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Effects of high-intensity interval training and moderate-intensity continuous training on endothelial function and cardiometabolic risk markers in obese adults

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Sawyer BJ, Tucker WJ, Bhammar DM, Ryder JR, Sweazea KL, Gaesser GA. Effects of high-intensity interval training and moderate-intensity continuous training on endothelial function and cardiometabolic risk markers in obese adults. *J Appl Physiol* 121: 279–288, 2016. First published June 2, 2016; doi:10.1152/japplphysiol.00024.2016.—We hypothesized that high-intensity interval training (HIIT) would be more effective than moderate-intensity continuous training (MICT) at improving endothelial function and maximum oxygen uptake ($V_{O_2\,max}$) in obese adults. Eighteen participants [35.1 ± 8.1 (SD) yr; body mass index = 36.0 ± 5.0 kg/m^2] were randomized to 8 wk (3 sessions/wk) of either HIIT [10 × 1 min, 90-95% maximum heart rate (HR_{max}), 1-min active recovery] or MICT (30 min, 70–75% HR_{max}). Brachial artery flow-mediated dilation (FMD) increased after HIIT (5.13 ± 2.80% vs. 8.98 ± 2.86%, $P = 0.02$) but not after MICT (5.23 ± 2.82% vs. 3.05 ± 2.76%, $P = 0.16$). Resting artery diameter increased after MICT (3.68 ± 0.58 mm vs. 3.86 ± 0.58 mm, $P = 0.02$) but not after HIIT (4.04 ± 0.70 mm vs. 4.09 ± 0.70 mm; $P = 0.63$). There was a significant ($P = 0.02$) group × time interaction in low flow-mediated constriction (L-FMC) between MICT (0.63 ± 2.00% vs. −2.79 ± 3.20%; $P = 0.03$) and HIIT (−1.04 ± 4.09% vs. 1.74 ± 3.46%; $P = 0.29$). $\dot{V}_{O_2\,max}$ increased ($P < 0.01$) similarly after HIIT (2.19 ± 0.65 l/min vs. 2.64 ± 0.88 l/min) and MICT (2.24 ± 0.48 l/min vs. 2.55 ± 0.61 l/min). Biomarkers of cardiovascular risk and endothelial function were unchanged. HIIT and MICT produced different vascular adaptations in obese adults, with HIIT improving FMD and MICT increasing resting artery diameter and enhancing L-FMC. HIIT required 27.5% less total exercise time and ~25% less energy expenditure than MICT.

flow-mediated dilation; exercise; fitness; cardiovascular; obesity

NEW & NOTEWORTHY

This study is the first to show that high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) produce different vascular adaptations in adults with obesity. HIIT improved brachial artery flow-mediated dilation whereas MICT increased resting brachial artery diameter and enhanced low flow-mediated constriction. These vascular adaptations occurred without reductions in body weight, fat mass, or visceral adipose tissue. HIIT required 27.5% less total exercise time and ~25% less energy expenditure than MICT.

ENDOTHELIAL DYSFUNCTION IS considered the first step in the progression of atherosclerosis (57). Aerobic exercise training is a well-established means of improving vascular health in individuals with endothelial dysfunction (20, 50). Most studies show that high-intensity interval training (HIIT) improves endothelial function, assessed by flow-mediated dilation (FMD), to a greater extent than moderate-intensity continuous training (MICT) (32, 35, 46, 53, 61), although two studies have reported equal improvements in FMD after each mode of training (11, 34). Consistent with these findings, HIIT has been reported to increase antioxidant status (32, 53, 61) and nitric oxide (NO) availability (32, 53) to a greater extent than MICT. Antioxidant capacity has been shown to be a significant predictor of FMD (15).

An exception to these findings is a study of obese adults that found that HIIT increased FMD more than MICT despite no change in total antioxidant status (46). Although antioxidant status did not appear to contribute to the increases in FMD in obese subjects (46), a number of circulating biomarkers that affect endothelial function, such as NO, C-reactive protein (CRP), and vascular adhesion molecules, were not assessed in that study. It has also recently been reported that neither HIIT nor MICT increased FMD in adults who were overweight or obese (5). To our knowledge, only two studies (5, 46) have been published comparing the effects of HIIT and MICT on FMD in obese adults. This is an important public health issue because of the high prevalence of obesity (38) and its association with endothelial dysfunction (3). Another limitation of the studies on obese adults (5, 46), as well as all but one (30) of the other studies comparing HIIT and MICT (11, 32, 34, 35, 53, 61), is that FMD was assessed only at the beginning and end of 6–16 wk of training. Although one 2-wk training study indicated that neither HIIT nor MICT improved FMD after six training sessions (30), increases in FMD have been reported to occur within the first 2 wk of MICT training (7, 52) with subsequent declines in FMD after 4 wk (7) and 8 wk (7, 52) of training. A lack of increase in FMD with training may reflect structural changes in the vasculature or changes in vascular tone (21). Thus it is possible that previous studies of HIIT vs. MICT missed functional adaptations that occurred during the initial weeks of training. Evidence suggests that structural and functional adaptations to both the conduit and resistance vessels play a role in the improvements in vascular function seen with exercise training (22, 31).

In addition to FMD, low flow-mediated constriction (L-FMC), which reflects the ability of arteries to constrict when blood flow is reduced, is an emerging measurement of vascular function (23, 24, 41). It has been suggested that L-FMC may complement the measurement of FMD and that a composite vascular end point that includes both FMD and L-FMC may provide additional insight into vascular health (24). Whether HIIT and MICT differentially affect L-FMC is unknown.

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Therefore the primary purpose of this study was to compare the effects of HIIT and MICT on endothelial function in sedentary obese adults. Secondarily, we compared the effects of both types of exercise training on L-FMC, maximum oxygen uptake ($\dot{V}O_{2\,max}$), and a number of circulating biomarkers of endothelial function and cardiovascular disease risk. The potential importance of $\dot{V}O_{2\,max}$ is evidenced by the significant correlation between FMD and $\dot{V}O_{2\,max}$ (8) and metaanalyses demonstrating greater increases in $\dot{V}O_{2\,max}$ after HIIT compared with MICT (26, 60). We hypothesized that HIIT would improve FMD more than MICT and that this would be associated with greater improvements in $\dot{V}O_{2\,max}$, total antioxidant capacity, and circulating biomarkers of endothelial function.

MATERIALS AND METHODS

Subjects

The study was approved by the Arizona State University Institutional Review Board and conformed to the ethical standards of the Declaration of Helsinki. All subjects provided written informed consent before participation. On the basis of previously published data (61, 62) we calculated that completing eight subjects in each group would yield 90% power to detect a 2% difference in FMD between groups (at a two-tailed alpha level of 0.05). Planning for subject attrition, we enrolled 11 subjects in each group. Two participants in each group dropped out, resulting in a final sample size of 18. All subjects met the following inclusion criteria: free from known chronic disease, obese [body mass index (BMI) $\geq$ 30 kg/m^2], between 18 and 45 yr of age (men) and 18 and 55 yr (women) (1), completion of the Physical Activity Readiness Questionnaire (PAR-Q) without "yes" answers, and a suitable acoustic window to perform the FMD procedure (Table 1).

Testing Overview

Baseline testing was conducted after abstaining from vigorous exercise and vitamin supplements for 48 h as well as alcohol and caffeine for 24 h. The FMD at 4 wk was ~48–72 h after their last exercise session. Eight-week testing was conducted ~72 h after the last exercise session. All tests within subjects were completed at the same time of day.

Day 1. For both the preintervention and postintervention testing, subjects arrived at the laboratory in the afternoon ~36 h before testing. At this time, subjects were given the prepared meals to be eaten over the 24-h period preceding the testing. Subjects were asked to record the exact time and quantity of each food item consumed so that precise timing and content matching could be performed for the posttesting.

Day 2. After the 24-h controlled diet period, subjects returned to the laboratory the next morning after at least a 10-h fast. During this visit we performed the following tests in the order listed: anthropometric measurements, FMD, dual-energy X-ray absorptiometry (DXA), fasting blood draw, and the maximal exercise test.

Anthropometrics

Height, weight, and waist circumference were all assessed at baseline and 8 wk in the morning while subjects were fasting. All anthropometric measurements were taken by the same researcher on all subjects.

Brachial Artery Ultrasound

FMD was measured with a Terason t3000 high-resolution ultrasound machine (Terason Ultrasound, Burlington, MA) with a 10-MHz multifrequency linear array probe. We followed the criteria set forth by the Brachial Artery Reactivity Task Force and the latest guidelines (10, 49). Participants were asked to lie quietly in a dimly lit room for 20 min on a vascular imaging table before a sonographer obtained preocclusion baseline diameter images for 60 s from the participant's left arm. After the preocclusion baseline images were completed a blood pressure cuff was inflated on the participant's forearm to a pressure of 250 mmHg for 5 min. During the last 60 s of occlusion, images were recorded to measure minimum occlusion diameter. After 5 min of occlusion the cuff was rapidly deflated and images were recorded continuously for the next 5 min. To reduce error between the three measurement periods (0, 4, and 8 wk), the distance of the probe from the medial epicondyle of the humerus was measured, and all ultrasound settings were noted in each subject's file. Images were analyzed by a single blinded investigator using previously validated, brachial artery edge-detection software (62). Female subjects completed the ultrasound measurements during *days 1–7* of the follicular phase of their menstrual cycle for each measurement period. Intraclass correlations in our laboratory for preocclusion baseline diameter, peak postocclusion diameter, and FMD are 0.998, 0.998, and 0.997, respectively. The following equations were used to calculate the brachial artery ultrasound outcomes (24):

$$\text{FMD} = \frac{\text{Peak postocclusion diameter} - \text{Preocclusion baseline diameter}}{\text{Preocclusion baseline diameter}} \times 100\% \quad (1)$$

$$\text{L-FMC} = \frac{\text{Minimum occlusion diameter} - \text{Preocclusion baseline diameter}}{\text{Preocclusion baseline diameter}} \times 100\% \quad (2)$$

Table 1. *Subject characteristics and pretraining and posttraining anthropometrics and body composition changes for MICT and HIIT groups*

	MICT (n = 9)			HIIT (n = 9)			
	Pre	Post	Time Effect Within-Group P Value	Pre	Post	Time Effect Within-Group P Value	Group × Time Interaction P Value
Weight, kg	99.7 ± 10.9	99.7 ± 11.4	0.89	112.7 ± 26.6	112.6 ± 26.0	0.91	0.88
BMI, kg/m^2	34.5 ± 3.2	34.5 ± 3.2	0.88	37.4 ± 6.2	37.4 ± 6.1	0.99	0.85
Waist circumference, cm	113.9 ± 8.2	112.5 ± 7.8	0.04	117.4 ± 18.8	114.7 ± 19.4	<0.01	0.12
Body fat%	46.7 ± 7.3	46.4 ± 7.3	0.07	45.6 ± 5.3	44.8 ± 5.8	0.04	0.22
Fat mass, kg	46.4 ± 8.2	46.0 ± 8.1	0.17	51.5 ± 14.0	50.6 ± 14.1	0.10	0.38
Fat-free mass, kg	53.3 ± 10.6	53.6 ± 10.9	0.35	61.2 ± 14.9	62.0 ± 14.6	0.18	0.47
Android fat%	55.5 ± 8.4	55.4 ± 8.5	0.61	54.8 ± 5.1	54.0 ± 5.7	0.25	0.39
Gynoid fat%	46.5 ± 7.1	45.8 ± 7.2	0.02	44.6 ± 7.0	43.1 ± 6.9	<0.01	0.03
Visceral adipose tissue, cm^3	1,740 ± 894	1,760 ± 890	0.64	2,434 ± 1,145	2,428 ± 1,323	0.95	0.81

Values are means ± SD. MICT subjects, aged 34.8 ± 7.7 yr, four men, five women; HIIT subjects, aged 35.6 ± 8.9 yr, five men, four women.

$$\text{Composite end point of vascular reactivity} = \frac{\text{Peak postocclusion diameter} - \text{Minimum occlusion diameter}}{\text{Preocclusion baseline diameter}} \times 100\% \quad (3)$$

Dual-Energy X-ray Absorptiometry

DXA was used to determine percent body fat, regional fat distributions, and visceral fat (Lunar iDXA GE Healthcare, Little Chalfont, UK). Women underwent a urine pregnancy test in our laboratory prior to each DXA measurement. A negative test was required before DXA could be performed. All DXA scans were performed by a certified radiology technician.

Blood Analyses

A fasting venous blood sample was collected before and 72 h after the last training session. Total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides, and glucose were measured in plasma with an automated chemistry analyzer (Cobas C111; Roche Diagnostics, Indianapolis, IN) using colorimetric enzymatic reagents. Measured intraassay coefficient of variation (CV) values were 1.4% for total cholesterol, 0.9% for HDL-c, 1.1% for LDL-c, 1.6% for triglycerides, and 0.5% for glucose. Insulin was measured in plasma using the ultrasensitive human radioimmunoassay kit (Millipore, Billerica, MA). Measured intraassay CV for insulin was 3.7%. Insulin sensitivity was assessed by calculating the homeostatic model assessment (HOMA-IR) score [HOMA-IR = glucose (mmol/l) × insulin (μU/ml)/22.5]. Plasma high-sensitivity C-reactive protein (hsCRP) was measured with a turbidimetric enzymatic assay using an automated chemistry analyzer (Cobas C111; Roche Diagnostics, Indianapolis, IN). Measured intraassay CV for hsCRP was 0.9%.

Total antioxidant capacity (TAC; Cayman Chemical, Ann Arbor, MI), thiobarbituric acid-reactive substances (TBARS; ZeptoMetrix, Buffalo, NY), and NO were measured using colorimetric assay kits (Cayman Chemical). The TAC assay relies on the ability of antioxidants in the sample to inhibit the oxidation of 2,2′-azino-di-[3-ethylbenzthiazoline sulphonate] (ABTS) to the radical cation ABTS+ by metmyoglobin. The TBARS assay was used to detect plasma malondialdehyde as an index of lipid peroxidation in the plasma. For NO, plasma total nitrates/nitrites were determined in a two-step process, first converting nitrates to nitrites and then adding Greiss reagent to convert nitrites into a chromophore that can be measured photometrically to determine nitrite concentration. Measured intraassay CV was 1.0% for TAC, 1.3% for TBARS, and 1.3% for NO. The concentrations of soluble intracellular adhesion molecule 1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1), and soluble E-selectin were measured via ELISA (R&D Systems, Minneapolis, MN) with intraassay CVs of 2.9, 2.0, and 4.7%, respectively. All samples were run in duplicates and the mean value was calculated.

Maximal Exercise Test

All subjects performed a ramp-style maximal exercise test on an electronically braked cycle ergometer (VIAsprint 150P; Ergoline, Bitz, Germany) at baseline and after 4 and 8 wk of training. Pulmonary ventilation and gas exchange were measured continuously with a Parvo Medics TrueOne 2400 (Parvo Medics, Sandy, UT). Standard three-point calibration was performed before each test. Heart rate was measured with a Polar heart rate monitor (Polar, Lake Success, NY). After 2 min of rest, subjects pedaled on cycle ergometer at a cadence of their choice, between 50 and 90 rpm, at 50 W (men) or 25 W (women) for 5 min for the warm-up phase. The chosen cadence was maintained for the remainder of the ramp test. After the warm-up, power was increased in ramp fashion by 30 W/min (men) or 15 W/min (women) until exhaustion. Verbal encouragement was given to all subjects throughout the entire test. After a cooldown period of 5–10 min, in which subjects pedaled at the warm-up work rate, each subject performed a verification phase test (VP) on the cycle ergometer at a constant power of 100% of the peak power attained during the ramp test. Subjects were asked to keep their cadence above 50 rpm and pedal for as long as possible during the VP. For both the ramp and VP, the mean of the two highest consecutive 15-s $\dot{V}O_2$ averages during the test was taken as $\dot{V}O_{2\,max}$. If a subject achieved a higher heart rate or $\dot{V}O_2$ during the verification phase, the verification results were used as the "max" value for that test. See Sawyer et al. (45) for details on using VP in obese, sedentary adults.

Exercise Training

All subjects completed 3 supervised exercise sessions per week for 8 wk for a total of 24 exercise sessions. Subjects were randomized to either HIIT or MICT upon enrollment in the study. All exercise training was conducted on cycle ergometers, and the maximum heart rate (HR_{max}) achieved during either phase of the maximal exercise test (ramp or verification, at baseline and at 4 wk) was used for exercise intensity prescription. Heart rate was continuously monitored by Polar heart rate monitors and recorded by research technicians. Each HIIT training session consisted of a 5-min warm-up at 50–60% of HR_{max} followed by ten 1-min intervals designed to elicit 90–95% of HR_{max} separated by 1 min of cycling at a low intensity (~25–50 W), with a 5-min cooldown at 50–60% of HR_{max}. Each MICT training session consisted of a 5-min warm-up at 50–60% of HR_{max} followed by 30 min of exercise at 70–75% of HR_{max}, with a 5-min cooldown at 50–60% of HR_{max}. Each session lasted 40 min for the MICT group (960 total min for 24 training sessions) and 29 min for the HIIT group (696 total min for 24 training sessions). On the basis of pretraining $\dot{V}O_{2\,max}$ data, estimated total energy expenditure for each training session was ~180 kcal for HIIT (56) and 240 kcal for MICT (17).

Data Analysis

Descriptive statistics (means ± SD) for the study participants were calculated across gender and intervention groups (i.e., HIIT and MICT) (Table 1). One-way analysis of variance (ANOVA) was used to test baseline mean differences between groups. A mixed within-between ANOVA was used to test mean differences for each outcome measure across groups, time, and group × time interaction factors. Bonferroni post hoc tests were also used to detect mean differences between the three time points (baseline, 4 wk, 8 wk) for the brachial artery data.

Inadequate scaling for FMD was present as evidenced by the upper confidence limit of the regression slope of the relationship between the logarithmically transformed preocclusion baseline diameter and peak postocclusion diameter being <1.00 [β ± SE = 0.89 ± 0.04; 95% confidence interval (CI) = 0.81–0.97] (4). Therefore we utilized linear mixed models to detect the group × time interaction in FMD. The analysis was conducted using the difference between logarithmically transformed peak postocclusion diameter and preocclusion baseline diameter as the dependent variable and logarithmically transformed preocclusion baseline diameter as the covariate. We subsequently back-transformed the allometrically scaled arterial diameter change and presented the values as percentage diameter change. In contrast to FMD, L-FMC showed adequate scaling as evidenced by the upper and lower confidence limits of the regression slope of the relationship between the logarithmically transformed preocclusion baseline diameter and minimum occlusion diameter including 1.00 (β ± SE = 1.02 ± 0.03; 95% CI = 0.96–1.07) (4).

All *P* values were two-tailed, and values of <0.05 were considered to indicate statistical significance. All statistical procedures were performed by using SPSS 20 (IBM, Armonk, NY).

RESULTS

Brachial Artery Ultrasound

The FMD results are presented in Fig. 1 and Table 2. There were no significant differences between groups for any variable at baseline. There was a significant group × time interaction for both FMD ($P = 0.01$) and allometrically scaled FMD ($P < 0.01$). The HIIT group significantly increased FMD ($P = 0.04$, time effect; $P = 0.05$, baseline vs. 4 wk) and allometrically scaled FMD ($P = 0.02$, time effect; $P = 0.02$, baseline vs. 8 wk). By contrast, FMD and allometrically scaled FMD were unchanged after MICT.

MICT had a significant increase in preocclusion baseline diameter ($P = 0.02$, time effect; $P < 0.01$, baseline vs. 8 wk). MICT exhibited no change in postocclusion peak diameter ($P = 0.48$). Conversely, HIIT had a significant increase in postocclusion peak diameter ($P < 0.01$, time effect; $P = 0.03$, baseline to 8 wk). Preocclusion baseline diameter was unchanged after HIIT.

Post-cuff deflation shear rate area under the curve (SR_{AUC}) was reduced after HIIT ($P = 0.02$, time effect; $P = 0.08$, baseline to 4 wk) but was unchanged after MICT. The reduced SR_{AUC} in HIIT was associated with a lower average velocity of blood flow ($P = 0.03$, time effect; $P = 0.06$, baseline to 4 wk) and increased average arterial diameter ($P < 0.01$, time effect; $P = 0.02$, baseline vs. 8 wk) during the FMD procedure after HIIT. There was a significant interaction for L-FMC ($P = 0.02$), with MICT showing a significant decrease in L-FMC ($P = 0.03$, time effect; $P = 0.02$, baseline vs. 8 wk) and no change after HIIT. For the composite end point of vascular reactivity, there were no significant ($P = 0.97$) group × time interactions or time effects.

$\dot{V}O_{2\,max}$

One subject in the HIIT group chose not to perform the 8-wk maximal exercise test. Therefore results for HIIT included only eight subjects. There were significant increases (baseline vs. 8 wk) in $\dot{V}O_{2\,max}$ after training for both HIIT (2.19 ± 0.65 l/min vs. 2.64 ± 0.88 l/min, $P = 0.01$) and MICT (2.24 ± 0.48 l/min vs. 2.55 ± 0.61 l/min, $P < 0.01$), but no group × time interaction ($P = 0.53$; see Fig. 2). Similar results were observed when $\dot{V}O_{2\,max}$ was expressed relative to body weight, with increases (baseline vs. 8 wk) for both HIIT (20.3 ± 4.9 ml·kg^{-1}·min^{-1} vs. 24.4 ± 5.9 ml·kg^{-1}·min^{-1}, $P < 0.01$) and MICT (22.4 ± 3.6 ml·kg^{-1}·min^{-1} vs. 25.5 ± 4.5 ml·kg^{-1}·min^{-1}, $P < 0.01$), but no group × time interaction ($P = 0.56$).

Anthropometrics and Body Composition

There were no significant differences between groups at baseline for any of the anthropometric or body composition

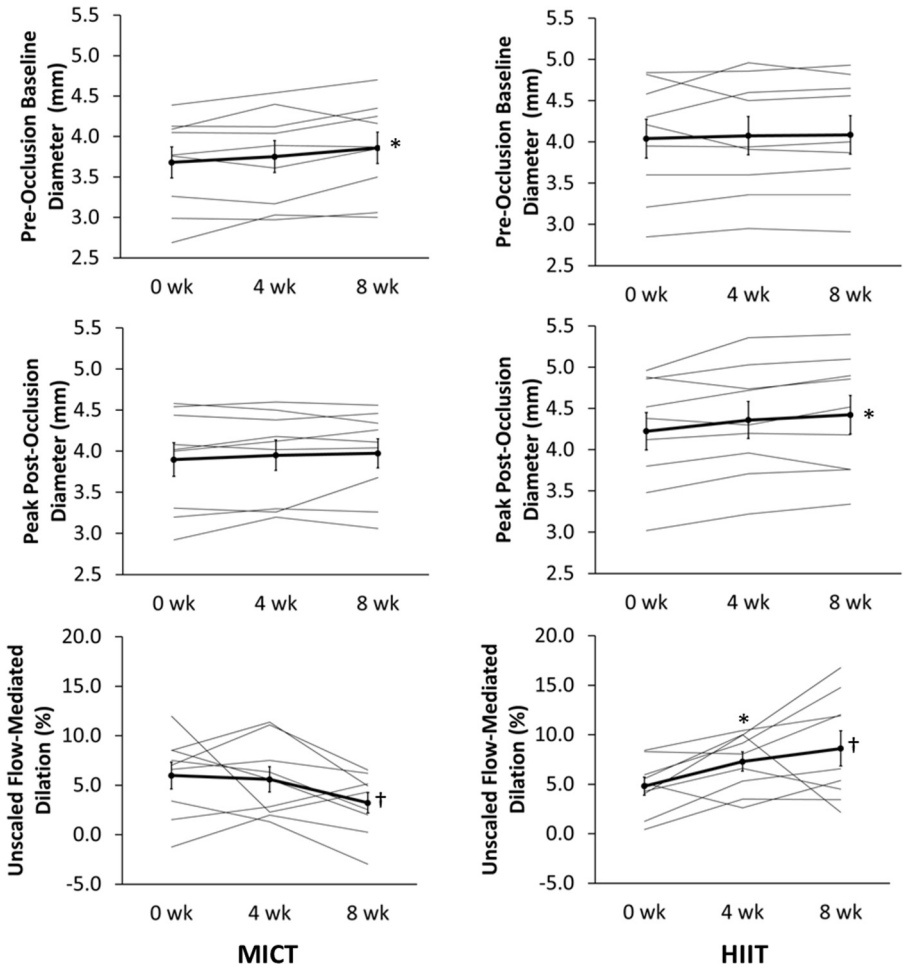

Fig. 1. Brachial artery preocclusion baseline diameter, peak postocclusion diameter, and unscaled flow-mediated dilation percentage in both groups over the course of the study. Bold lines represent means ± SD, and light lines are individual subjects. *Significant difference from baseline within the group. †Significant group × time interaction.

Table 2. *Brachial artery ultrasound measurements at baseline and after 4 wk and 8 wk of exercise training*

	MICT (n = 9)				HIIT (n = 9)				
	Baseline	4 wk	8 wk	Time Effect Within-Group P Value	Baseline	4 wk	8 wk	Time Effect Within-Group P Value	Group × Time Interaction P Value
Preocclusion baseline diameter, mm	3.68 ± 0.58	3.75 ± 0.59	3.86 ± 0.58*	0.02	4.04 ± 0.70	4.08 ± 0.70	4.09 ± 0.70	0.63	0.26
Postocclusion peak diameter, mm	3.90 ± 0.61	3.95 ± 0.55	3.97 ± 0.53	0.48	4.22 ± 0.68	4.36 ± 0.67	4.42 ± 0.70*	<0.01	0.25
Minimum occlusion diameter, mm	3.70 ± 0.56	3.72 ± 0.57	3.75 ± 0.57	0.52	4.00 ± 0.74	4.09 ± 0.74	4.16 ± 0.75	0.06	0.46
Flow-mediated dilation, %	5.99 ± 4.05	5.59 ± 3.84	3.21 ± 3.10	0.10	4.82 ± 2.74	7.29 ± 2.94†	8.62 ± 5.33	0.04	0.01
Flow-mediated dilation (allometrically scaled), %	5.23 ± 2.82	5.02 ± 2.80	3.05 ± 2.76	0.16	5.13 ± 2.80	7.68 ± 2.84	8.98 ± 2.86*	0.02	<0.01
Shear rate area under the curve, $s^{-1} \times 10^3$	16.7 ± 5.8	16.0 ± 8.6	17.2 ± 7.4	0.80	16.7 ± 9.1	12.1 ± 6.4†	11.9 ± 5.3	0.02	0.12
Average velocity, cm/s	25.3 ± 6.8	24.4 ± 11.4	26.7 ± 9.4	0.67	26.3 ± 9.4	20.0 ± 6.3†	20.1 ± 6.3	0.03	0.10
Average diameter, mm	3.81 ± 0.63	3.83 ± 0.59	3.87 ± 0.58	0.55	4.11 ± 0.70	4.24 ± 0.71	4.31 ± 0.71*	<0.01	0.21
Time to peak, s	64.8 ± 13.2	68.4 ± 16.2	69.0 ± 20.4	0.90	88.6 ± 56.7	68.7 ± 18.5	69.0 ± 19.5	0.35	0.37
Low flow-mediated constriction, %	0.63 ± 2.00	−0.74 ± 2.11	−2.79 ± 3.20*	0.03	−1.04 ± 4.09	0.29 ± 3.96	1.74 ± 3.46	0.29	0.02
Composite end point of vessel reactivity, %	5.37 ± 2.66	6.32 ± 3.69	6.00 ± 4.15	0.44	5.85 ± 4.40	7.01 ± 4.20	6.88 ± 3.99	0.53	0.97

Values are means ± SD. There were no significant differences between groups for any variable at baseline. *Post hoc results, significantly different from baseline, $P < 0.05$. †Post hoc results, significantly different from baseline, $0.05 \leq P < 0.10$.

variables (Table 1). Both HIIT and MICT decreased waist circumference and gynoid fat percent, with a significant group × time interaction for gynoid fat percent. Body fat percent decreased in HIIT ($P = 0.04$, time effect) but not in MICT ($P = 0.07$), but neither group had a significant decrease in absolute fat mass. There were also no significant changes in body weight, fat-free mass, BMI, or visceral adipose tissue.

Blood Markers for Cardiometabolic Risk

There were no changes in any blood markers of endothelial function or cardiovascular risk (see Table 3).

DISCUSSION

The primary finding of this study was that HIIT and MICT produced different vascular adaptations in previously sedentary obese adults, with HIIT improving FMD and MICT increasing resting brachial artery diameter and enhancing L-FMC. Our FMD results support our hypothesis and are consistent with most of the studies that have compared HIIT and MICT with regard to endothelial function (32, 35, 43, 46, 53, 61). Because of the effects of preocclusion baseline artery diameter on FMD, and on the potential influence of changes in preocclusion baseline diameter after training on FMD, we also performed analyses on the allometrically scaled FMD data as suggested by Atkinson et al. (4). The results remained unchanged (Table 2).

An unexpected finding in the present study was the increase in resting brachial artery diameter after 8 wk of MICT, with no change in FMD. In previous comparisons of HIIT vs. MICT, arterial diameters either were not reported (30, 34, 35, 53, 61) or did not change in either group after training (11, 32, 46). Although results from some previous studies suggest that an increase in arterial diameter may occur only in the musculature that is being exercised (13, 42), a pooled analysis of 182 subjects participating in 13 endurance training studies that consisted predominantly (90%) of cycle and treadmill exercise revealed that ~24% of subjects exhibited an increase in brachial artery diameter after endurance training (21). The 4.9% increase in diameter reported in that pooled analysis is the same as that observed in our MICT subjects (~4.9%; Table 1). In the pooled analysis study, the FMD of the group that increased brachial artery diameter was significantly reduced after training, from 6.1 to 4.5% (21). Although FMD was not statistically significantly reduced after MICT, the baseline (5.99%) and 8-wk (3.21%) FMD values are consistent with the findings of the pooled data from 13 previous studies (21). The high reliability of our diameter measurements, coupled with the observation that the brachial arterial diameter after 4 wk of MICT (Table 2) was already indicating an increase (although only statistically significant after 8 wk), suggest that the ~4.9% increase in brachial artery diameter after 8 wk of MICT was not an artifact.

Green et al. (21) proposed that a lack of change (or even a decrease) in FMD after training should not by itself be considered a "nonresponse." Those who fail to increase FMD may undergo structural remodeling in arteries that provides cardio-

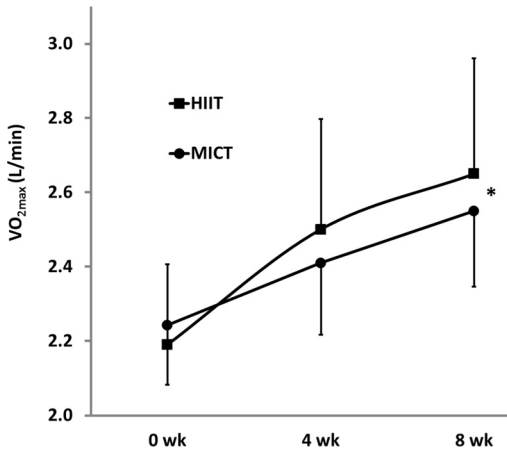

Fig. 2. Mean $\dot{V}O_{2\,max}$ (l/min) in both groups over the course of the study. Error bars represent SE. *Significant increase from baseline in both groups.

Table 3. *Pretraining and posttraining blood biomarkers for MICT and HIIT groups*

	MICT (n = 9)			HIIT (n = 9)			
	Pre	Post	Time Effect Within-Group P Value	Pre	Post	Time Effect Within-Group P Value	Group × Time Interaction P Value
Total cholesterol, mg/dl	160.0 ± 41.1	164.8 ± 46.7	0.53	181 ± 36.4	186 ± 36.9	0.35	0.98
Low-density lipoprotein, mg/dl	96.8 ± 36.9	99.4 ± 35.8	0.70	122.7 ± 28.6	127.6 ± 35.3	0.22	0.75
High-density lipoprotein, mg/dl	45.0 ± 12.2	44.3 ± 12.5	0.67	38.3 ± 6.4	39.3 ± 8.5	0.50	0.44
Triglycerides, mg/dl	138.3 ± 88.3	161.9 ± 98.9	0.11	147.7 ± 63.7	144.5 ± 44.6	0.84	0.21
Glucose, mg/dl	92.7 ± 4.2	95.1 ± 10.8	0.48	91.7 ± 3.8	88.7 ± 6.7	0.07	0.14
Insulin, mU/l	19.6 ± 7.0	17.3 ± 4.5	0.10	21.3 ± 7.2	19.1 ± 6.2	0.18	0.96
HOMA-IR	4.5 ± 1.7	4.0 ± 1.2	0.30	4.8 ± 1.7	4.2 ± 1.5	0.10	0.78
High-sensitivity C-reactive protein, mg/l	2.6 ± 1.9	3.0 ± 2.4	0.46	3.3 ± 2.6	3.8 ± 3.6	0.56	0.98
E-selectin, ng/ml	39.8 ± 18.6	41.1 ± 17.4	0.54	36.9 ± 10.5	36.0 ± 12.4	0.66	0.45
Intracellular adhesion molecule 1, ng/ml	226.4 ± 54.2	233.9 ± 55.1	0.15	236.0 ± 46.5	260.2 ± 69.9	0.14	0.30
Vascular cell adhesion molecule 1, ng/ml	798.0 ± 134.1	834.9 ± 96.3	0.33	685.2 ± 140.4	700.2 ± 116.9	0.52	0.61
Nitric oxide, μM	11.7 ± 6.3	10.9 ± 3.3	0.72	12.3 ± 5.5	10.2 ± 3.1	0.12	0.58
TBARS, μM	3.9 ± 2.6	3.2 ± 1.6	0.34	3.6 ± 2.2	3.4 ± 1.7	0.60	0.49
Total antioxidant capacity, mM	2.5 ± 1.0	2.3 ± 0.4	0.73	2.3 ± 0.6	2.6 ± 0.7	0.11	0.30

Values are means ± SD. There were no significant differences between groups for any variable at baseline.

protection (21, 47). The mechanism behind the increase in brachial artery diameter in our MICT group is not readily apparent. The increased size could reflect structural remodeling, but could also be due to decreases in vascular tone. Since arterial diameter is influenced by competing vasodilator and vasoconstrictor factors, changes in artery diameter may not be a legitimate index of vascular structure and remodeling after exercise training (50). For example, Tinken et al. (52) demonstrated a progressive increase in brachial artery vasodilator capacity [as a surrogate measure for arterial remodeling (20, 52)] throughout 8 wk of aerobic training despite no increase in resting brachial artery diameter.

It is also possible that we missed early functional adaptations in the MICT group. Although we did not measure shear rate during exercise, it has been reported that the mean brachial artery shear rate during leg cycling is similar at intensities of 70 and 85% of HR_{max} (6). Our MICT group trained at 70–75% HR_{max}, and our HIIT protocol elicits an average HR of ~85% HR_{max} (56). If the shear stress was elevated to a similar degree across the two training types but for a longer time during training sessions in MICT (30 min) vs. HIIT (10 × 1-min intervals), the greater sustained increased shear stress in MICT may have induced transitory functional adaptations prior to our 4-wk FMD assessment. In two training studies that used protocols similar to our MICT group in frequency, intensity, and duration of exercise sessions (7, 52), FMD increased significantly after 2 wk of training but was no longer significantly different from baseline after 4 wk (7) and 8 wk (7, 52) of training. The increases in FMD in these two studies, however, may have occurred by different mechanisms. In the study by Birk et al. (7) the FMD increase after 2 wk of training was due to an increase in postocclusion peak diameter with no change in resting diameter [Table 1 and Fig. 2 given by Birk et al. (7)]. By contrast, data from Table 2 given by Tinken et al. (52) show that the increase in FMD after 2 and 4 wk of training can be accounted for mostly by a 0.1–0.2 mm lower resting arterial diameter at these time points compared with pretraining. Furthermore, a training study in postmenopausal women consisting of six sessions of HIIT or MICT similar to our protocols over a 2-wk period indicated that neither training stimulus improved FMD (30). More time-course studies may be necessary to resolve these dissimilar findings.

Another novel finding is the training-induced reduction in SR_{AUC} during the FMD procedure in the HIIT group. The reduction in SR_{AUC} can be explained by the lower average velocity of blood flow and increase in average arterial diameter during the FMD procedure in the HIIT group after training. For within-subject comparisons, the magnitude of the FMD response has been shown to be proportional to SR_{AUC} (40). Our results suggest that HIIT may alter this relationship, as FMD increased significantly after HIIT despite a decrease in SR_{AUC}.

Our study is the first to compare the effects of HIIT and MICT on L-FMC. It has been proposed that L-FMC allows for an assessment of arterial vasoconstrictor function (19, 23, 24). Diminished L-FMC in the radial artery has been reported in patients with hypertension and coronary artery disease (19). L-FMC has not been consistently demonstrated in the brachial artery (23, 59). In fact, ~40% of adults with varied cardiovascular disease risk profiles displayed either no change or an increase in brachial arterial diameter after several minutes of low flow during the FMD procedure (23). In our study, L-FMC was affected differently by training protocol, as evidenced by the significant group × time interaction and a significantly greater L-FMC response after MICT. The significance of these results is uncertain. We are aware of only one other study that has reported changes in L-FMC after training (41). In that study, brachial artery FMD was not changed after interval exercise training, but L-FMC was enhanced (i.e., greater constriction) under low-flow conditions. The investigators interpreted their results as evidence of an augmented vasoconstrictor response to decreased shear stress. The clinical relevance is unclear because L-FMC is artery specific (59) and the occurrence of L-FMC in radial and brachial arteries appears to differ on the basis of health status of the subjects [see Weissgerber et al. (57) for discussion].

It has also recently been proposed that a composite end point that includes both FMD and L-FMC may provide additional insight into vascular health (24). For our results, the composite

end point had the effect of offsetting the improvement in FMD shown by the HIIT group and the increase (i.e., greater constriction) in L-FMC with a trend for a decrease in FMD by the MICT group. We calculated the composite end point as suggested by Humphreys et al. (24) (*Eq. 3*). Others have proposed slightly different calculations (12, 19, 41), but they all require measurement of preocclusion baseline diameter, minimum occlusion diameter during the last minute of cuff occlusion, and peak postocclusion diameter after cuff release. Only one other study has reported changes in L-FMC and composite end point after training (41). Although brachial artery FMD was not changed after interval exercise training in that study (41), L-FMC was enhanced, and the composite end point, calculated as $(\text{diameter}_{max} - \text{diameter}_{min})/\text{diameter}_{min} \times 100$, increased. The investigators interpreted their results as evidence of an augmented vasoconstrictor response to decreased shear stress. The importance of this local adaptation in a relatively noncritical vascular bed is unclear since brachial artery vasomotor function may not be indicative of overall systemic vasomotor function (51). Thus we hesitate to ascribe clinical significance to our novel findings for L-FMC and composite end point.

The results for $\dot{V}O_{2\,max}$ did not support our hypothesis, as both HIIT and MICT groups had similar increases in $\dot{V}O_{2\,max}$ after 8 wk of training. Although most previous studies (2, 5, 30, 32, 34, 37, 46, 53, 61), including two metaanalyses (25, 60) and one review (29), indicate that HIIT is superior to MICT for improving $\dot{V}O_{2\,max}$, there are several exceptions (9, 11, 39, 58). Our results could be explained in part by the fact that the training was not isocaloric and that the MICT group trained at the very high end of the intensity range that is considered moderate (17). Not counting warm-up (5 min) and cooldown (5 min), which were identical for both groups, the MICT group trained for 30 min per session compared with the 19 min of interval exercise in the HIIT group. Our HIIT protocol (including active recovery intervals) elicits ~67% of $\dot{V}O_{2\,max}$ (56). This is higher than the ~60% $\dot{V}O_{2\,max}$ associated with 70–75% of HR_{max} (17) for our MICT group, but not enough to offset the shorter duration of the HIIT exercise session. Thus the ~30–35% greater energy expenditure per exercise session at the high end of the moderate-intensity domain could have contributed to the comparable increase in $\dot{V}O_{2\,max}$ for MICT compared with HIIT.

The improvement in $\dot{V}O_{2\,max}$ in both groups despite only the HIIT group improving FMD suggests that the association between $\dot{V}O_{2\,max}$ and FMD reported in cross-sectional studies (36) is not causal. Dissociation between changes in $\dot{V}O_{2\,max}$ and FMD has also been reported in previous studies of HIIT vs. MICT (5, 30, 35, 46). Collectively, the findings are consistent with the results of the 13 pooled studies of 182 subjects, which showed that changes in FMD after training were not correlated with changes in $\dot{V}O_{2\,peak}$ ($r = 0.066$) (21).

Our results are also in line with the bulk of previous findings indicating that exercise training-induced improvements in FMD are not contingent upon improvements in many traditional and nontraditional cardiovascular risk markers (21). Neither group had any significant changes in blood lipids, glucose, insulin, hsCRP, vascular adhesion molecules, NO, TBARS, or antioxidant capacity. Most of the studies comparing HIIT and MICT have shown no changes in total cholesterol (9, 58), HDL-c (9, 34, 58), LDL-c (9, 32, 58), triglycerides (9, 29, 32, 34, 53, 58), and hsCRP (34). We expected that the HIIT group would improve antioxidant capacity to a greater extent than the MICT group. HIIT has been reported to increase total antioxidant status whereas MICT has not (32, 61). Wisløff et al. (61) reported that HIIT improved FMD and total antioxidant capacity in the blood more than MICT and that the change in FMD was significantly correlated with the change in total antioxidant status. Our results indicate that the improvement in FMD in our HIIT group occurred despite no increase in total antioxidant capacity or a decrease in oxidative stress (TBARS). Our results also show that the increase in FMD of the HIIT group occurred in the absence of an increase in plasma NO. It has been previously reported that the greater increase in FMD after HIIT was associated with significant increases in NO (32). Our results suggest that plasma NO may not be a meaningful surrogate of brachial artery endothelial function or that improvements in FMD in our HIIT group may have occurred in part via NO-independent mechanisms. The results of our HIIT group suggest that the increased FMD after training is not contingent upon improvements in antioxidant capacity or reductions in oxidative stress, and are consistent with the only other comparable study of HIIT and MICT in obese adults, which reported an increase in FMD after HIIT but no change in total antioxidant capacity (46).

It is generally acknowledged that obesity is associated with impaired endothelial function (54). Furthermore, it has been demonstrated that weight loss is associated with improved FMD (28), although this is not a universal finding (14). A recent metaanalysis that included 4 randomized controlled trials involving 265 subjects revealed that a mean weight loss of 8.6 kg was associated with an improvement in FMD of 3.29% (28). The subjects in our HIIT group improved FMD by 3.8% with no loss of body weight or body fat (Table 1). Our results are similar to those of a number of exercise-training studies showing significant improvements in FMD with no change in body weight (16, 21). Thus weight loss per se may not be necessary to improve vascular function.

Strengths and Limitations

A strength of this study is that adherence to the intervention was 100%. All subjects completed all 24 exercise sessions, and each session was supervised by research technicians while heart rate was being monitored. We also provide data on both scaled and unscaled FMD and on L-FMC and a composite end point reflecting both FMD and L-FMC. Our study also used a verification phase after the maximal incremental exercise tests to enhance determination of $\dot{V}O_{2\,max}$ (45). We also included several plasma biomarkers of endothelial function and cardiovascular disease risk that had not been reported in most previous studies comparing HIIT and MICT. By performing all posttraining assessments ~72 h after the last training session, it is unlikely that residual effects of an acute bout of exercise confounded our experimental design of examining the influence of chronic exercise on our primary outcome measures.

A limitation of this study is the lack of dietary control during the course of the intervention. To minimize the influence of diet, we continually reminded subjects of their commitment to maintain their current dietary habits. The lack of weight change suggests that subjects did not start a hypocaloric diet over the course of the study, which could have affected our primary outcome (FMD). We did not have a sedentary control group.

This is fairly common in comparative studies of HIIT vs. MICT (5, 11, 30, 33, 46). Furthermore, in studies comparing HIIT and MICT that have included a control group, no changes in FMD were observed in the control group (32, 35, 53, 61). The absence of vascular measurements within the first 2–3 wk of training may have precluded us from determining whether improvements in FMD preceded increases in resting arterial diameter during MICT.

Conclusions

In conclusion, we report that in sedentary, obese adults, HIIT and MICT produced different brachial artery vascular adaptations and that these adaptations occurred without reductions in body weight, fat mass, or visceral adipose tissue. HIIT improved FMD whereas MICT increased resting brachial artery diameter and enhanced L-FMC. The increase in FMD of 3.8% after 8 wk of HIIT is clinically relevant, as a 1.0% higher FMD has been shown to be associated with an 8–13% lower risk of cardiovascular disease (27, 44). The increase in brachial artery diameter and greater L-FMC after MICT are novel findings that require additional research to establish their significance. Both HIIT and MICT improved $\dot{V}O_{2\,max}$ to the same extent. A major deterrent to participating in regular exercise is the time commitment required (18, 48, 55). The time commitment for subjects in the HIIT group was 27.5% less than that of the MICT group (29 min vs. 40 min per exercise session), yet HIIT was more effective for improving FMD and equally effective for improving $\dot{V}O_{2\,max}$. This study adds to the mounting evidence that HIIT is a time-efficient strategy for improving FMD.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

B.J.S. and G.A.G. conception and design of research; B.J.S., W.J.T., D.M.B., J.R.R., and K.L.S. performed experiments; B.J.S. analyzed data; B.J.S., W.J.T., D.M.B., J.R.R., K.L.S., and G.A.G. interpreted results of experiments; B.J.S. prepared figures; B.J.S. and G.A.G. drafted manuscript; B.J.S., W.J.T., D.M.B., J.R.R., K.L.S., and G.A.G. edited and revised manuscript; B.J.S., W.J.T., D.M.B., J.R.R., K.L.S., and G.A.G. approved final version of manuscript.

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