Time-course of V̇O2 kinetics responses during moderate-intensity exercise subsequent to HIIT vs moderate-intensity continuous training in type 2 diabetes

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TITLE

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RUNNING HEAD:

Low-volume HIIT vs MICT on $\dot{V}O_2$ kinetics in type 2 diabetes

NEW AND NOTEWORTHY

High-intensity interval training and moderate-intensity continuous training elicited faster pulmonary oxygen uptake ($\dot{V}O_2$) kinetics during moderate-intensity cycling within 3 weeks of training with no further changes thereafter in individuals with type 2 diabetes. These adaptations were accompanied by unaltered near-infrared spectroscopy-derived muscle deoxygenation (i.e. deoxygenated haemoglobin and myoglobin concentration, [HHb+Mb]) kinetics and transiently reduced Δ[HHb+Mb]-to-$\Delta\dot{V}O_2$ ratio, suggesting an enhanced blood flow distribution within the active muscles subsequent to both training interventions.

Abstract

We assessed the time course of changes in oxygen uptake ($\dot{V}O_2$) and muscle deoxygenation (i.e., deoxygenated haemoglobin and myoglobin, [HHb+Mb]) kinetics during transitions to moderate-intensity cycling following 12-weeks of low-volume high-intensity interval training (HIIT) vs. moderate-intensity continuous training (MICT) in adults with type 2 diabetes (T2D). Participants were randomly assigned to MICT (*n*=10, 50 min of moderate-intensity cycling), HIIT (*n* =9, 10x1 min at ~90% maximal heart rate) or non-exercising control (*n*=9) groups. Exercising groups trained 3 times per week and measurements were taken every 3 weeks. [HHb+Mb] kinetics were measured by near-infrared spectroscopy at the vastus lateralis muscle. The local matching of O_2 delivery to O_2 utilization was assessed by the Δ[HHb+Mb]/$\Delta\dot{V}O_2$ ratio. The pretraining time constant of the primary phase of $\dot{V}O_2$ ($\tau\dot{V}O_{2p}$) decreased ($P<0.05$) at wk 3 of training in both MICT (from 44±12 to 32±5 s) and HIIT (from 42±8 to 32 ± 4 s) with no further changes thereafter; while no changes were reported in controls. The pretraining overall dynamic response of muscle deoxygenation (τ'[HHb+Mb]) was faster than $\tau\dot{V}O_{2p}$ in all groups, resulting in Δ[HHb+Mb]/$\dot{V}O_{2p}$ showing a transient "overshoot" relative to the subsequent steady-state level. After 3 wks, the Δ[HHb+Mb]/$\dot{V}O_{2p}$ overshoot was eliminated only in the training groups, so that τ'[HHb+Mb] was not different to $\tau\dot{V}O_{2p}$ in MICT and HIIT. The enhanced $\dot{V}O_2$ kinetics response consequent to both MICT and HIIT in T2D was likely attributed to a training-induced improvement in matching of O_2 delivery to utilization.

Keywords: muscle oxygenation, cycling, near-infrared spectroscopy, oxygen extraction, exercise tolerance.

Introduction

Exercise prescription is a well-established strategy, central in the treatment and management of T2D. Chronic exercise training serves to curtail the progression of the disease itself and to reduce the increased propensity of cardiovascular morbidity and mortality in this clinical population (22, 77). Despite this, adherence to exercise is low in T2D. This may be influenced by the increased perception of effort (23) and decreased exercise capacity/tolerance consistently shown in this population. Specifically, peak oxygen uptake ($\dot{V}O_{2peak}$) is reduced in individuals with T2D across all ages (4, 20, 36, 53, 54, 63) and in individuals with T2D under 60 years of age, the dynamic responses of $\dot{V}O_2$ during moderate-intensity exercise ($\dot{V}O_2$ kinetics) is blunted (i.e. slowed) as represented by a higher time constant of the primary phase of the $\dot{V}O_2$ response, $\tau\dot{V}O_{2p}$ (20). Such manifestations are of important clinical and functional relevance given that $\dot{V}O_{2peak}$ correlates strongly with all-cause mortality (77), and $\tau\dot{V}O_{2p}$, is an independent marker for, and recognized determinant of, exercise tolerance (24, 62, 78). The prolonged $\tau\dot{V}O_{2p}$ in T2D mandates the development of a larger O_2 deficit during submaximal exercise efforts, necessitating a greater reliance on anaerobic ATP resynthesis to generate sufficient ATP to sustain the activity (26) and contributes to premature muscle fatigue and exhaustion.

Although the mechanisms governing the impaired $\tau\dot{V}O_{2P}$ herein are not well understood, they are likely influenced, at least partly, by cardiovascular defects, for example impaired left ventricular filling (83, 84), and/or limitations in peripheral O_2 delivery/supply to contracting muscles in the lower limbs (8, 30, 31, 34, 38, 59), although restrictions in the oxygen extraction ability have also been reported (29, 65). Our laboratory recently showed a larger mismatch in local (microvascular) O_2 delivery to utilization in the quadriceps muscle in T2D compared with

healthy controls, which was accompanied with slowed $\tau\dot{V}O_{2p}$ (66). This was reflected by a greater ratio of change in near-infrared spectroscopy (NIRS)-derived deoxygenated hemoglobin and myoglobin concentration ([HHb+Mb] to change in $\dot{V}O_2$ (Δ[HHb+Mb]/$\Delta\dot{V}O_2$) (66). This is consistent with findings showing a transient lowering of capillary PO_2 at the onset of exercise in rodent models with T2D, thereby limiting O_2 transport from the capillary to the myocyte (10) as well as reduced microvascular blood flow responses during transitions to moderate-intensity cycling in adults with uncomplicated T2D (7).

Previous studies have shown that 12-weeks of traditional endurance training interventions, involving ~150 min of continuous exercise per week [intensities ranging from ~60 to 80% maximum heart rate (HR_{max})], improve $\tau\dot{V}O_{2p}$ during transitions to moderate-intensity cycling in T2D (11, 21, 37), that the magnitude of this change is not different for men and women, and that these effects are not related to changes in systemic cardiovascular dynamics (21). However, in light of the poor exercise engagement in this clinical cohort (76), with "lack of time" often cited as a key barrier (75), a great interest has emerged in low-volume high-intensity interval training (HIIT) interventions (involving ~75 min per week of intermittent vigorous exercise, typically including less than 15 min of high-intensity efforts per session (81)) due to their time efficient nature. While HIIT induces similar benefits in cardiorespiratory fitness as traditional longer duration aerobic continuous training interventions (17, 41, 64, 82), whether HIIT can elicit benefits in $\dot{V}O_2$ kinetics in T2D is unknown. Moreover, the time-course of effects and mechanisms underlying the benefits on $\dot{V}O_2$ kinetics following training in T2D is poorly understood. Accordingly, the primary aim of this study was to examine the time course and mechanisms of adaptation in the dynamic responses of $\dot{V}O_2$ during moderate-intensity cycling

subsequent to 12 weeks of HIIT and moderate-intensity [i.e., below ventilatory threshold (VT)] continuous training (MICT) interventions in individuals with uncomplicated T2D. We hypothesized that both interventions would speed the $\dot{V}O_2$ kinetics response and reduce the $\Delta[HHb+Mb]/\Delta\dot{V}O_2$ ratio (i.e. reflecting a better matching of O_2 delivery to O_2 utilization) early in training.

Methods

Participants

This study is part of a larger randomized controlled trial reported in a companion paper (18). Participants were recruited from the Diabetes Outpatient Clinics of St. Columcille's and St. Vincent's University Hospitals (Dublin) by advertisements placed on the notice boards. Participant's eligibility was initially checked following chart review. Specifically, participants were included if they had a clinical history of diabetes < 11 yr, were untrained and had HbA_{1c} levels of <10%. Participants were excluded if they were treated by exogenous insulin, were smokers, had a disease contraindicating physical training, or demonstrated evidence of renal, liver or cardiovascular disease. All individuals completed a 12-lead electrocardiogram treadmill stress test (Bruce protocol) at St. Columcille's Hospital prior to attending the laboratory tests.

Thirty four participants completed the baseline laboratory assessments (*see testing*) and were given opaque sealed envelopes randomly allocating them to one of the 3 intervention groups (MICT, initially n = 12; HIIT, initially n = 10; or Control, initially n = 12). Eight participants dropped out of the study for personal reasons unrelated to the experiment (MICT, n = 2; HIIT, n = 3; Control, n = 3). Participants in the Control group were offered re-randomisation to one of

the exercise training groups after the intervention period, of which 2 accepted (HIIT, $n = 2$) and subsequently completed the training intervention. The final study population consisted of 26 participants undergoing the intervention, of whom 2 underwent both Control and HIIT. Thus, 28 completed responses from the study intervention were included for statistical analysis (MICT, $n = 10$; HIIT, $n = 9$; Control, $n = 9$). All participants provided written informed consent prior to participation. The study was approved by the Faculty of Health Sciences' Research Ethics Committee, Trinity College Dublin, and St Vincent's Healthcare Ethics and Medical Research Committee, and conducted in accordance with the principles outlined by the Declaration of Helsinki.

Supervised exercise interventions

Overview. Participants in the HIIT and MICT groups carried out a 12-week supervised exercise intervention, training 3 times per week on non-consecutive days at a local health and fitness centre in Co. Dublin, whereas participants in the Control group received no intervention and continued with their normal daily routine. All exercise training sessions were supervised by a study investigator. Training intensity was adjusted at 3-week intervals (i.e. every 9 sessions) to reflect changes in fitness levels. Participants were equipped with a heart rate monitor (Cardiosport, USA) to adhere to the prescribed exercise intensity. Both exercise groups completed a 5 min warm up and 5 min cool down before and after each session on an aerobic machine of their choice (elliptical, treadmill, rowing or cycle ergometer). The main component of each training session was completed on a cycle ergometer as follows:

Low-volume high-intensity interval training: The HIIT group completed 10 x 60-s bouts of high-intensity cycling interspersed with 60-s of light cycling. The high-intensity bout was completed

147 at a power output equivalent to 70% of the difference between participant's peak power output
148 (PO_{peak}) and the power output at ventilatory threshold (VT) (70% Δ) achieved during the ramp
149 exercise test (see *testing*). This output was designed to elicit a target heart rate of ~90% HR_{max}
150 during the high-intensity bouts, whereby participants were expected to exercise in the severe-
151 intensity domain.
152
153 *Continuous training:* Each MICT session comprised of 50 minutes of cycling at a power output
154 equivalent to ~80-90% VT as calculated from the ramp test (see *testing*). The energy expenditure
155 from the supervised exercise sessions was estimated based on the American College of Sports
156 Medicine's equation (19).
157
158 *Testing*
159 Initially, physical activity levels were assessed by the use of 5-day RT3 triaxial accelerometry
160 (Stayhealthy Inc, CA) (Table 1). The threshold for sedentary or inactive behaviour (<1.5
161 metabolic equivalents or METs) was set as < 100 counts/min (5), counts/min between 101 and
162 1317 were considered light activity (1.5-3 METs); and counts/min >1317 corresponded to
163 moderate-to-vigorous physical activity (>3 MET) (68). Then, prior to the commencement of, and
164 every 3 weeks throughout the intervention, participants were required to attend the exercise
165 testing facility in St. Columcille's Hospital on two separate occasions to complete a ramp
166 incremental test to exhaustion and 2-4 bouts of constant-load moderate-intensity cycling. For
167 each participant all tests were performed at the same time of day. All exercise tests were carried
168 out in an upright position on an electrically braked cycle ergometer (Excalibur Sport; Lode B.V.,
169 Groningen, Netherlands). Participants were asked to refrain from consuming alcohol, caffeine

and non-prescribed nutritional supplements as well as avoiding any strenuous exercise in the 24 hours prior to testing. At baseline (pretraining) and at the end of the intervention period (posttraining) fasting venous blood samples were collected to assess glycosylated haemoglobin (HbA_{1c}). Participants were familiarised with the ramp incremental test and constant-load tests prior to commencing the intervention.

Ramp incremental cycling tests: The test started with an initial workload of 10 W for 2 min (i.e. 'unloaded' cycling). This was followed by 10-25 W/min increments in power output based on participants' activity levels. Pedalling rate was held constant at an individually selected cadence between 60-75 revolutions per minute (rpm) and was maintained throughout all further testing. Failure/exhaustion in a test was determined as a drop in cadence exceeding 10 rpm for >5 s. Peak workload was the power output achieved at the point of failure. $\dot{V}O_{2peak}$ was the highest $\dot{V}O_2$ value (15-s average) attained during the test. The first ventilatory threshold (VT) was determined by two investigators using the V-slope method as previously described (9).

Moderate-intensity cycling exercise transitions: All participants performed 2-4 bouts of constant-load moderate-intensity cycling at 80% of each participant's VT obtained during the ramp incremental test at the pretraining time point, so that for each participant the same absolute power output was used at all 5 time points during the intervention. The duration of each step transition was 6 min and each transition was preceded by a 3 min 'baseline' cycling period at 10W. There was at least a 15 min rest period between consecutive cycling bouts. Due to time constraints, in 30% of the laboratory visits 2 moderate-intensity bouts were completed, while in the rest of the visits 3-4 transitions were completed. Heart rate (HR), gas exchange/ventilatory

variables and muscle oxygenation & deoxygenation were continuously measured during each cycling bout.

Measurements

During exercise, participants wore a facemask to continuously collect expired air using an online metabolic system (Innocor, Innovision A/S, Odense, Denmark) that measured airflow using a pneumotachometer. Carbon dioxide analysis was performed by using a photoacoustic gas analyzer and oxygen was analyzed using an oxygen sensor (Oxigraf Inc., USA) based on the principle of laser diode absorption spectroscopy. The system was calibrated prior to each test as per manufacturer's recommendations. Both the oxygen sensor and photoacoustic gas analyser require multi-point calibration that is routinely performed by the manufacturer every 6-12 months. Analysis of expired air allowed determination of pulmonary O_2 uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$) and the respiratory exchange ratio (RER) breath-by-breath. Heart rate (HR) was recorded every 5 s (Polar S610i, Polar Ltd, Finland), with peak HR (HR_{peak}) defined as the highest HR attained within the last 15 s of termination of the test. Peak O_2 pulse was calculated as $\dot{V}O_{2peak}/HR_{peak}$.

A continuous wave NIRS system (Hamamatsu Niro 200Nx; Hamamatsu Photonics, Hamamatsu, Japan), was used to determine muscle oxygenation status non-invasively through the spatially resolved spectroscopy technique and modified Beer-Lambert principle, with three wavelengths of emitting light (λ = 735, 810, and 850 nm). The theoretical basis of NIRS and its use in exercise measurements have been described in detail elsewhere (14) but briefly, this technique estimates the optical density changes of oxygenated (O_2Hb+Mb) and deoxygenated haemoglobin

and myoglobin (HHb+Mb) based on the oxygen dependency of absorption changes for near-infrared light in these proteins. As the vastus lateralis (VL) muscle is a dominant locomotor muscle during cycling, the present study examined the Δ[HHb+Mb] profiles of the right VL muscle. After shaving, cleaning and drying the skin, the probes were placed on the belly of the muscle, 10-16 cm above the lateral femoral condyle, parallel to the major axis of the thigh with a 3 cm spacing between the emitter and receiver. The probes were housed in a black rubber holder and secured on the skin surface with bi-adhesive tape and then covered with a dark elastic bandage, which minimised extraneous movement and the intrusion of stray light throughout the exercise protocol. Since the depth of the measured area was estimated to be approximately one-half the distance between the emitter and the receiver (~1.5 cm), the present study determined the thickness of the skin and adipose tissue at the site of the probe placement via 2D ultrasound operating in B-mode (Zonare Ultra Smart Cart, Software version 4.7, USA), to ensure that data largely represented absorption of near-infrared light in muscle tissue and not in subcutaneous fat. Individuals presenting with adiposity >1.5 cm over the site of interrogation on the VL were excluded from the study.

Data Analysis

$\dot{V}O_2$ Kinetics: The breath-by-breath $\dot{V}O_2$ data for each transition were linearly interpolated to provide second-by-second values and time aligned such that time 0 represented the onset of exercise. Data from each transition were ensemble-averaged to yield a single, average response for each individual and further time-averaged into 5 s bins (27). Data were then fitted to a monoexponential function (eq. 1) or biexponential function (eq. 2). By visual inspection, the majority of the 140 responses (90%) consisted of a single (primary) phase and were fitted to eq.

1. The remaining responses (10%) displayed a second phase ("slow component") and were fitted to eq. 2. This second phase was observed in 14 responses (from 9 participants, Control, n = 3; HIIT, n = 3; MICT, n = 3), had a mean amplitude of 76 mL/min (SD = 21 mL/min), was only observed among control participants beyond week 3 of the intervention, and was likely due to the fact that in the present study the mean response times of $\dot{V}O_2$ during the ramp cycle exercise were not accounted for when calculating the target power outputs (28). The equations are as follows:

Equation 1 $$\dot{V}O_2(t) = \dot{V}O_2\,\text{baseline} + A_p[1\text{-}e^{-(t\text{-}TDp)/\tau p)}]\cdot F1$$

Equation 2 $$\dot{V}O_2(t) = \dot{V}O_2\,\text{baseline} + A_p[1\text{-}e^{-(t\text{-}TDp)/\tau p)}]\cdot F1 + A_s[1 - e^{-(t - TDs)/\tau s)}]\cdot F2$$

where $\dot{V}O_2(t)$ represents the absolute $\dot{V}O_2$ at a given time t; $\dot{V}O_2$ baseline is the mean $\dot{V}O_2$ in the final 30 s of unloaded cycling; A_p and $A_{s,}$ are the amplitudes of the increase in $\dot{V}O_2$ of the primary and slow component phases respectively; TD_p and TD_s are the phase delays, and τ_p and τ_s are the time constants, defined as the duration of time for which $\dot{V}O_2$ increases to a value equivalent to 63% of the amplitude. The conditional expressions F1 and F2 limit the fitting of the phase to the period at and beyond its time delay. The first 20 s of data after the onset of exercise (i.e., the phase I $\dot{V}O_2$ response) were deleted, and while still allowing TD to vary freely (to optimize accuracy of parameter estimates), $\dot{V}O_2$ data were modelled from 20 s to 360 s of the step transition to ensure that each subject had attained a $\dot{V}O_2$ steady state (51). So, in this approach the TD is not used as a proxy for, nor is it synonymous with, phase I duration (51). Fitting used a weighted least-squares non-linear regression procedure (TableCurve 2D, Systat, USA) performed in 2 steps, with outliers (>95% prediction interval) removed after the initial fit

of a model. Parameter estimates of the best-fit function were used and only estimates representing the primary phase are presented. Whilst the presence of a slow component was detected in 14 responses, the presence of this phase does not appear to significantly affect the parameter estimates of the earlier phases (79). The end-exercise $\dot{V}O_2$ response, referred to as End-exercise A, was calculated as the averaged $\dot{V}O_2$ over the last 30 s of the primary $\dot{V}O_2$ response. The functional "gain" of the primary $\dot{V}O_2$ response was calculated as the difference between End-exercise A and $\dot{V}O_2$ baseline normalized to the difference in power outputs between the moderate-intensity exercise and unloaded cycling.

Deoxygenated haemoglobin/myoglobin [HHb+Mb] kinetics. To provide information on muscle deoxygenation throughout the protocol, we modelled the [HHb+Mb] response to exercise. As per the $\dot{V}O_2$ data, the NIRS-derived Δ[HHb+Mb] data for each transition were linearly interpolated to provide second-by-second values and time aligned. Data from each transition were ensemble-averaged to yield a single average response for each individual, and further time-averaged into 5 s bins. A time delay (TD) at the onset of exercise occurs in the [HHb+Mb] profiles before they increase. [HHb+Mb] data were fitted from the end of the TD to 180 s using *equation 1* as per $\dot{V}O_2$. The shorter fitting window of 180 s was selected to counteract the previously reported variations in the NIRS signal between 180-360 s from exercise onset (also observed herein), from impacting the fitting of the on-transient response whilst permitting the reaching of a steady-state (15, 16, 50). The time course for the increase in Δ[HHb+Mb] can be described by the τΔ[HHb+Mb], however, the time course for the overall change of the Δ[HHb+Mb] responses, referred to as the effective response time (τ'Δ[HHb+Mb]) was determined from the sum of the time delay and τ from the onset of exercise. Changes in total

285 blood volume were assessed by summing the [oxyHb+Mb] and [HHb+Mb] signals to provide an
286 estimate of total[Hb+Mb] in the area under investigation. Specifically, Δ total[Hb+Mb] was
287 calculated as the difference between baseline (30 s prior to each transition) and end-exercise
288 (final 30 s) values.
289
290 *Δ[HHb+Mb]/Δ$\dot{V}O_2$ ratio*. To calculate the Δ[HHb+Mb]/Δ$\dot{V}O_2$ ratio (49, 50) individual second-
291 by-second Δ[HHb+Mb] and $\dot{V}O_2$ data were firstly normalised (from 0%, corresponding to the
292 pre-transition 10W baseline value to 100% reflecting the steady-state within the initial 180 s for
293 Δ[HHb+Mb] or the steady-state of the primary $\dot{V}O_2$ response for $\dot{V}O_2$ data). Then, Δ[HHb+Mb]
294 and $\dot{V}O_2$ were time aligned by left-shifting the normalised $\dot{V}O_2$ data by 20 s, accounting for the
295 approximate duration of the cardiodynamic phase, to ensure that the onset of exercise coincided
296 with the beginning of the primary phase of $\dot{V}O_2$. The normalised and time aligned data was then
297 further averaged into 5 s bins for statistical comparisons. The overall Δ[HHb+Mb]/Δ$\dot{V}O_2$ ratio
298 for the adjustment during the exercise on-transient was derived for each individual as the mean
299 value from 20-150 s into the transition. The commencement point of 20 s was selected to begin
300 beyond the physiological TD Δ[HHb+Mb], with the 150 s end point indicative of the time point
301 at which a steady-state value of 1.0 had been achieved by the Δ[HHb+Mb]/Δ$\dot{V}O_2$ ratio (50).
302 Values > 1.0 represent a time period whereby during the exercise transition there was a greater
303 reliance on fractional O_2 extraction compared with the exercise steady-state (values = 1.0), thus
304 reflecting a poorer local O_2 delivery relative to muscle O_2 utilisation in the area of NIRS
305 interrogation.
306

Statistical Analysis

Physical characteristics and activity levels at baseline among groups were compared using a one-way ANOVA. Peak physiological responses as well as changes in total [HHb+Mb], the normalized Δ[HHb+Mb]/$\Delta\dot{V}O_2$ ratio and kinetics parameter estimates for $\dot{V}O_2$ and [HHb+Mb] during moderate-intensity exercise throughout the intervention were compared using a two-factor [time (pretraining, week 3, week 6, week 9, posttraining) vs. group (HIIT, MICT, CON)] mixed ANOVA. Body mass and HbA_{1c} results were also compared using a two-factor [time (pretraining, posttraining) vs. group (HIIT, MICT, CON)] mixed ANOVA. Differences were detected using a Student-Newman-Keuls *post hoc* test. To assess whether the Δ[HHb+Mb]/$\Delta\dot{V}O_2$ ratio was different from 1 (i.e. to identify if there was a mismatch between local O_2 delivery relative to muscle O_2 utilisation) a Student's t-test was used. Finally, correlations between training-induced changes in $\tau\dot{V}O_{2p}$ and changes in Δ[HHb+Mb]/$\Delta\dot{V}O_2$ ratios were established using the Pearson product-moment correlation coefficient (Pearson r). Significance was set at $P < 0.05$. All values are expressed as mean ± standard deviation (SD).

Results

Physical characteristics, pretraining peak exercise values and activity levels.

Participants' physical characteristics, peak exercise values and activity levels at baseline are presented in Table 1. There was a significant time x group interaction ($P = 0.022$) for body mass so that posttraining body mass was reduced ($P = 0.001$) in the MICT group (pre = 90.3 ± 18.6 kg, post = 87.2 ± 17.2 kg) but not in the HIIT (pre = 87.5 ± 12.4 kg, post = 86.5 ± 12.2 kg) or control (pre = 86.0 ± 14.0 kg, post = 86.4 ± 15.6 kg) groups. HbA_{1c} (%) (time x group interaction, $P < 0.012$) was reduced in the MICT (pre = 6.9 ± 0.5%, post = 6.6 ± 0.4%) and HIIT

groups (pre = 7.3 ± 0.5%, post = 7.0 ± 0.6%) but not in the control (pre = 6.8 ± 1.0%, post = 7.0 ± 1.0%) group.

Exercise adherence, caloric expenditure and work done

The mean exercise adherence was 94 ± 6% (range 31-36 sessions) and 98 ± 4% (range 32-36 sessions) in the HIIT and MICT groups respectively. The average training intensity (power output) increased significantly ($P < 0.05$) every 3 weeks (i.e. after each laboratory testing session) in the MICT group (weeks 1–3, 79 ± 29 W; weeks 4–6, 106 ± 39 W; weeks 7–9, 117 ± 42 W; weeks 10-12, 128 ± 42 W) while it also significantly increased every 3 weeks until week 9, but not between week 9 and 12 ($P = 0.24$) in the HIIT group (weeks 1–3, 166 ± 45 W; weeks 4–6, 181 ± 46 W; weeks 7–9, 193 ± 46 W; weeks 10-12, 197 ± 45 W). The average energy expenditure and total work done per training session (including the warm up) was ~228 kcal and ~165 kJ for the HIIT group, and ~478 kcal and ~326 kJ for the MICT group. No adverse training effects to training were observed throughout the intervention period in either exercising group.

Peak physiological responses from ramp incremental cycling

For absolute $\dot{V}O_{2peak}$ (L/min), as well as $\dot{V}O_{2peak}$ normalised to body (mass $mL.kg^{-1}.min^{-1}$), there was a significant time x group interaction ($P < 0.001$), so that $\dot{V}O_{2peak}$ did not increase in the control group ($\dot{V}O_{2peak}$ at pretraining = 1.86 ± 0.52 L/min; 21.5 ± 3.6 $mL.kg^{-1}.min^{-1}$), but it significantly increased after 3 weeks of MICT (from 2.14 ± 0.69 to 2.48 ± 0.65 L/min; and from 22.8 ± 4.4 to 27.0 ± 5.0 $mL.kg^{-1}.min^{-1}$) and HIIT (from 2.31 ± 0.51 to 2.50 ± 0.56 L/min; and from 26.4 ± 4.0 to 28.5 ± 4.2 $mL.kg^{-1}.min^{-1}$). There were no further significant changes in $\dot{V}O_{2peak}$ thereafter ($\dot{V}O_{2peak}$ at posttraining for MICT = 2.62 ± 0.72 L/min; 28.6 ± 4.7 $mL.kg^{-}$

353 ^{1}.min^{-1} and for HIIT = 2.62 ± 0.58 L/min; 30.0 ± 4.0 mL.kg^{-1}.min^{-1}). HR_{peak} did not change
354 throughout the intervention in any of the groups (pretraining HR_{peak} were, MICT = 159 ± 15
355 beats/min; HIIT = 162 ± 13 beats/min and Control = 164 ± 13 beats/min). Consequently, peak O_2
356 pulse significantly increased after 3 weeks of MICT and HIIT (13.5 ± 4.2 to 15.8 ± 3.7 mL/beat
357 and 14.4 ± 3.3 to 15.2 ± 3.6 mL/beat respectively) with no further changes thereafter (peak O_2
358 pulse at posttraining were 16.5 ± 4.3 and 16.3 ± 4.0 mL/beat, respectively), but it did not change
359 (time x group interaction, $P < 0.01$) in the control group (peak O_2 pulse at pretraining = 11.3 ±
360 3.2 mL/beat). $\dot{V}O_2$ responses (L/min) at VT also significantly increased after 3 weeks of MICT
361 (from 1.56 ± 0.51 to 1.67 ± 0.43 L/min) and HIIT (from 1.73 ± 0.40 to 1.85 ± 0.38 L/min) and
362 they further significantly increased from week 3 to 6 (1.92 + 0.55 L/min) in the MICT group and
363 week 3 to 9 (2.02 + 0.41 L/min) in the HIIT group with no further changes thereafter. $\dot{V}O_2$ at VT
364 did not change in the control group ($\dot{V}O_2$ at VT at pretraining = 1.31 ± 0.30 L/min).
365
366 *$\dot{V}O_2$ kinetics*
367 Individual $\tau\dot{V}O_{2p}$ responses throughout the intervention period are shown in Fig 1, while mean
368 $\tau\dot{V}O_{2p}$ values are summarised in Table 2 and Fig 2A. Pretraining $\tau\dot{V}O_{2p}$ values were not different
369 among the 3 groups. After 3 weeks of training, $\tau\dot{V}O_{2p}$ was significantly reduced in both the HIIT
370 and MICT groups with no further significant changes thereafter. In contrast, $\tau\dot{V}O_{2p}$ was not
371 changed throughout the 12 week period in the control group (time x group interaction, $P < 0.01$).
372 The $\dot{V}O_2$ at baseline, the amplitude of increase in $\dot{V}O_2$, end-exercise $\dot{V}O_2$ amplitude or the
373 functional $\dot{V}O_2$ gain were not different among groups and did not change throughout the
374 intervention (Table 2). There was a main effect of time ($P < 0.05$) for $\dot{V}O_2$ TD so that it was
375 larger at all time points than pretraining.

376

377 *Muscle deoxygenation kinetics, total[Hb+Mb] and normalized Δ[HHb+Mb]/Δ$\dot{V}O_2$ ratio index*

378 The effective response times of muscle deoxygenation (τ'[HHb +Mb]) as well as normalized
379 Δ[HHb+Mb]/Δ$\dot{V}O_2$ ratios are displayed in Table 3 and Fig 2 (panels B & C). The normalised
380 adaptation of Δ[HHb+Mb] and $\dot{V}O_2$ and the corresponding Δ[HHb+Mb]/Δ$\dot{V}O_2$ ratios for
381 representative individuals from each group, at each time point throughout the intervention are
382 shown in Fig 3. The baseline Δ[HHb+Mb], time delay-Δ[HHb+Mb], τ[HHb +Mb],
383 τ'[HHb+Mb], the change in total[Hb+Mb] or the ratio of the modelled amplitudes of Δ[HHb +
384 Mb]/Δ$\dot{V}O_{2p}$ were not different among groups and did not change throughout the intervention
385 (Table 3). There was a main effect of group ($P < 0.05$) for the amplitude of the increase as well
386 as end-exercise amplitude of Δ[HHb+Mb], so that they were larger in the HIIT group compared
387 with the other 2 groups. At pretraining, τ'[HHb +Mb] was shorter ($P < 0.05$) than τ$\dot{V}O_{2p}$ in all
388 groups, which induced a transient overshoot in the estimated normalized Δ[HHb + Mb]/Δ$\dot{V}O_2$
389 ratio (relative to the steady-state ratio of 1.0) (Table 3, Fig 2C). After 3 weeks of HIIT and
390 MICT, τ'[HHb + Mb] and τ$\dot{V}O_{2p}$ were not different and they remained as so throughout the
391 intervention. Similarly, by week 3 of training, the Δ[HHb + Mb]/Δ$\dot{V}O_2$ overshoot was eliminated
392 (i.e. it was not different from 1.0) in both training groups and remained that way for the rest of
393 the intervention. In contrast, in the control group τ$\dot{V}O_{2p}$ remained longer ($P < 0.05$) than τ'[HHb
394 +Mb] throughout the intervention period and was accompanied with a Δ[HHb + Mb]/Δ$\dot{V}O_2$
395 overshoot. In addition, in all participants, the percentage change in τ$\dot{V}O_{2p}$ was significantly
396 correlated with the percentage change in the normalized Δ[HHb + Mb]/Δ$\dot{V}O_2$ ratio at week 3 (r
397 = 0.46, $P = 0.02$), week 9 (r = 0.53, $P < 0.01$), and posttraining (r = 0.5, $P < 0.01$), but not at
398 week 6 (r = 0.23, $P = 0.25$). However, within each group or among the 2 exercising groups

399 together, the percentage change in $\tau\dot{V}O_{2p}$ was not significantly correlated with the percentage
400 change in the normalized Δ[HHb + Mb]/$\Delta\dot{V}O_2$ ratio at any time point.
401
402 **Discussion**
403 To our knowledge, this is the first study to assess the time-course of effects on $\dot{V}O_2$ kinetics
404 following exercise training in T2D, in addition to comparing these effects between MICT vs
405 low-volume HIIT. The principal findings of the present study were that both low-volume HIIT
406 and MICT significantly reduced $\tau\dot{V}O_{2p}$ during a transition to moderate-intensity cycling by
407 week 3 of training and that these effects were accompanied with a simultaneous reduction in the
408 normalized Δ[HHb + Mb]/$\Delta\dot{V}O_2$ ratio, suggestive of improvements of microvascular blood flow
409 delivery. These benefits in $\tau\dot{V}O_{2p}$ and microvascular blood flow delivery followed a similar time
410 course, being of a magnitude that was not different between exercising groups and were
411 maintained for the remainder of the intervention without further improvements.
412
413 The increased $\dot{V}O_{2peak}$ responses observed in the HIIT and MICT groups demonstrate the
414 effectiveness of both training protocols compared with the non-exercising control group. While
415 performing an additional incremental test and/or verification test at each time point would have
416 been beneficial to add confidence in this outcome, the training-induced increases in $\dot{V}O_{2peak}$ were
417 apparent without any changes in HR_{peak}. Thus, the improvement in $\dot{V}O_{2peak}$ appears to be more
418 likely due to physiological factors rather than motivational factors which verification testing
419 attempts to control for. In this regard, the rapid improvement in cardiorespiratory fitness is of
420 great clinical relevance, given that improvements in cardiorespiratory fitness are associated with
421 reduced mortality risk (67). That in the present study, both HIIT and MICT also significantly

reduced HbA1c, an indicator of long-term glycaemic control, is also of major clinical significance, as a 1% decrease in HbA1c can result in up to 15-20% reduction in major cardiovascular events (71) and up to 37% reduction in microvascular complications (74). On the other hand, the fact that only the MICT group significantly reduced whole body mass herein was likely related to the larger energy expenditure during the actual MICT exercise sessions. In contrast, Winding et al. (85) observed significant reductions in whole body mass following low-volume HIIT but not continuous aerobic training (50% PO_{peak}) in uncomplicated T2D, despite a 36% higher energy expenditure during the MICT intervention, and Madsen et al (41) also reported significant whole body mass reductions subsequent to low-volume HIIT in T2D. These authors highlighted that the significant weight loss associated with HIIT could be related to an increased energy expenditure in the recovery phase of the HIIT sessions and higher production of plasma catecholamine levels during HIIT, inducing lipolysis post exercise. However, neither these studies nor the present study monitored energy intake and physical activity counts throughout the interventions, so, further research is needed to determine the physical and metabolic impact of compensatory behavioural changes consequent to different exercise training interventions in T2D.

In the present study, both interventions significantly reduced $\tau\dot{V}O_{2p}$ after the 12 week intervention period by a magnitude that was not different between them (42% MICT; 36% HIIT). These findings cohere with previous studies showing significant improvements in $\tau\dot{V}O_{2p}$ during moderate-intensity cycling in men and women with T2D, following aerobic continuous training (~60 to 80% HR_{max}) interventions of similar duration (11, 21, 37). Importantly, the present study showed that the greatest reduction in $\tau\dot{V}O_{2p}$ occurred after just 3 weeks of training,

445 (26% MICT; 24% HIIT), with no further significant changes thereafter despite progressive
446 increases in training intensity. While these time course of adaptations in $\tau\dot{V}O_{2p}$ herein have not
447 been reported in T2D, they are overall in agreement with observations in older untrained
448 individuals following 12 weeks of aerobic continuous training (~70% $\dot{V}O_{2max}$). Specifically,
449 older males and females presenting with an initially slowed $\tau\dot{V}O_{2p}$ (43 and 55 s, respectively)
450 experienced significant reductions in $\tau\dot{V}O_{2p}$ (19% and 33% respectively) within 3 weeks (after
451 completing 6 exercise sessions) of their intervention with no further changes thereafter (48, 49).
452 On the other hand, interestingly, McKay et al. (44) demonstrated among recreationally active
453 young males, that only 2 sessions of aerobic continuous training (~65% $\dot{V}O_{2max}$) or low-volume
454 HIIT elicited a significant improvement in $\tau\dot{V}O_{2p}$ during moderate-intensity cycling (17 and
455 19%) and that $\tau\dot{V}O_{2p}$ responses were further reduced (41% and 39%) posttraining (after 8
456 exercise sessions). Further studies are needed to establish the shorter (<3 weeks) time-course
457 effects of MICT vs HIIT in T2D.
458
459 Given that the training volume herein was ~50% lower in the HIIT compared with the MICT
460 group, it would appear that the specific nature of the training was more important than the total
461 volume in speeding the $\dot{V}O_2$ kinetics response. It is possible that the high rates or 'steps' of
462 muscle fiber recruitment and repetitive shear stress during the HIIT exercise sessions influenced
463 the current outcome (39). However, it remains unclear why a levelling off in the $\dot{V}O_2$ kinetics
464 adaptations beyond 3 weeks of training was observed in both exercising groups herein despite
465 progressive adjustments in exercise intensity; a phenomenon also previously observed among
466 older untrained participants following aerobic continuous training (48, 49). It is noteworthy that
467 herein, $\dot{V}O_{2peak}$ responses also levelled off beyond the initial weeks of training, which is

consistent with findings by Astorino et al. (3) among healthy individuals during short-term low-volume HIIT. In a follow-up study, Astorino and colleagues (2) showed that in order to further increase $\dot{V}O_{2max}$ beyond the initial 3-4 weeks of low-volume HIIT training, a modification in the structure (i.e. employing sprint interval training sessions), rather than in the volume (i.e. increasing the duration of each interval within the sessions) of training was needed (2). It is possible that this would plausibly apply to $\dot{V}O_2$ kinetics adaptations at least following HIIT, given both parameters are influenced by the interaction of mechanisms of muscle oxygen delivery and utilization.

The underlying physiological mechanisms responsible for the improved $\dot{V}O_2$ kinetics with training must influence the rates of change of O_2 delivery to the working muscle, be that perfusively or diffusively, and/or utilisation therein (61). In the present study we measured the dynamic responses of the NIRS-derived [HHb+Mb] alongside $\dot{V}O_2$ to estimate the training-induced effects on microvascular oxygen delivery/utilization within the active musculature. When applying this measure simultaneously with $\dot{V}O_2$ kinetics measurements, our laboratory recently showed that the rate of adjustment in the NIRS-derived [HHb+Mb] was faster than the adjustment in $\tau\dot{V}O_{2p}$ in uncomplicated T2D, suggesting an over reliance in fractional oxygen extraction and thus, a reduced blood flow response (66). Findings in keeping with T2D-induced impairments in the dynamic response of vasodilation and matching of capillary blood flow to metabolism in contracting myocytes (30, 38, 57, 58, 60). Herein, in agreement with studies on untrained older (48, 49) as well as young (44, 80) participants, despite the significant speeding of $\tau\dot{V}O_{2p}$, the overall dynamic response of muscle deoxygenation (τ'[HHb+Mb]) as well as the amplitude of the [HHb+Mb] response and the Δ total[HH+Mb] were not affected by training in

either group at any time point, implying that training-induced decreases in $\tau\dot{V}O_{2p}$ were likely explained by greater muscle blood flow and O_2 delivery relative to muscle O_2 demand rather than greater overall blood volume and O_2 content. To better elucidate this, we assessed the Δ[HHb+Mb]/$\Delta\dot{V}O_2$ profile, an index indicative of the degree of O_2 extraction required for a given increment in $\dot{V}O_2$ (13, 49, 50). We observed, as expected (66), that all 3 groups displayed a transient overshoot (relative to the steady-state ratio of 1.0) at the pretraining time point. However, by week 3, this transient overshoot was abolished in the MICT and HIIT groups and remained as so throughout the intervention; while the overshoot persisted at all time points in the non-exercising controls. Furthermore, after 3 weeks of exercise training, even if the τ'[HHb+Mb] values were unchanged from pretraining values, they were not different to $\tau\dot{V}O_{2p}$ and remained that way until the completion of the intervention. These findings reinforce the notion that both exercise interventions improved $\tau\dot{V}O_{2p}$, at least in part, by enhancing the dynamic matching of local blood flow and O_2 supply relative to demand within the active muscle. It must be acknowledged, however, that the demonstration of this greater muscle O_2 delivery relative to $\dot{V}O_2$ herein, does not exclude the possibility that training also enhanced mitochondrial $\dot{V}O_2$ dynamics inherently, and subsequently increased oxidative capacity (35).

Whether the training-induced rapid blood flow adaptations in the microvasculature of active muscles observed herein are also apparent at a systemic level in T2D remains to be established. For instance, consequent to 12 weeks of aerobic continuous training (~70-80% HR_{max}), MacAnaney et al. (37) demonstrated accelerated $\tau\dot{V}O_{2p}$ responses which were accompanied by a more rapid rate of increase in cardiac output during submaximal cycling using, as was the case in the present study, the same absolute intensities before and after training (80% VT of pretraining

514 $\dot{V}O_{2peak}$). However, a limitation therein was the fact that cardiac output responses were recorded
515 only at 2 time points (at 30 s and 240 s) during each bout. In contrast, a more recent study has
516 shown unaltered cardiac output dynamic responses (again, based on recordings taken at the same
517 2 time points) despite observing significant improvements in $\dot{V}O_2$ kinetics during submaximal
518 efforts, but performed at the same relative intensity before and after training (i.e. 80% VT of
519 time specific $\dot{V}O_{2peak}$) (21). On the other hand, whether both training modalities improve the
520 dynamic response of vasodilation (i.e. vascular conductance) of conduit arteries feeding the
521 active muscles has not been studied in T2D, but unpublished observations from our laboratory
522 suggest that leg vascular conductance kinetics responses during high-intensity calf plantar-
523 flexion exercise are enhanced after 12 weeks of MICT in men and women with T2D. This is
524 consistent with Shoemaker et al (73) who demonstrated among non-diabetic healthy participants
525 a rapid enhanced femoral artery vascular conductance kinetics following 10 MICT exercise
526 sessions.
527
528 It is likely that vascular functional and structural improvements contributed to changes in the
529 training-induced microvascular oxygen delivery/utilization profile herein. For instance, both
530 low-volume HIIT and aerobic continuous training improve endothelial function assessed by
531 brachial artery flow mediated dilation (40, 46, 70). In addition, short-term HIIT induces
532 increases in brachial artery outwards remodelling (40) and diameter (12), while short-term
533 aerobic continuous training (50% PO_{peak}) as well as longer term HIIT-style soccer training
534 increase the capillary-to-fibre ratio within the VL muscle (1, 47). Although further studies are
535 needed to better establish how low-volume HIIT and MICT impact these vascular adaptations,
536 they seem to be attributed to reduction in localised oxidative stress within the vasculature and/or

537 enhanced capillary-to-myocyte interface for tissue perfusion and substrate delivery possibly by
538 increasing the proportion of red blood cell-flowing capillaries in the exercising muscle which is
539 reduced in T2D, at least in animal models (56). Other important mechanisms potentially at play,
540 relate to training-induced adaptations in skeletal muscle fibre oxidative capacity. Specifically,
541 both, short to medium-term aerobic continuous training (~55-75% $\dot{V}O_{2max}$) as well as low-
542 volume HIIT enhance the oxidative capacity of skeletal muscles (35, 45, 72) and increase the
543 total mitochondrial content (33, 52) in individuals living with T2D.
544
545 *Limitations*
546 A number of limitations of the present study must be acknowledged. First, while it would have
547 been relevant to assess 3 additional non-diabetic control groups (HIIT, MICT and Con) to
548 compare how changes in $\dot{V}O_2$ kinetics among healthy individuals compare with those in people
549 with T2D following the same exercise training interventions, this was not feasible given the very
550 large time commitment associated with the current intervention. Future studies should attempt to
551 compare these responses between individuals with T2D and healthy controls. Second, the NIRS-
552 derived findings herein relate to a single muscle, the VL, and therefore, interpretation of this data
553 is limited to the site of interrogation. In addition potential structural (vascularity and fibre type)
554 (25), and functional (fibre recruitment, vascular control and blood flow) (32, 43) differences
555 therein are acknowledged, as well as temporal and spatial heterogeneity in NIRS-derived
556 responses extant both among and within muscles (55, 69). Third, the fact that 2 participant were
557 re-randomized into one of the training groups might be considered a limitation of the study. We
558 believe, however, that this does not influence the findings of the current study given that when
559 data from these 2 control participants (who accepted re-randomization and completed one of the

560 interventions) were eliminated from the control group, the main outcomes of the study were
561 unaffected. Finally, even if some of the participants completed only 2 exercise transitions, the
562 CI_{95} for $\tau\dot{V}O_{2P}$ were not affected when comparing values from participants who completed 2 vs
563 3-4 constant-load transitions (4.0 ± 1.01 vs 4.0 ± 1.70 s, respectively), therefore, the potential
564 impact of performing a lower number of transitions on the signal-to-noise ratio of the $\dot{V}O_2$
565 response was not a confounding factor.
566
567 *Conclusions*
568 In the present study the time course and magnitude of changes in $\tau\dot{V}O_{2p}$ were similar following
569 both low-volume HIIT and MICT interventions. The improvements in $\tau\dot{V}O_{2p}$ were accompanied
570 by simultaneous reductions in the initial transient overshoot in the Δ[HHb+Mb]/$\Delta\dot{V}O_2$ profile,
571 suggesting that both exercise interventions improved $\tau\dot{V}O_{2p}$, at least in part, by enhancing blood
572 flow distribution at the level of the microvasculature within the active muscle. Thus, it appears
573 that training adaptations induced by HIIT and MICT in individuals with uncomplicated T2D, are
574 equally capable of rapidly attenuating some local limiting factors governing the initially
575 impaired $\dot{V}O_2$ kinetics response during submaximal exercise efforts. The specific focus on the
576 transition to moderate-intensity exercise is of great functional relevance, given its transferability
577 to the metabolic transitions performed on a day-to-day basis, which are perceived as being more
578 difficult in individuals with T2D than healthy counterparts (23). As such, a faster provision of
579 aerobic metabolism would serve to reduce premature muscle fatigue during light- to moderate-
580 intensity transitions, as carried out during routine everyday tasks (11, 37). Importantly, given
581 that the training volume and time commitment herein was ~50% lower in the HIIT group and
582 that HIIT programmes seem to be as enjoyable as traditional endurance interventions (6, 42),

clinical care teams should consider low-volume HIIT as a suitable and effective exercise modality to enhance oxidative metabolism in individuals living with T2D.

Grants

This publication has emanated from research conducted with the financial support of the Health Research Board (Grant No 08/RFP/BMT1342).

Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

Author contributions

N.G., A.M'D., J.R., M.E., D.O'S. and S.G. conception and design of research; N.G., A.M'D. and J.R. performed experiments; N.G., A.M'D. and M.E. analyzed data; N.G., J.R., A.M'D., S.G. and M.E. interpreted results of experiments; N.G. and M.E. prepared figures; N.G. and M.E. drafted manuscript; N.G., A.M'D., J.R., D.O'S., S.G. and M.E. edited and revised manuscript; N.G., J.R., A.M'D., D.O'S., S.G. and M.E. approved final version of manuscript.

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Figure captions

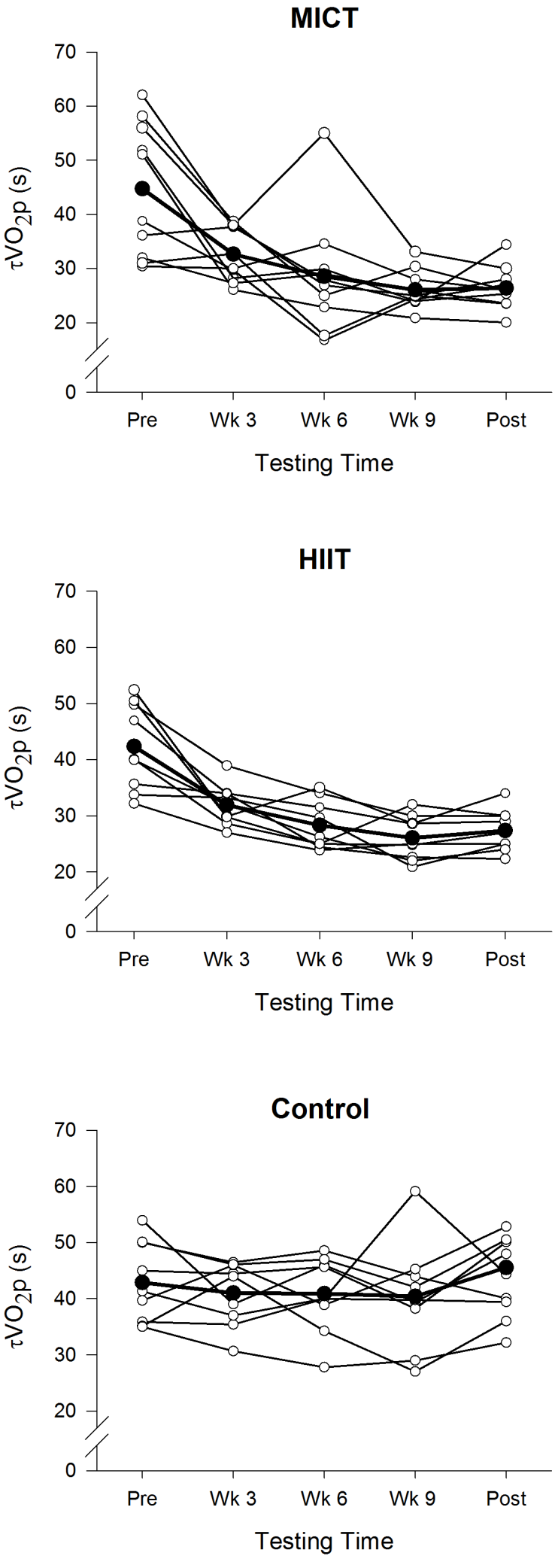
Figure 1. Individual time course of changes in the time constant of the primary phase of the oxygen uptake response ($\tau\dot{V}O_{2p}$) in the moderate-intensity continuous training (MICT), high-intensity interval training (HIIT) and non-exercising control groups. Thin lines are individual participants and thick lines represent the mean change in each group.

Figure 2. Mean time course of changes in the time constant of the primary phase of the oxygen uptake response ($\tau\dot{V}O_{2p}$; *A*) in the effective response time of the deoxygenated hemoglobin and myoglobin concentration ($\tau'\Delta$[HHb+Mb]; *B*) and Δ[HHb+Mb]-to-$\Delta\dot{V}O_2$ ratio index derived from the mean value from 20 to 150 s into the transition (*C*) in the moderate-intensity continuous training (MICT), high-intensity interval training (HIIT) and non-exercising control groups. ***** HIIT and MICT significantly different from pretraining ($P < 0.05$); † HIIT and MICT significantly different from control ($P < 0.05$).

Figure 3. Representative time course of changes for the adjustment in normalised deoxygenated hemoglobin and myoglobin concentration (Δ[HHb+Mb]; open circles) and oxygen uptake ($\dot{V}O_2$; black circles) from baseline to moderate-intensity cycling transitions (i.e. initial 180 s) for individuals in the moderate-intensity continuous training (MICT), high-intensity interval training (HIIT) and non-exercising control groups. The vertical line represents the abrupt transition to the higher work rate. Corresponding profiles for the adjustment of the Δ[HHb+Mb]/$\Delta\dot{V}O_2$ ratio index (initial 150 s) are also shown (grey circles). Note that the transient overshoot in the Δ[HHb + Mb]/$\Delta\dot{V}O_2$ ratio (relative to the steady-state ratio of 1.0) apparent at pretraining among the 3 representative participants, is attenuated in the participants from the HIIT and MICT groups

beyond week 3 of training, while the overshoot remains apparent in the participant from the control group.

Fig 1


MICT
70
60
50
40
30
20
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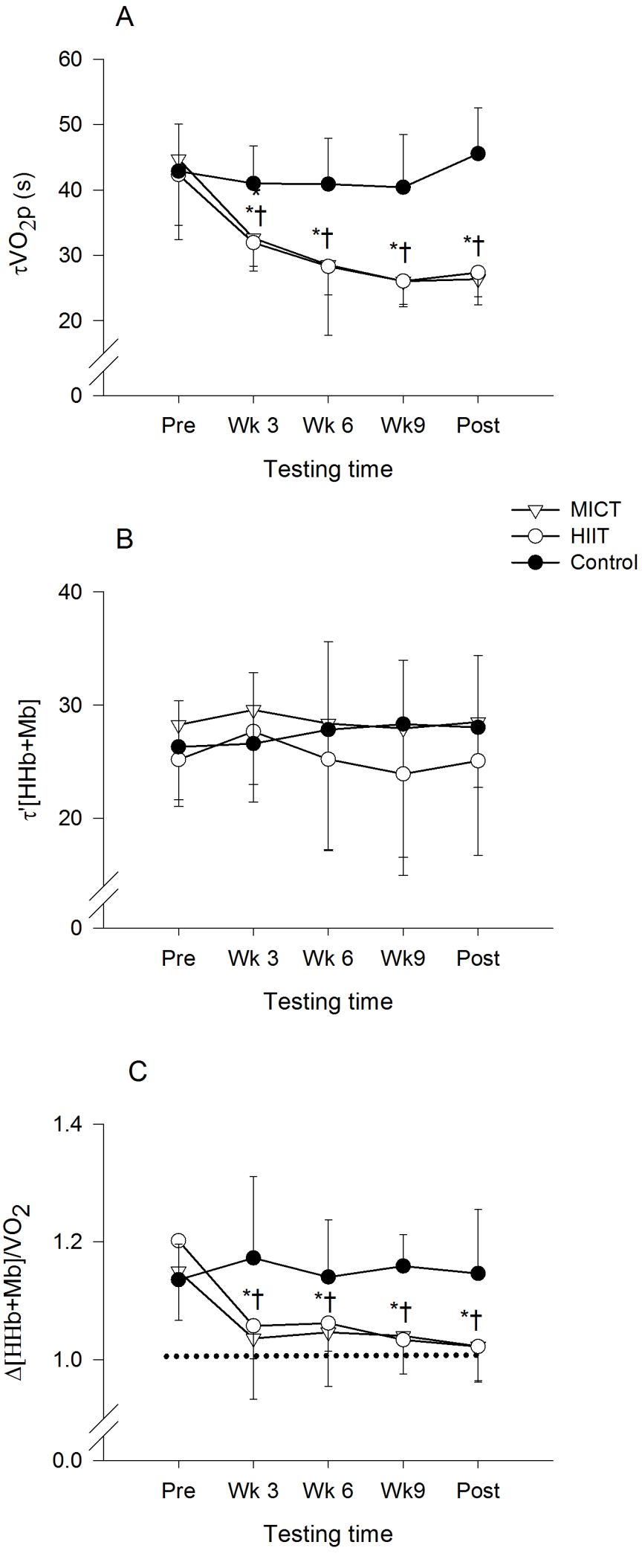
τVO2p (s)
Pre
Wk 3
Wk 6
Wk 9
Post
Testing Time
HIIT
70
60
50
40
30
20
0
τVO2p (s)
Pre
Wk 3
Wk 6
Wk 9
Post
Testing Time
Control
70
60
50
40
30
20
0
τVO2p (s)
Pre
Wk 3
Wk 6
Wk 9
Post
Testing Time

Fig 2


A
60
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τVO2p (s)
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Pre
Wk 3
Wk 6
Wk9
Post
Testing time
MICT
HIIT
Control
B
40
30
20
0
τ'[HHb+Mb]
Pre
Wk 3
Wk 6
Wk9
Post
Testing time
C
1.4
1.2
1.0
0.0
Δ[HHb+Mb]/VO2
*†
*†
*†
*†
Pre
Wk 3
Wk 6
Wk9
Post
Testing time

Fig 3

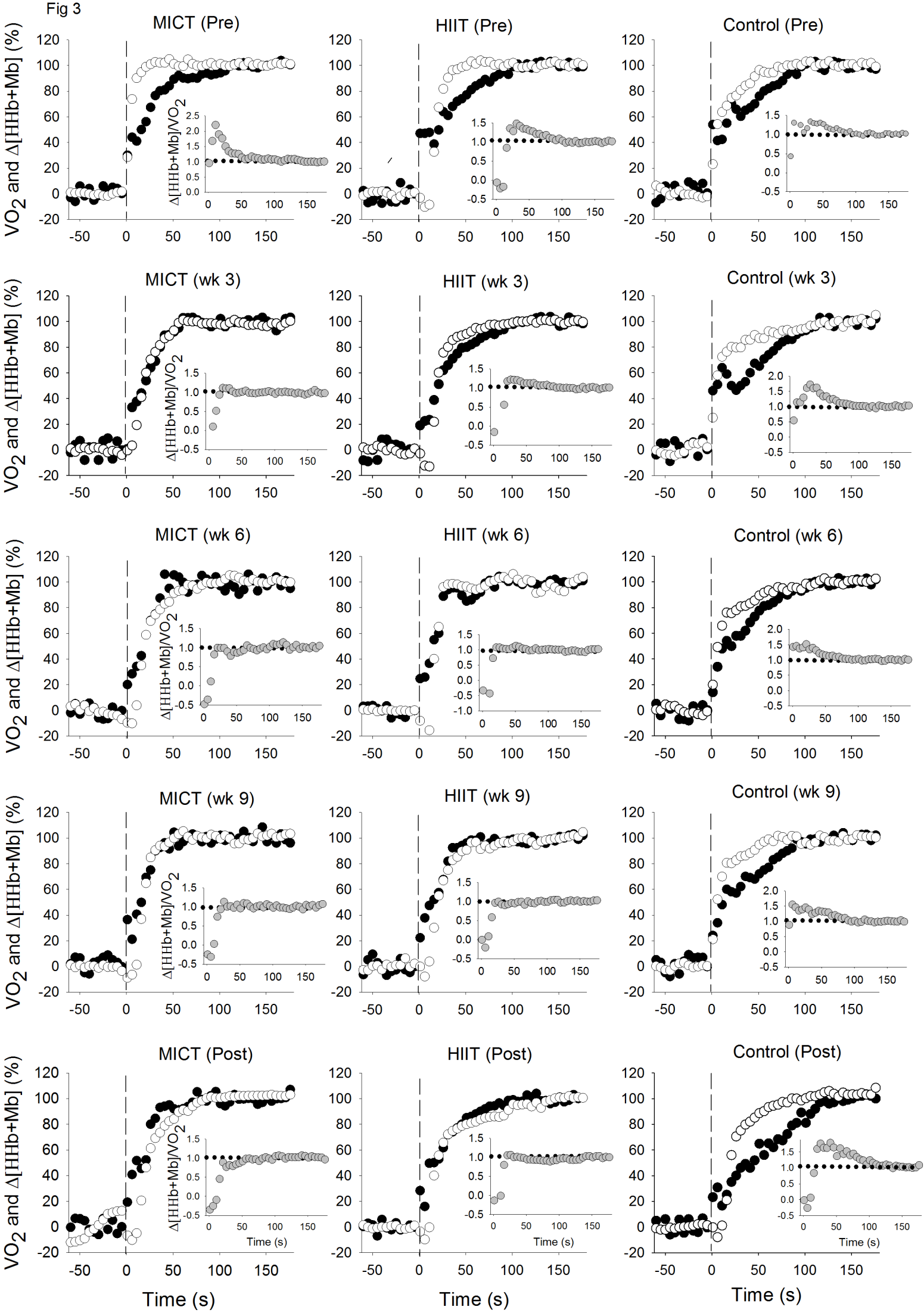
MICT (Pre)
HIIT (Pre)
Control (Pre)
MICT (wk 3)
HIIT (wk 3)
Control (wk 3)
MICT (wk 6)
HIIT (wk 6)
Control (wk 6)
MICT (wk 9)
HIIT (wk 9)
Control (wk 9)
MICT (Post)
HIIT (Post)
Control (Post)
VO2 and Δ[HHb+Mb] (%)
Δ[HHb+Mb]/VO2
Time (s)

Table 1. *Physical characteristics, pretraining peak exercise values, and activity levels.*

	MICT	HIIT	Control
n	10	9	9
Sex (male, female), *n*	7, 3	6, 3	4, 5
Age, yr	53 ± 10	52 ± 10	54 ± 9
BMI, kg/m^2	30.0 ± 5.7	28.7 ± 3.0	30.5 ± 3.6
Time since diabetes diagnosis, yr	6.4 ± 3.8	6.6 ± 3.5	6.6 ± 3.3
HbA_{1c}, %	6.9 ± 0.5	7.3 ± 0.5	6.8 ± 1.0
Fat layer of VL, mm	6.8 ± 2.8	6.4 ± 2.6	8.6 ± 3.2
Diabetes medication			
Diet only, *n*		1	1
Metformin, *n*	7	7	6
Sulfonylurea, *n*	1	3	2
DPP-4 inhibitor, *n*			2
GLP-1 analogues, *n*	1		1
Anti-hypertensive medication			
Angiotensin converting enzyme inhibitor, *n*		1	
Angiotensin II receptor blocker, *n*	1		1
Statins, *n*	5	3	3
Aspirin, *n*	3	1	2
PO_{peak}, W	168 ± 50	187 ± 51	148 ± 49
PO @ 80% VT, W	78 ± 25	92 ± 25	66 ± 20
Habitual physical activity			
Inactive, h/day	17.4 ± 1.6	17.5 ± 2.2	17.9 ± 1.9
Light, h/day	5.8 ± 1.7	5.8 ± 2.6	5.4 ± 1.2
MVPA, h/day	0.8 ± 0.7	0.8 ± 0.3	0.7 ± 0.9

Data are mean ± SD. BMI, body mass index; HbA_{1c}, glycosylated haemoglobin; VL, vastus lateralis; DPP-4, Dipeptidyl-peptidase 4; GLP-1, Glucagon-like peptide 1. PO, power output; MVPA, moderate-to-vigorous physical activity.

Table 2 *Dynamic response characteristics of $\dot{V}O_2$ during the intervention for the MICT, HIIT and Control groups.*

	Pretraining	Week 3	Week 6	Week 9	Posttraining
Baseline $\dot{V}O_2$, L/min					
MICT	0.92 ± 0.21	0.93 ± 0.18	0.92 ± 0.24	0.95 ± 0.22	0.90 ± 0.16
HIIT	0.80 ± 0.21	0.83 ± 0.15	0.82 ± 0.10	0.83 ± 0.14	0.81 ± 0.12
Control	0.78 ± 0.17	0.74 ± 0.10	0.76 ± 0.14	0.78 ± 0.14	0.76 ± 0.13
$\dot{V}O_2$ TD, s [a]					
MICT	14 ± 6	18 ± 6	15 ± 4	18 ± 3	16 ± 4
HIIT	15 ± 6	15 ± 4	15 ± 3	17 ± 5	16 ± 3
Control	17 ± 7	16 ± 5	21 ± 4	16 ± 5	18 ± 3
$\dot{V}O_{2p}$ A, L/min					
MICT	0.68 ± 0.30	0.64 ± 0.29	0.65 ± 0.21	0.65 ± 0.25	0.67 ± 0.27
HIIT	0.85 ± 0.35	0.82 ± 0.32	0.83 ± 0.27	0.81 ± 0.29	0.82 ± 0.26
Control	0.51 ± 0.20	0.55 ± 0.22	0.52 ± 0.23	0.51 ± 0.22	0.53 ± 0.21
$\dot{V}O_{2p}$ end-exercise A, L/min					
MICT	1.60 ± 0.41	1.58 ± 0.33	1.58 ± 0.37	1.60 ± 0.39	1.57 ± 0.37
HIIT	1.65 ± 0.36	1.65 ± 0.30	1.64 ± 0.31	1.64 ± 0.30	1.64 ± 0.31
Control	1.29 ± 0.31	1.28 ± 0.28	1.29 ± 0.32	1.29 ± 0.34	1.28 ± 0.31
$\dot{V}O_{2p}$ gain, $mL.min^{-1}.W^{-1}$					
MICT	9.9 ± 1.9	9.3 ± 1.8	9.9 ± 1.8	9.4 ± 1.2	9.7 ± 1.2
HIIT	10.0 ± 2.2	9.8 ± 1.7	10.0 ± 1.0	9.9 ± 1.5	10.0 ± 0.7
Control	9.2 ± 1.5	9.7 ± 1.1	9.1 ± 1.3	9.0 ± 0.9	9.4 ± 0.8
$\tau\dot{V}O_{2p}$, s					
MICT	45 ± 12	33 ± 5*†	29 ± 11*†	26 ± 4*†	26 ± 4*†
HIIT	42 ± 8	32 ± 4*†	28 ± 4*†	26 ± 4*†	27 ± 4*†
Control	43 ± 7	41 ± 6	41 ± 7	40 ± 8	45 ± 7
CI_{95} $\tau\dot{V}O_{2p}$, s					
MICT	4.4 ± 1.3	4.0 ± 1.5	4.1 ± 1.1	3.4 ± 1.1	3.3 ± 1.1
HIIT	4.4 ± 0.4	4.3 ± 1.1	4.0 ± 0.9	3.2 ± 0.9	3.9 ± 0.7
Control	4.0 ± 1.1	3.7 ± 0.6	3.8 ± 0.8	4.2 ± 1.4	5.2 ± 1.4

Data are mean (SD). $\dot{V}O_2$, oxygen consumption; TD, time delay; A, amplitude; p, primary phase response; τ, time constant; CI_{95}, 95% confidence interval.

* Significantly different from pretraining ($P < 0.05$); † significantly different from Control ($P < 0.05$); [a] significantly different at pretraining than all other timepoints ($P < 0.05$).

Table 3 *Dynamic response characteristics of [HHb + Mb], normalised Δ[HHb + Mb]/Δ$\dot{V}O_2$ ratio and total [Hb+Mb], during the intervention for the MICT, HIIT and Control groups.*

	Pretraining	Week 3	Week 6	Week 9	Posttraining
Baseline Δ[HHb + Mb] μM.cm					
MICT	-73 ± 44	-81 ± 69	-79 ± 59	-80 ± 82	-77 ± 57
HIIT	-56 ± 42	-57 ± 41	-60 ± 42	-53 ± 45	-60 ± 32
Control	-50 ± 36	-47 ± 29	-55 ± 31	-52 ± 38	-55 ± 31
Δ[HHb + Mb] A, μM.cm					
MICT	85 ± 42	95 ± 69	87 ± 46	93 ± 52	87 ± 30
HIIT [b]	164 ± 115	157 ± 103	159 ± 102	169 ± 105	164 ± 111
Control	72 ± 60	73 ± 50	69± 51	68 ± 55	69 ± 43
Δ[HHb + Mb] end-exercise A, μM.cm					
MICT	18 ± 62	14 ± 80	8 ± 45	20 ± 76	13 ± 70
HIIT [b]	133 ± 103	123 ± 95	116 ± 117	133 ± 119	130 ± 127
Control	20 ± 65	30 ± 64	21± 70	15 ± 67	15± 50
Δ[HHb + Mb] τ, s					
MICT	16 ± 7	16± 6	16 ± 10	15 ± 10	15 ± 6
HIIT	11 ± 4	13 ± 6	11 ± 7	11 ± 6	11 ± 6
Control	13 ± 5	12 ± 6	16 ± 9	15 ± 6	15 ± 7
Δ[HHb + Mb] TD, s					
MICT	12 ± 4	14 ± 6	13 ± 4	13 ± 4	14 ± 2
HIIT	14 ± 2	15 ± 4	14 ± 3	13 ± 5	14 ± 3
Control	14 ± 3	15 ± 2	12 ± 4	13 ± 3	13 ± 3
Δ[HHb + Mb] τ‘, s					
MICT	28 ± 7	30 ± 7	28 ± 11	28 ± 11	29 ± 6
HIIT	25 ± 4	28 ± 6	25 ± 8	24 ± 9	25 ± 8
Control	26 ± 4	27 ± 6	28 ± 8	28 ± 6	28 ± 6
Δ[HHb + Mb]/Δ$\dot{V}O_{2p}$ μMol.cm.(L/min)					
MICT	138 ± 87	145 ± 82	140 ± 78	150 ± 74	142 ± 62
HIIT	178 ± 123	180 ± 108	185 ± 102	196 ± 122	193 ± 133
Control	120 ± 89	117 ± 58	124 ± 77	116± 74	124 ± 69
Normalized Δ[HHb + Mb]/Δ$\dot{V}O_2$ ratio					
MICT	1.15 ± 0.08	1.04± 0.10*†	1.05 ± 0.09*†	1.04 ± 0.06*†	1.02 ± 0.06*†
HIIT	1.20 ± 0.08	1.06 ± 0.06*†	1.06 ± 0.05*†	1.03 ± 0.06*†	1.02 ± 0.06*†
Control	1.14 ± 0.06	1.17 ± 0.14	1.14 ± 0.10	1.16 ± 0.05	1.15 ± 0.11
Δ total[Hb+Mb], μMol.cm					
MICT	86 ± 50	76 ± 54	93 ± 63	108 ± 59	109 ± 67
HIIT	127 ± 65	100 ± 104	110 ± 66	103 ± 60	112 ± 73
Control	63 ± 35	68 ± 54	80 ± 39	79 ± 47	61 ± 50

Data are mean (SD). TD, time delay; A, amplitude; [HHb + Mb], deoxygenated haemoglobin and myoglobin concentration; τ, time constant; τ’ [HHb + Mb], effective time constant (τ + TD); normalized Δ[HHb + Mb]/Δ$\dot{V}O_2$, calculated as the 20 to 150 s average of the normalized Δ[HHb + Mb]-to-Δ$\dot{V}O_2$ ratio; total[Hb+Mb], total haemoglobin and myoglobin concentration.

* Significantly different from pretraining ($P < 0.05$); † significantly different from Control ($P < 0.05$); [b] significantly different from MICT & Control ($P < 0.05$).