Comparison of Three Popular Exercise Modalities on $\dot{V}O_{2max}$ in Overweight and Obese

FREDRIK HJULSTAD BÆKKERUD[1], FREDERIC SOLBERG[1], INGEBORG MEGÅRD LEINAN[1,2], ULRIK WISLØFF[1], TRINE KARLSEN[1,2], and ØIVIND ROGNMO[1,2]

[1]*K. G. Jebsen Center of Exercise in Medicine, Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, NORWAY; and* [2]*Department of Cardiology, St. Olav's University Hospital, Trondheim, NORWAY*

ABSTRACT

BÆKKERUD, F. H., F. SOLBERG, I. M. LEINAN, U. WISLØFF, T. KARLSEN, and Ø. ROGNMO. Comparison of Three Popular Exercise Modalities on $\dot{V}O_{2max}$ in Overweight and Obese. *Med. Sci. Sports Exerc.*, Vol. 48, No. 3, pp. 491–498, 2016. **Introduction**: In this prospective randomized trial, we examined the effect of three popular exercise training modalities on maximal oxygen uptake ($\dot{V}O_{2max}$) in overweight and obese individuals. In addition, we examined possible concomitant adaptations in endurance exercise performance (time to exhaustion (TTE)), citrate synthase (CS) activity, venous and arterial function, blood volume, and calculated stroke volume (SV). **Methods**: Thirty subjects were recruited (age, 41 ± 9 yr; weight, 91 ± 14 kg; height, 173 ± 8 cm; body mass index, 30 ± 4 $kg \cdot m^{-2}$) and randomized to either 6 wk of 4 × 4-min high-intensity interval training (4HIIT) at 85%–95% of HR_{max}, 10 × 1-min HIIT (1HIIT) at $\dot{V}O_{2max}$ load, or 45-min moderate-intensity continuous training (MICT) at 70% of HR_{max}. $\dot{V}O_{2max}$, TTE, CS activity, venous and arterial function, as well as blood volume were measured before and after the training period. O_2 pulse was calculated and used to estimate SV. Analysis was conducted per protocol. **Results**: Only 4HIIT increased $\dot{V}O_{2max}$ ($P < 0.01$) and significantly more compared with 1HIIT ($P = 0.04$) and MICT ($P = 0.03$) (4HIIT, 10%; 1HIIT, 3.3%; and MICT, 3.1%). All groups increased TTE (4HIIT, 198%; 1HIIT, 116%; MICT, 52%), with a higher increase after 4HIIT compared with that after MICT ($P = 0.02$). Calculated SV increased only after 4HIIT (14.4%). Plasma volume and hemoglobin mass increased after 1HIIT only (5.6% and 6.5%); however, no group differences were found. All groups increased CS activity (4HIIT, 35%; 1HIIT, 35%; MICT, 56%), with no group differences. Arterial inflow (15.7%) and venous outflow (22.7%) decreased after MICT, but there were no group differences. **Conclusions**: 4HIIT was superior to 1HIIT and MICT in improving $\dot{V}O_{2max}$ likely because of an increased SV. **Key Words:** HIIT, MICT, RUNNING, AEROBIC CAPACITY, $\dot{V}O_{2max}$

One of the largest health challenges faced by the community today is lifestyle-related disease. High body mass index (BMI) is now the sixth leading risk for global death (18). The health risk associated with obesity is highly increased in inactive individuals (35), and improving fitness may be more important than reducing body weight (17).

Lack of time is the number one reported reason for not exercising (3). Therefore, several less time-consuming exercise training interventions have been tested. Two of the most common interventions are the 4 × 4-min high-intensity interval training (4HIIT) intervention (14,37) and a short-term sprint interval training (SIT) intervention, consisting of repeated 30-s all-out sprints (11). The 4HIIT approach has been shown to be more effective than work-matched moderate exercise training for improving maximal oxygen uptake ($\dot{V}O_{2max}$) in both healthy subjects (14) and various patient groups (25,39). The rationale behind the 4HIIT approach has been to mainly induce "central adaptations" to increase the capacity of the oxygen supply chain because this is known to limit $\dot{V}O_{2max}$ for most individuals (2,26). The rationale behind the SIT protocol, however, has primarily been to induce peripheral skeletal muscle adaptations to improve exercise performance (19,20) and reduce risk factors related to diabetes (19). It has been demonstrated that SIT is able to improve exercise performance that is aerobic in nature (6) as well. In addition, SIT has proven to induce comparable skeletal muscle and performance adaptations to more time- and energy-demanding traditional high-volume endurance training (11). Because of the demanding nature of these 30-s all-out sprints, Little et al. (20) proposed 10 × 1-min intervals (1HIIT) as a more practical model of low-volume HIIT for the general population. As far as we know, the difference between moderate-intensity continuous training (MICT), 4HIIT, and 1HIIT in terms of improving $\dot{V}O_{2max}$ has never been examined.

The aim of the present study was to compare the effect of 6 wk of 4HIIT at 85%–95% of HR_{max}, 1HIIT at $\dot{V}O_{2max}$ workload, and 45 min of MICT at 70% of HR_{max} on $\dot{V}O_{2max}$

Address for correspondence: Øivind Rognmo, Ph.D., Faculty of Medicine, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Postbox 8905, 7491 Trondheim, Norway; E-mail: oivind.rognmo@ntnu.no.
Submitted for publication April 2015.
Accepted for publication September 2015.

0195-9131/16/4803-0491/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000000777

in overweight and obese individuals. The secondary aims included the effect of exercise training on endurance exercise performance (time to exhaustion (TTE)), citrate synthase (CS) activity, venous and arterial function, blood volume, and stroke volume (SV). We hypothesized 4HIIT to improve $\dot{V}O_{2max}$ to a greater extent than the other two groups, mediating a greater increase in exercise performance, arterial and venous function, CS activity, as well as blood volume and SV.

METHODS

Subjects. Subjects were recruited through social media and public announcements, via the research group's Facebook and Twitter pages as well as posters placed at St. Olav's University Hospital in Trondheim, Norway. Those who were interested were invited for a talk about the study before they signed an informed consent form. The inclusion criterion was BMI ≥25 $kg \cdot m^{-2}$, and exclusion criteria were heart diseases or any other illness not reconcilable with high-intensity exercise and structured exercise training within the last 6 months. Thirty subjects joined the study. At inclusion, the subjects demographics for the groups were as follows: 4HIIT (n = 12; seven women; age, 39 ± 10 yr; weight, 91.7 ± 17.4 kg; height, 170.7 ± 9 cm; BMI, 31.4 ± 5.3 $kg \cdot m^{-2}$), 1HIIT (n = 9; 6 women; age, 45 ± 8 yr; weight, 91.1 ± 10.1 kg; height, 172.0 ± 5.7 cm; BMI, 30.8 ± $kg \cdot m^{-2}$), and MICT (n = 9; 5 women; age, 41 ± 10 yr; weight, 89.5 ± 12.4 kg; height, 175.5 ± 8.8 cm; BMI, 29 ± 2.7 $kg \cdot m^{-2}$). There were no statistical differences between groups regarding these parameters.

Subject preparation. The subjects visited the laboratory on three occasions before randomization. One the first day of testing, the subjects met for a $\dot{V}O_{2max}$ test. On the second day of testing, the subjects met for arterial and venous assessments followed by blood volume assessment. On the third day of testing, subjects met for a muscle biopsy. To avoid the acute effects of exercise and carbon monoxide (CO) rebreathing, there was at least 48 h between the first, second, and third day of testing, respectively. Because of the possible influence of factors such as caffeine, vitamin C, or tobacco (8) on vascular reactivity, the participants were told to fast during the 8–10 h before the vascular examination and to drink 0.5 L of water in the morning.

After completion of the baseline investigations, subjects were randomized to either 4 × 4-min 4HIIT, 10 × 1-min 1HIIT, or 45 min of MICT. It was stratified for gender. Randomization was performed by a Web-based randomization system developed and administered by the Unit of Applied Clinical Research, Institute of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

Treadmill testing. $\dot{V}O_{2max}$ was tested using Metamax II (Cortex Biophysik GmbH, Leipzig, Germany) with the subjects running or walking on a calibrated treadmill (Woodway GmbH, D-79576, Weil am Rhein, Germany). We used an individualized ramp protocol, as described previously (1). All subjects warmed up for 10 min at a self-selected speed before work economy was measured during 5 min of walking at 5 $km \cdot h^{-1}$ and 5% inclination. After this, the test continued with the ramp protocol until exhaustion. Work economy was calculated as the average $\dot{V}O_2$ over the last minute of the 5-min period. HR_{max} was the highest HR seen at the end of the $\dot{V}O_{2max}$ test, and five additional beats were added to this when calculating training intensity (16). O_2 pulse (mL per beat) was calculated as $\dot{V}O_{2max}$ divided by HR at the end of the $\dot{V}O_{2max}$ test and was then used to estimate SV as described by Wasserman et al. (34). At the first and last training sessions, endurance performance was assessed as TTE. Subjects ran until exhaustion on a treadmill set at the same speed they reached on the pretraining $\dot{V}O_{2max}$ test but with a 2% reduction in inclination. The TTE tests were conducted without temporal feedback. The test was terminated when the subject voluntarily stopped running.

Vascular examination. Upper arm brachial vein and artery diameter and flow was measured using high-resolution vascular ultrasound (14-MHz Doppler probe, Vivid 7 System; GE Vingmed Ultrasound, Horten, Norway). Measurements were done at the same location on the arm before and after occlusion when measuring both the artery and the vein. The examination started with 10 min of supine rest in an air-conditioned room (22°C ± 1°C). Participants' resting blood pressure was measured before the vascular examination occlusion protocol was initiated, with baseline measurements of both venous and arterial diameter and flow velocities. Two occlusion cuffs (CS5 straight segmental cuff; Hokanson, Bellevue, WA) were placed at the subjects' arm, one at the wrist and the other around the upper arm. The cuff surrounding the wrist was inflated to 240 mm Hg, and after 1 min, the upper arm cuff was inflated to 7 mm Hg below the subjects' baseline diastolic blood pressure. Upper arm occlusion lasted for 5 min, with continuous sampling of venous diameter starting 1 min before deflation and lasting 30 s after deflation of the upper arm occlusion cuff. Continuous sampling of changes in venous diameter and venous outflow during this 90-s period was done. Directly after measuring venous diameter and outflow, flow-mediated dilation (FMD) in the brachial artery was measured during reactive hyperemia. Continuous sampling of changes in brachial arterial diameter and flow velocity started 20 s before deflation of the wrist occlusion cuff and lasted 3 min after deflation. Diameters and flow velocities were analyzed offline using automated edge-detection Brachial Analyzer software (Medical Imaging Applications, LLC, Coralville, IA).

Blood volume. Total blood- and hemoglobin (Hb) mass were measured by the improved CO-rebreathing technique (Blood Tec, Bayreuth, Germany), directly after the examination of venous compliance. This method uses the change in CO bound to Hb after rebreathing a defined volume of CO gas to calculate blood and plasma volume (13,27). As the participants had a BMI >25 $kg \cdot m^{-2}$, the dose of CO was calculated on the basis of an estimated body weight corresponding to a BMI of 25 $kg \cdot m^{-2}$ according to the equation

(kg) = 25 × height (m^{-2}). This is a safety precaution to prevent the HbCO to exceed 6%. After 15 min of rest and a complete exhalation, the participants inhaled a bolus of 99.9% CO (men, 0.8 per kg body weight; women, 0.7 per kg body weight) followed by 100% O_2, held their breath for 10 s, and continued to rebreathe the gas mixture in a 3-L bag for 2 min (13,27). Capillary blood samples were collected before the CO breathing and 6 and 8 min after the start of the rebreathing and analyzed for percentage of CO bound to Hb (HbCO%) on a blood gas analyzer ABL800 Basic Analyzer (Radiometer Medical ApS, Denmark). End-tidal CO concentration was measured before and 4 min after the CO inhalation using a gas tester (Draeger®, Luebeck, Germany), and the gas volume and concentration of CO in the spirometer were measured after the procedure. A venous blood sample (EDTA) was collected after the test, and Hb and hematocrit were analyzed at St. Olav's University Hospital in Trondheim, Norway.

Muscle biopsy. A muscle biopsy was taken from the vastus lateralis under local anesthetic (1% Xylocaine) with a modified Bergström needle 6 mm in diameter. The muscle sample was immediately frozen in liquid nitrogen.

Cs activity. Frozen muscle samples were thawed and homogenized in a CelLytic buffer (Sigma-Aldrich, St Louis, MO) for 2 × 8 s at 6000 shakes per minute in Precellys24 homogenizer (Bertin Technologies, Montigny-le-Bretonneux, France). The homogenate was centrifuged for 10 min at 10,000*g* at 4°C, after which the supernatant was tested for CS activity, as described in another study (30), using a CS activity assay kit (Sigma-Aldrich). A FLUOstar omega spectrometer (BMG Labtech, Ortenburg, Germany) was used to measure the absorbance at 412 nm, and activity was divided by protein concentration in the muscle extract to obtain CS activity ($mol \cdot kg^{-1} \cdot h^{-1}$).

Exercise training. All groups trained three times a week, for a total of 18 sessions. If a session was missed, the subject was allowed to make up for it in the next week by performing four sessions. All training sessions were supervised to make sure the subjects trained according to the prescription.

The 4HIIT group warmed up for 10 min at 70% HR_{max} before doing four intervals of 4 min, each at 85%–95% of HR_{max}, interspaced by 3 min of treadmill walking at 70% HR_{max}. The sessions ended with a 3-min cooldown period at 70% of HR_{max}. In the 1HIIT group, the warm-up and cooldown periods were identical to those in the 4HIIT group. 10 × 1-min intervals were performed at the speed and inclination from the subjects' $\dot{V}O_{2max}$ test. This corresponded to approximately 90% of their HR_{max}. The active recovery between intervals was performed walking around on the floor in the training room. The MICT group did 45 min of steady-state running/walking at 70% HR_{max}. This training session has previously been shown to be isocaloric, with the training program performed in the 4HIIT group (14). All training sessions were supervised by at least one exercise physiologist, controlling that all subjects trained according to the protocol. If HR dropped below the exercise training zone during the course of the training period, speed or inclination was increased to bring it back up to the correct zone.

Statistical power. With an expected difference in $\dot{V}O_{2max}$ of 0.7 ($L \cdot min^{-1}$) and SD of 0.5 ($L \cdot min^{-1}$), nine subjects were needed in each group to reach a power of 0.8.

Ethics statement. The study was conducted according to the Declaration of Helsinki, and the regional committee for medical research ethics gave approval before start. The study is registered in clinicaltrials.gov, #NCT01453972. All subjects signed informed consents approved by the regional ethical committee for medical research.

Statistical analysis. A dependent *t*-test was used to detect differences from before to after training within groups. For CS activity, a Wilcoxon signed-rank test was used because of the lack of normal distribution. ANCOVA (dependent variable, delta values; covariate, prevalues; *post hoc*, least significant difference) was used to detect differences between groups, except for CS activity where a Kruskal–Wallis test was used. Statistical analyses were performed using SPSS 21 (SPSS Inc., Chicago, IL).

RESULTS

Four subjects withdrew from the 4HIIT group (two men and two women); three withdrew from the study for reasons unrelated to exercise training (one family emergency, one disease, one injury unrelated to the study), and one withdrew due to exercise-related hip pain. This left eight subjects in the 4HIIT group and nine each in 1HIIT and MICT. The 26 subjects who completed the exercise training period completed all of their prescribed training sessions. All results were analyzed on a per-protocol basis. There were no differences between the groups at baseline.

Exercise intensity. The mean exercise training intensity was 92% ± 3.7% and 90% ± 5.3% of HR_{max} during the intervals (calculated as the mean of all intervals) in the 4HIIT and 1HIIT group, respectively, whereas the MICT group exercised at 70% of HR_{max} during their entire training session.

Treadmill tests. $\dot{V}O_{2max}$ ($L \cdot min^{-1}$) increased by 10% ($P < 0.01$) in the 4HIIT group, 3.3% ($P = 0.42$) in the 1HIIT group, and 3.1% ($P = 0.54$) in the MICT group (Fig. 1; Table 1). The increase was significantly higher in the 4HIIT group compared with those in the 1HIIT group ($P = 0.04$) and the MICT group ($P = 0.03$). Work economy ($L \cdot min^{-1}$) improved significantly by 5.5% ($P = 0.03$), 5.8% ($P < 0.01$), and 11.1% ($P < 0.01$) in the 4HIIT, 1HIIT, and MICT groups, respectively (Table 1), with no difference between the groups. Estimated SV by O_2 pulse increased significantly by 14% in the 4HIIT group only (both $P = 0.01$), and this increase was significantly larger compared with those in the 1HIIT group ($P = 0.03$) and the MICT group ($P = 0.01$) (Table 1). There was a trend toward a higher ventilatory threshold in the 1HIIT group ($P = 0.10$) from before to after training, but there were no significant differences between the groups (Table 1).

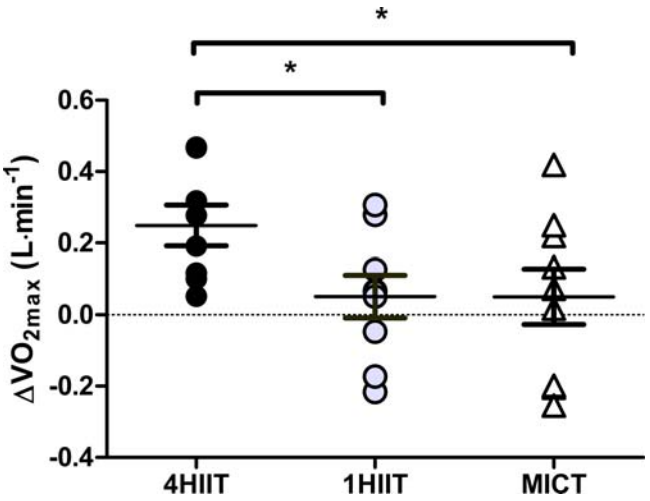

FIGURE 1—Changes in $\dot{V}O_{2max}$ from before to after training in the 4HIIT, 1HIIT, and MICT groups, respectively. Values are presented as dot plot with mean ± SE. *Significant difference between groups ($P \leq 0.05$).

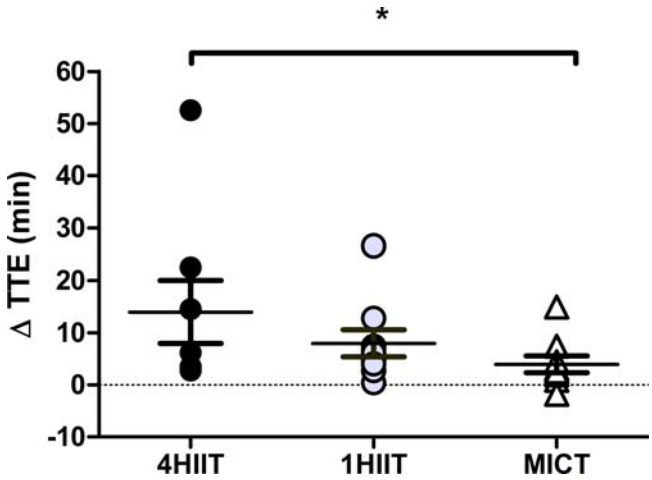

FIGURE 2—Changes in TTE from before to after training in the 4HIIT, 1HIIT, and MICT groups, respectively. Values are presented as dot plot with mean ± SE. *Significant difference between groups ($P \leq 0.05$).

TTE improved by 198% ($P = 0.05$) in 4HIIT, 116% ($P = 0.02$) in 1HIIT, and 52% ($P = 0.04$) in the MICT group. The 4HIIT group's improvement was significantly larger compared with the MICT group ($P = 0.02$) (Fig. 2).

Cs. Because of difficulties in acquiring biopsies from some subjects, the *n* for CS activity was five in the 4HIIT and 1HIIT groups and seven in the MICT group. All groups increased their CS activity. The 4HIIT group increased from 8.05 ± 2.88 mol·kg^{-1}·h^{-1} to 10.92 ± 2.82 mol·kg^{-1}·h^{-1} ($P = 0.04$); the 1HIIT group increased from 6.64 ± 0.71 mol·kg^{-1}·h^{-1} to 8.96 ± 1.65 mol·kg^{-1}·h^{-1} ($P = 0.04$); the MICT group increased from 7.84 ± 0.83 mol·kg^{-1}·h^{-1} to 12.24 ± 3.97 mol·kg^{-1}·h^{-1} ($P = 0.02$). No group differences were found (Fig. 3).

Vascular changes. Because of equipment failure, vascular examination results were not obtained in three participants (one from each group). These participants are therefore not included in the vascular examination analysis. No difference was found in upper arm venous compliance between the groups, and upper arm venous compliance did not change after exercise training in any groups. These results persisted after normalization for total blood volume. No changes were found in resting or maximal venous volume from before to after training in either group, and the groups did not differ (Table 2). Peak venous outflow and arterial inflow both decreased after training in the MICT group by 22.7% and 15.7%, respectively. No difference was found in FMD between the groups, and FMD remained unchanged after exercise training in all groups (Table 2).

Blood parameters. Only 1HIIT increased plasma volume (mL·kg^{-1}) (5.6%, $P = 0.01$) and blood volume (mL·kg^{-1}) (5.0%, $P = 0.02$). There was also a concomitant increase in Hb mass by 6.2% ($P = 0.02$), leaving hematocrit unchanged. There were no significant differences between the groups (Table 3).

Body weight. Body weight did not change significantly over the course of the training period.

DISCUSSION

To our knowledge, this is the first study to compare 4HIIT, 1HIIT, and MICT. The main finding of the present study was that 4HIIT improved $\dot{V}O_{2max}$ to a greater extent compared with 1HIIT and MICT, most likely mediated through an increase in SV. We also found that 4HIIT increased TTE more than MICT.

TABLE 1. Treadmill tests.

	4HIIT ($n = 8$)		1HIIT ($n = 9$)		MICT ($n = 9$)	
	Before	After	Before	After	Before	After
$\dot{V}O_{2max}$						
(L·min^{-1})	3.0 ± 0.9	3.3 ± 0.9*	3.0 ± 0.6	3.1 ± 0.7	3.2 ± 0.7	3.3 ± 0.9
(mL·kg^{-1}·min^{-1})	31.9 ± 6.9	34.7 ± 8.7*	33.6 ± 6.8	34.5 ± 7.8	36.2 ± 6.8	36.6 ± 5.1
Work economy						
(L·min^{-1})	1.8 ± 0.4	1.7 ± 0.4*	1.7 ± 0.2	1.6 ± 0.2*	1.8 ± 0.3	1.6 ± 0.2*
(mL·kg^{-1}·min^{-1})	19.8 ± 1.7	18.1 ± 1.1*	18.8 ± 0.7	17.2 ± 1.1*	20.1 ± 1.9	18.3 ± 1.5*
TTE (min:s)	07:03 ± 03:36	21:02 ± 19:35*	06:54 ± 02:03	14:52 ± 09:15*	07:39 ± 03:27	11:34 ± 07:11*
HR_{max} (bpm)	183 ± 11	177 ± 15	181 ± 14	179 ± 17	186 ± 12	184 ± 12
Maximal O_2 pulse (mL per beat)	16.4 ± 4.5	18.5 ± 4.9*	15.9 ± 1.9	16.4 ± 1.6	17.1 ± 3.0	17.4 ± 4.2
Estimated maximal SV (mL)	113.4 ± 21.8	129.7 ± 25.9*	109.8 ± 10.8	113 ± 7.8	119.2 ± 21.0	121.1 ± 28.5
Ventilatory threshold (L·min^{-1})	2.5 ± 0.6	2.3 ± 0.7	2.2 ± 0.3	2.3 ± 0.3	2.3 ± 0.5	2.4 ± 0.7

Data are presented as mean ± SD.
*Denotes a significant difference from prevalue in the same group, $P \leq 0.05$.

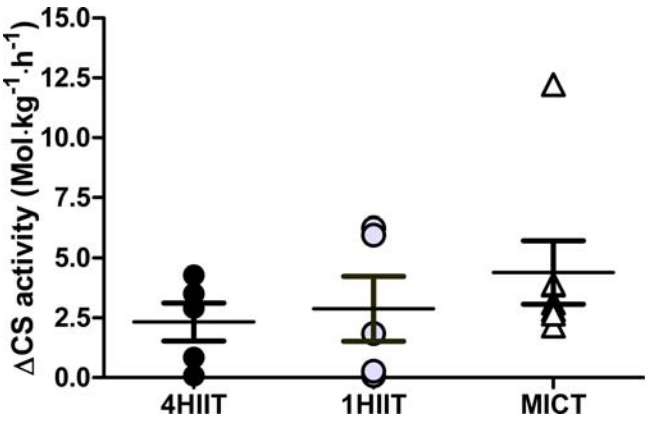

FIGURE 3—Changes in CS activity from before to after training in the 4HIIT, 1HIIT, and MICT groups, respectively. Values are presented as dot plot with mean ± SE. No significant differences between groups were found.

The improvement in $\dot{V}O_{2max}$ due to 4HIIT is highly linked to improvements in the oxygen supply chain (14,38). The novel finding of a larger increase in $\dot{V}O_{2max}$ after 4HIIT compared with that after 1HIIT indicates that the two modes of exercise training stimulates different aspects of the oxygen supply and demand chain and that time spent at high intensity affects the exercise training response. On the demand side of the chain, the mass of the mitochondria, indicated by CS activity, increased in all groups after exercise training (Fig. 3), suggesting that exercise training with both high and moderate intensity improves skeletal muscle mitochondrial potential. This is in line with previous studies (9,20). Peripheral mitochondrial adaptations are therefore not likely the explanation for the higher increase in $\dot{V}O_{2max}$ after 4HIIT compared with those after 1HIIT and MICT. Rather, our findings indicate that enhanced oxygen supply stimulates the increase in $\dot{V}O_{2max}$ in our participants because all groups increased CS activity but only 4HIIT, which additionally improved estimated SV, increased $\dot{V}O_{2max}$.

The fact that only 4HIIT increased estimated SV (Table 1) may thus explain the larger improvement of $\dot{V}O_{2max}$ in this group. Increased SV after 4HIIT, but not after MICT, is in accordance with previous findings (14). The present study also indicates that 6 wk of 1HIIT does not increase SV. As exercise SV has been found to increase progressively until $\dot{V}O_{2max}$ (12,40), a difference in intensity between 4HIIT and 1HIIT could have influenced the different improvement in $\dot{V}O_{2max}$ found between the groups. Recently, a relation between 4HIIT intensity and improvement in $\dot{V}O_{2max}$ was reported, indicating that higher intensity even within the 4HIIT intensity zone of 85%–95% HR_{max} is crucial for increasing $\dot{V}O_{2max}$ (23). However, the 1HIIT in the current study corresponded to 90% $HR_{max,}$ which is comparable with the mean 4HIIT intensity (92% HR_{max} in the current study). Hence, the group difference in $\dot{V}O_{2max}$ between the 1HIIT and 4HIIT was most likely unrelated to exercise intensity.

An estimate of caloric expenditure (25) found 4HIT, 1HIIT, and MICT to be isocaloric at baseline (4HIIT, 474 ± 153 kcal; 1HIIT, 391 ± 78 kcal; MICT, 473 ± 100 kcal; P = 0.23). Therefore, a difference in total training volume was probably not the reason for the group difference in improved $\dot{V}O_{2max}$. It has however been suggested that a certain volume of high-intensity work is crucial for improving $\dot{V}O_{2max}$ (9). Nevertheless, intensity seems to matter more than duration in this context, because Tjønna et al. (32) found that in untrained, overweight individuals, as little as one 4-min bout of HIIT was sufficient for improving $\dot{V}O_{2max}$ in the same manner as ordinary 4 × 4-min HIIT. Thus, the total high-intensity duration of 16 min of HIIT versus 10 min of 1HIIT in the present study did not likely account for the different improvement of $\dot{V}O_{2max}$ between the groups. One may however speculate whether the shorter duration of the intervals during 1HIIT, with 1-min bouts and where a majority of the training time is spent with increasing or decreasing HR, may play a role. The limited time at a steady-state workload above 90% of HR_{max} supports the view that time spent at a steady-state HR above 90% HR_{max} might be a key factor in SV-related increase in $\dot{V}O_{2max}$. Consequently, our study supports previous randomized trials where 4HIIT has been found to be superior to MICT (14,25) and 1HIIT to be equal to MICT in terms of improving $\dot{V}O_{2max}$ (5).

As total blood volume did not change in the 4HIIT group, the improvements seen in SV are likely not a factor of

TABLE 2. Vascular parameters.

	4HIIT (n = 7)		1HIIT (n = 8)		MICT (n = 8)	
	Before	After	Before	After	Before	After
Venous						
Venous compliance ($mm^3 \cdot mm\ Hg^{-1}$)	0.77 ± 0.50	0.93 ± 0.93	0.91 ± 0.87	1.04 ± 0.80	1.01 ± 0.65	1.10 ± 0.85
Venous compliance normalized blood volume ($mm^3 \cdot mm\ Hg^{-1} \cdot L^{-1}$)	0.13 ± 0.09	0.15 ± 0.18	0.24 ± 0.15	0.16 ± 0.10	0.16 ± 0.11	0.24 ± 0.13
Resting venous volume (mm^3)	172.4 ± 70.9	173.4 ± 62.9	159.2 ± 63.8	169.4 ± 73.2	136.9 ± 54.7	172.3 ± 84.4
Maximal venous volume (mm^3)	216.9 ± 86	228.2 ± 69.6	211.8 ± 59.0	233.6 ± 118.7	195.9 ± 77.9	236.8 ± 111.6
Peak venous outflow ($cm \cdot s^{-1}$)	44.0 ± 18.7	41.0 ± 17.1	56.0 ± 22.6	48.4 ± 16.1	53.1 ± 7.5	41.1 ± 11.7*
Arterial						
Arterial inflow ($cm \cdot s^{-1}$)	70.2 ± 16.5	64.2 ± 19.1	65.5 ± 13.5	57.2 ± 21.9	72.0 ± 19.5	60.7 ± 13.4*
Resting arterial diameter (mm)	3.63 ± 0.98	3.79 ± 0.96	3.78 ± 0.37	3.79 ± 0.46	3.75 ± 0.46	3.82 ± 0.39
Maximal arterial diameter (mm)	4.13 ± 0.91	4.27 ± 0.77	4.02 ± 0.36	4.11 ± 0.50	3.83 ± 0.51	4.09 ± 0.53
FMD (%)	8.0 ± 7.1	8.7 ± 5.9	6.2 ± 7.1	8.5 ± 6.4	5.0 ± 4.0	7.7 ± 5.3

Values are presented as mean ± SD. Maximal values are values measured after 5 min of upper arm occlusion; venous outflow refers to the velocity of venous blood at the release of upper arm cuff pressure; arterial inflow refers to the velocity of arterial blood.
*Denotes a statistically significant difference from prevalue in the same group, $P \leq 0.05$.

TABLE 3. Blood parameters.

	4HIIT (n = 7)		1HIIT (n = 8)		MICT (n = 6)	
	Before	After	Before	After	Before	After
Blood volume (L)	5.8 ± 0.6	5.8 ± 0.6	5.7 ± 1.1	5.9 ± 0.9	6 ± 1.2	6.0 ± 1.2
Plasma volume (L)	3.5 ± 0.3	3.6 ± 0.3	3.5 ± 0.6	3.7 ± 0.5*	3.6 ± 0.7	3.7 ± 0.7
Total Hb mass (g)	758 ± 126	763 ± 116	729 ± 148	760 ± 155*	789 ± 192	803 ± 186
Erythrocyte volume (L)	2.3 ± 0.6	2.4 ± 0.5	2.2 ± 0.5	2.2 ± 0.4	2.3 ± 0.5	2.4 ± 0.5
Blood volume (mL·kg^{-1})	61.9 ± 11.4	62.2 ± 10.5	63.5 ± 9.0	66.7 ± 6.8*	66.6 ± 10.9	67.7 ± 6.8
Plasma volume (mL·kg^{-1})	37.6 ± 6.2	38.0 ± 5.9	39.2 ± 5.2	41.4 ± 4.4*	40.8 ± 7.0	41.4 ± 4.6
Total Hb mass (g·kg^{-1})	8.1 ± 2.0	8.2 ± 1.7	8.1 ± 1.2	8.6 ± 1.3*	8.8 ± 1.6	8.9 ± 1.0
Erythrocyte volume (mL·kg^{-1})	24.8 ± 4.5	24.6 ± 4.4	24.3 ± 3.9	25.3 ± 3.0	25.8 ± 4.0	30.8 ± 1.3
HTC (%)	42.8 ± 2.5	42.5 ± 1.6	42.0 ± 1.4	41.7 ± 2.3	42.5 ± 1.6	42.6 ± 2.3
Hb (g·dL^{-1})	14.6 ± 1.3	14.3 ± 0.9	14.3 ± 0.9	14.1 ± 1.1	14.5 ± 0.9	14.6 ± 1.1

Data are presented as mean ± SD.
*Denotes a statistically significant within group difference from prevalue, $P \leq 0.05$.
HTC, hematocrit.

increased preload due to increased blood volume; however, preload might have increased because of a redistribution of blood or improved diastolic suction as a result of increased contractility (10,15). HIIT of 8 min at 85%–90% of HR_{max} has been found to induce improvements in cardiac contractility that is twice as high as that in moderate intensity (65%–70% of HR_{max}) in an animal model (33). A larger improvement in contractility after 4HIIT in the present study might have led to a higher SV in this group compared with those in the other two.

As no improvements were found in Hb-mass or blood volume after 4HIIT, the increase in $\dot{V}O_{2max}$ after 4HIIT was not due to increased oxygen carrying capacity. Plasma volume and Hb mass increased significantly after 1HIIT. This indicates an increased oxygen carrying capacity after exercise training, which should lead to improved $\dot{V}O_{2max}$. An increase in Hb mass of 1 g·kg^{-1} has previously been associated with an increase of 4.4 mL·kg^{-1}·min^{-1} in $\dot{V}O_{2max}$ (28). Therefore, the increase of 0.5 g·kg^{-1} in Hb mass seen after 1HIIT in our study may reflect the smaller increase of 1 mL·kg^{-1}·min^{-1} in $\dot{V}O_{2max}$ seen in this group, as no central SV changes was detected. No group differences were found with regard to changes in plasma volume and Hb mass, in accordance with a previous study comparing the influence of MICT and 4HIIT on blood volume, plasma volume, and Hb mass (14), and no change was found in these parameters after a prolonged training program comparing moderate and high intensities (33).

No difference was found within or between the groups with regard to upper arm venous compliance or arterial endothelial function, indicating that vascular plasticity in the arm was not affected by exercise training in our subjects. As conductive blood transport exists in the "bridge" between central and peripheral adaptations to endurance exercise training, the data from this study adds knowledge to the overall picture of physiological adaptations to different intensities and durations of exercise training. Previously, a positive association between endurance performance and venous capacitance has been reported, indicating that venous flexibility is important for endurance performance. However, as a large portion of subjects in this study (36) were heart failure patients on diuretic medication, the association found may be due to the medical treatment affecting the venous physiology. It has been suggested that exercise-induced changes in venous compliance takes place secondary to exercise-induced hypervolemia (21), and because no change was found in the total blood volume (L) within or between the groups, this might explain why upper arm venous compliance did not change after 6 wk of exercise training in our study. The three groups displayed normal endothelial function (FMD, >5%) (29), and no change in FMD was found within or between groups after the exercise training period. This is in accordance with previous studies showing that exercise training has little effect on endothelial function if the function is well preserved at baseline (24). Arterial inflow and venous outflow were both found to decrease after exercise training in the MICT group. The decrease in arterial inflow might be explained by a small (nonsignificant) increase in resting and maximal arterial diameter, and the decrease in venous outflow was likely a reflection of decreased arterial inflow, as seen in a study by Welsch et al. (36). The mirror image between arterial and venous function illustrates the close regulation between the high- and low-pressure parts of the vasculature and needs to be examined in future studies to investigate whether this is an important peripheral response to moderate exercise training.

Although all groups improved TTE significantly, the improvement after 4HIIT was larger than that after MICT. There are three factors that determine endurance performance: $\dot{V}O_{2max}$, lactate threshold, and work economy (22). In line with a previous study (14), work economy improved similarly after 4HIIT and MICT and cannot be the factor responsible for the group difference seen in TTE. The 4HIIT group improved $\dot{V}O_{2max}$ to a higher extent than the other two groups, which probably contributed to this group's superior increase in TTE over MICT. Lactate threshold was not tested, but has previously been shown not to remain unchanged after 4HIIT when expressed as a percentage of $\dot{V}O_{2max}$ (14). Despite the 4HIIT group's superiority in increasing $\dot{V}O_{2max}$, it did not improve TTE to a higher extent than 1HIIT. A possible improvement of the lactate threshold could have influenced the TTE in the 1HIIT group. Lactate threshold was not measured; however, there was a trend toward an improvement in the ventilatory threshold after 1HIIT (P = 0.10) (Table 1). In addition, lower lactate accumulation

during exercise has been found after 1HIIT training previously (4). More research is needed to compare the effect of 4HIIT and 1HIIT on the lactate threshold.

This study was done on a per protocol basis, which may be a limitation with regard to generalization of the results. The sample size was also small, and the four dropouts in the 4HIIT group could have compromised the statistical power and hence the results of the study. Even if we take these limitations into consideration, the results are in line with former smaller studies regarding the superiority of 4HIIT for improving $\dot{V}O_{2max}$ (37). It has however not escaped our awareness that larger 4HIIT trials such as the SAINTEX-CAD (7) trial and preliminary results from the SMARTEX-HF (31) study show equal benefits from 4HIIT and MICT with regard to improvements in $\dot{V}O_{2max}$. Future studies should evaluate the reason for this.

CONCLUSIONS

HIIT at 85%–95% of HR_{max} was superior to 1HIIT and MICT with regard to improvements in $\dot{V}O_{2max}$. We have indications that the results are likely due to an increase in oxygen supply by larger SV after 4HIIT, although attributing the gain in $\dot{V}O_{2max}$ solely to an increase in calculated SV should be done with care. All exercise training modes induced peripheral adaptations as mitochondrial content increased after 4HIIT, 1HIIT, and MICT. In addition, 4HIIT was found to be superior to MICT in terms of improving TTE. Exercise training did not change upper arm venous compliance or FMD. Future studies should examine the combination of two or more of these training forms to assess whether some of the adaptations discovered here can have additive effects.

The study was financially supported by the K. G. Jebsen Center of Exercise in Medicine, Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway, and the liaison committee between the Central Norway Regional Health Authority and Norwegian University of Science and Technology. We thank all the subjects for participating in the study and Nina Zisko for helping with the CS activity analysis.

Fredrik Hjulstad Bækkerud and Frederic Solberg contributed equally to the study.

None of the authors have any conflict of interests.

The results of the present study do not constitute endorsement by the American College of Sports Medicine.

REFERENCES

1. Aspenes ST, Nilsen TI, Skaug EA, et al. Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. *Med Sci Sports Exerc*. 2011;43(8):1465–73.
2. Bassett DR Jr, Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc*. 2000;32(1):70–84.
3. Booth ML, Bauman A, Owen N, Gore CJ. Physical activity preferences, preferred sources of assistance, and perceived barriers to increased activity among physically inactive Australians. *Prev Med*. 1997;26(1):131–7.
4. Burgomaster KA, Heigenhauser GJ, Gibala MJ. Effect of short-term sprint interval training on human skeletal muscle carbohydrate metabolism during exercise and time-trial performance. *J Appl Physiol (1985)*. 2006;100(6):2041–7.
5. Burgomaster KA, Howarth KR, Phillips SM, et al. Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans. *J Physiol*. 2008; 586(1):151–60.
6. Burgomaster KA, Hughes SC, Heigenhauser GJ, Bradwell SN, Gibala MJ. Six sessions of sprint interval training increases muscle oxidative potential and cycle endurance capacity in humans. *J Appl Physiol (1985)*. 2005;98(6):1985–90.
7. Conraads VM, Pattyn N, De Maeyer C, et al. Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: the SAINTEX-CAD study. *Int J Cardiol*. 2015;179:203–10.
8. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol*. 2002; 39(2):257–65.
9. Duscha BD, Annex BH, Johnson JL, Huffman K, Houmard J, Kraus WE. Exercise dose response in muscle. *Int J Sports Med*. 2012;33(3):218–23.
10. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2001;104(14):1694–740.
11. Gibala MJ, Little JP, van Essen M, et al. Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. *J Physiol*. 2006;575(pt 3):901–11.
12. Gledhill N, Cox D, Jamnik R. Endurance athletes' stroke volume does not plateau: major advantage is diastolic function. *Med Sci Sports Exerc*. 1994;26(9):1116–21.
13. Gore CJ, Bourdon PC, Woolford SM, Ostler LM, Eastwood A, Scroop GC. Time and sample site dependency of the optimized co-rebreathing method. *Med Sci Sports Exerc*. 2006;38(6):1187–93.
14. Helgerud J, Høydal K, Wang E, et al. Aerobic high-intensity intervals improve VO_{2max} more than moderate training. *Med Sci Sports Exerc*. 2007;39(4):665–71.
15. Hori M, Yeliin EL, Sonnenblick EH. Left ventricular diastolic suction as a mechanism of ventricular filling. *Jpn Circ J*. 1982;46(1):124–9.
16. Ingjer F. Factors influencing assessment of maximal heart rate. *Scand J Med Sci Sports*. 1991;1(3):134–40.
17. Lee DC, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation*. 2011;124(23):2483–90.
18. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012; 380(9859):2224–60.
19. Little JP, Gillen JB, Percival ME, et al. Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. *J Appl Physiol (1985)*. 2011;111(6):1554–60.
20. Little JP, Safdar A, Wilkin GP, Tarnopolsky MA, Gibala MJ. A practical model of low-volume high-intensity interval training induces mitochondrial biogenesis in human skeletal muscle: potential mechanisms. *J Physiol*. 2010;588(Pt 6):1011–22.
21. Louisy F, Jouanin JC, Guezennec CY. Filling and emptying characteristics of lower limb venous network in athletes. Study by postural plethysmography. *Int J Sports Med*. 1997;18(1):26–9.

22. Mclaughlin JE, Howley ET, Bassett DR Jr, Thompson DL, Fitzhugh EC. Test of the classic model for predicting endurance running performance. *Med Sci Sports Exerc*. 2010;42(5):991–7.
23. Moholdt T, Madssen E, Rognmo Ø, Aamot IL. The higher the better? Interval training intensity in coronary heart disease. *J Sci Med Sport*. 2014;17(5):506–10.
24. Moyna NM, Thompson PD. The effect of physical activity on endothelial function in man. *Acta Physiol Scand*. 2004;180(2): 113–23.
25. Rognmo Ø, Hetland E, Helgerud J, Hoff J, Slørdahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil*. 2004;11(3): 216–22.
26. Saltin B, Strange S. Maximal oxygen uptake: "old" and "new" arguments for a cardiovascular limitation. *Med Sci Sports Exerc*. 1992;24(1):30–7.
27. Schmidt W, Prommer N. The optimised CO-rebreathing method: a new tool to determine total haemoglobin mass routinely. *Eur J Appl Physiol*. 2005;95(5–6):486–95.
28. Schmidt W, Prommer N. Effects of various training modalities on blood volume. *Scand J Med Sci Sports*. 2008;18(1 Suppl):57–69.
29. Skaug EA, Aspenes ST, Oldervoll L, et al. Age and gender differences of endothelial function in 4739 healthy adults: the HUNT3 Fitness Study. *Eur J Prev Cardiol*. 2013;20(4):531–40.
30. Srere PA. Citrate synthase. In: Lowenstein JM, editor. *Methods in Enzymology*. United Kingdom: Academic Press; 1969. pp. 3–11.
31. Støylen A, Conraads V, Halle M, Linke A, Prescott E, Ellingsen Ø. Controlled study of myocardial recovery after interval training in heart failure: SMARTEX-HF—rationale and design. *Eur J Prev Cardiol*. 2012;19(4):813–21.
32. Tjønna AE, Leinan IM, Bartnes AT, et al. Low- and high-volume of intensive endurance training significantly improves maximal oxygen uptake after 10-weeks of training in healthy men. *PLoS One*. 2013;8(5):e65382.
33. Warburton DE, Haykowsky MJ, Quinney HA, et al. Blood volume expansion and cardiorespiratory function: effects of training modality. *Med Sci Sports Exerc*. 2004;36(6):991–1000.
34. Wasserman K, Hansen JE, Sue D, et al. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. Philadelphia (PA): Wolters Kluwer Health/ Lippincott Williams & Wilkins; 2012. pp. 82–3.
35. Wei M, Kampert JB, Barlow CE, et al. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA*. 1999;282(16):1547–53.
36. Welsch MA, Alomari M, Parish TR, Wood RH, Kalb D. Influence of venous function on exercise tolerance in chronic heart failure. *J Cardiopulm Rehabil*. 2002;22(5):321–6.
37. Weston KS, Wisløff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med*. 2014; 48(16):1227–34.
38. Wisløff U, Ellingsen Ø, Kemi OJ. High-intensity interval training to maximize cardiac benefits of exercise training? *Exerc Sport Sci Rev*. 2009;37(3):139–46.
39. Wisløff U, Støylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. 2007;115(24):3086–94.
40. Zhou B, Conlee RK, Jensen R, Fellingham GW, George JD, Fisher AG. Stroke volume does not plateau during graded exercise in elite male distance runners. *Med Sci Sports Exerc*. 2001;33(11):1849–54.