randomised clinical trial on the effect of exercise training intensity on HRV in physically inactive adults from the Latin-American population. Our findings suggest that HIT was a more effective medium-term

strategy to increase HRV, specifically SDNN and LF/HF ratio, than MCT was. Collectively, the magnitude of the change for both training groups was not significantly different in the remaining parameters, suggesting that either training protocol may provide similar medium-term benefits in cardiovascular health. Additionally, we did not find differences in the ‘responder’ prevalence in relation to improvements HRV in any of these or secondary outcomes.

Increasing attention is being focused on the role of the autonomic nervous system in health and disease [51]. Exercise has been reported to be effective in improving HRV because exercise serves to reduce the activity of sympathetic nervous system while increasing the activity of the parasympathetic nervous system [10]. Specifically, aerobic exercise training increases cardiac vagal modulation via functional and structural adaptations in cardiovascular system (e.g., stroke volume) [38,45]. Our study showed an increase in SDNN in the HIT group compared to the MCT group. SDNN reflects the cyclic components responsible for variability in the period of recording and is reflective of both sympathetic and parasympathetic tone [27]. In this sense, studies in adults with Type 2 diabetes also did not report improvements in HRV after 12 [32] or 16 weeks [16] of aerobic exercise programs, although improvements did occur in programs of 24 weeks [43]. Thus, HRV improvement may be affected by the length of the exercise period. Therefore, HIT seems to favour a greater impact on neurocardiac activity than MCT in the medium-term [44]. The mechanism by which HIT has greater effects on the markers of cardiac autonomic outflow compared to MCT is not clear. It may be that supramaximal exercise generates higher catecholamine concentrations compared to lower-intensity exercise [31]. This finding may contribute to the observed autonomic modulation [1]. Furthermore, the higher catecholamine levels could explain major reductions in percentage of body fat in the HIT group, as catecholamines would stimulate lipolysis, which is primarily responsible for fat release from adipose tissue fat stores [57]. However, the observed increase in HRV is consistent with a study in middle-aged men following 2 weeks of HIT (4–6 x 30

s of all-out cycling efforts with 4-min recovery) compared to aerobic training (40–60 min at 60% of peak workload) [33].

Our findings also indicate differences between groups in LF/HF ratio changes. Although the mechanisms are not clear, this result could be explained by a larger increase in vagal- or baroreflex-mediated modulation of the sinoatrial node with HIT compared with MCT [33]. Additionally, differences in the hemodynamic oscillations experienced during the exercise sessions could be involved as could alterations, according to several authors, of intrinsic HR, S-A node sensitivity [7] and/or alterations of myocardial phenotype [2]. HIT might be an efficient short-term strategy to improve cardiac autonomic function and may have an important antiarrhythmic effect [22]. Therefore, the results of the present study indicate that the decrease in sympathetic activity after HIT is smaller than the increase in parasympathetic activity.

Another finding of the current study is our demonstration of variability in the individual responses following different training protocols (MCT and HIT). Several reports have recommended that before individuals are classified as responders or non-responders, it is important to determine if variability in the individual responses within the experimental condition are greater than within-subject variation [7,59,60]. Specifically, our results demonstrated that intervention protocols which differ in intensity, time, and metabolic demand, like MCT and HIT, can induce different adaptive responses in HRV indices, blood pressure and cardiorespiratory fitness within a given individual [7]. This indicates that following the same stimulus, some subjects may achieve positive benefits (i.e., responders – ‘R’), whereas other subjects may experience a worsened or unchanged response after training (i.e., non-responders – ‘NR’). Environmental and genetic factors have been described as the main reasons for this phenomenon [7]. Thus, it is relevant to understand the unexplored environmental factors that may be related to eliciting an increased or decreased NR incidence to plan future well-designed genetic studies.

Additionally, we observed a stronger correlation between Ln rMSSD and R-R interval in the HIT group ($r_s = 0.834$; $p < 0.05$, i.e., positive training adaptation). However, for the first time in this study, we demonstrate how these variables can also change during positive adaptation to HIT. In this context, parasympathetic tone is likely maintained and/or increased. As such, the expected increases in Ln rMSSD (a measure of vagal modulation) were blunted by the high levels of vagal tone and parasympathetic saturation in the case of the HIT group. In this case, vagal saturation and decreases in cardiac parasympathetic indices of HRV after regular training can be related to positive, healthy outcomes [15,22,33,34]. The main changes observed in vagal-related indices with additional HIT training may well be due to the greater training intensity needed for HRV change in healthy participants [22].

Finally, the impact of HIT on body composition compared to MCT is controversial. Cycling protocols showed that HIT interventions are superior to MCT in inducing FM loss [19], or generate similar improvements [20]. Contrasting our results, studies using treadmill protocols have not shown any difference in body weight and composition between these isocaloric programmes [7]. Our results support that HIT interventions are superior in terms of enhancing fat oxidation than MCT [19,20]. Therefore, difference between fat reductions following HIT compared with MCT could suggest that obesity is a key contributing factor to vascular dysfunction; which has been corroborated in obese [37,50] and type 2 diabetic subjects [32]. Considering the sedentary lifestyle of the population, obesity and the risk for non-communicable diseases are increasing, the knowledge of a more effective mode of training (i.e., training modes as endurance, HIT, or other protocols that achieve a reduced amount of responders – ‘R’ prevalence after training interventions), in accordance with the profile of individuals (i.e., physically inactive, unhealthy individuals, or athletes) and achievement of improvements in their risk factors may be useful information for practitioners, public health exercise programs, and

populations with/at risk of CAD. This may positively affect disease morbidity, mortality and health care expenditures [35].

The strengths of this study included state of the art measures of HRV, physical fitness and supervised exercise training in a non-clinical setting. Additionally, adherence to the intervention was approximately 98%. All subjects completed 32 of the 36 exercise sessions, and research technicians supervised each session while HR was being monitored. A primary limitation of this study was the lack of a true non-exercising control group. Thus, we are unable to determine causality in our interpretation of the observed exercise-induced improvements in cardiovascular health parameters. However, among studies comparing HIT and MCT that included a control group, no changes in autonomic function were observed in the control group [44]. Second, BIA was used in the present study as a common tool to assess body weight and the relevant parameters of body composition. However, BIA is not the “gold standard” in body composition measurement. Future studies may consider tighter control of these factors such that the effects of these different factors may be isolated and identified in a relatively longer intervention.

Practical applications

These data underline the importance of a multidisciplinary approach aiming at promoting HIT exercise programme in physically inactive adults. For the practitioners/clinicians or trainer working with inactive populations should promote HIT exercise longer than 12 weeks in order to improve outcomes in cardiovascular health, due to HRV is a direct predictor of cardiovascular risk and all-cause mortality. Additional randomised controlled trials are required to elucidate the mechanisms responsible for these results in physically inactive adults and other populations, such as metabolic syndrome, obese, or insulin resistance adults.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

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