Time course of changes in V̇O2peak and O2 extraction during ramp cycle exercise following HIIT vs moderate-intensity continuous training in type 2 diabetes

Norita Gildea
Adam McDermott
Joel Rocha
Donal O'Shea
Simon Green
Mikel Egaña

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TITLE

Time course of changes in $\dot{V}O_{2peak}$ and O_2 extraction during ramp cycle exercise following HIIT vs moderate-intensity continuous training in type 2 diabetes.

AUTHORS

Norita Gildea[1], Adam McDermott[1*], Joel Rocha[2], Donal O'Shea[3,4], Simon Green[5], Mikel Egaña[1]

AFFILIATIONS & ADDRESSES

1. Department of Physiology, School of Medicine, Trinity College Dublin, Dublin 2, Ireland.
2. Division of Sport and Exercise Sciences, Abertay University, Dundee, UK.
3. Department of Endocrinology, St. Columcille's Hospital, Dublin, Ireland.
4. Department of Endocrinology and Diabetes Mellitus, St. Vincent's University Hospital, Dublin, Ireland.
5. Schools of Health Sciences and Medicine, Western Sydney University, Sydney, Australia.

* N Gildea and A McDermott contributed equally to this work

CONTACT INFORMATION (corresponding author):

Mikel Egaña

Department of Physiology, School of Medicine; Trinity College Dublin, Dublin 2, Ireland.

E-mail: megana@tcd.ie; Telephone: +353 1 896 1770; Fax: +353 1 679 3545

RUNNING HEAD:

HIIT vs MICT on $\dot{V}O_{2peak}$ & fractional O_2 extraction in T2D

Abstract

In the present study we assessed the time course of adaptations in peak oxygen uptake ($\dot{V}O_{2peak}$) and muscle fractional oxygen (O_2) extraction (using near-infrared spectroscopy) following 12 weeks of low-volume high-intensity interval training (HIIT) vs. moderate-intensity continuous endurance training (MICT) in adults with uncomplicated type 2 diabetes (T2D). Participants with T2D were randomly assigned to MICT (n = 12, 50 min of moderate-intensity cycling), HIIT (n = 9, 10 x 1 min at ~90% maximal heart rate) or to a non-exercising control group (n = 9). Exercising groups trained 3 times per week and measurements were taken every 3 weeks. The rate of muscle deoxygenation (i.e. deoxygenated haemoglobin and myoglobin concentration, Δ[HHb+Mb]) profiles of the vastus lateralis muscle were normalised to 100% of the response, plotted against % power output (PO) and fitted with a double linear regression model. $\dot{V}O_{2peak}$ increased (P<0.05) by week 3 of MICT (+17%) and HIIT (+8%), with no further significant changes thereafter. Total increases in $\dot{V}O_{2peak}$ posttraining (P<0.05) were 27% and 14% respectively. The %Δ[HHb+Mb] vs %PO slope of the first linear segment ($slope_1$) was reduced (P<0.05) beyond 3 weeks of HIIT and MICT with no further significant changes thereafter. No changes in $\dot{V}O_{2peak}$ or $slope_1$ were observed in the control group. Low-volume HIIT and MICT induced improvements in $\dot{V}O_{2peak}$ following a similar time course and these improvements were likely, at least in part, due to an improved microvascular O_2 delivery.

Keywords: cardiorespiratory fitness, high-intensity interval training, muscle deoxygenation, near-infrared spectroscopy, exercise tolerance.

Introduction

The last two decades have seen an unprecedented global increase in type 2 diabetes (T2D) rendering this disease a major public health and economic burden of the 21st century. This is a direct consequence of the metabolic complexities and underlying comorbidities associated with T2D, with which approximately 366 million people worldwide live. Specifically, these individuals have an increased propensity for the development of coronary artery, cerebrovascular and peripheral vascular disease (13, 46). A critical concern among individuals with T2D is the consistent demonstration of significantly reduced (~20%) peak oxygen uptake ($\dot{V}O_{2peak}$) (3, 20, 30, 42, 43, 50) an established independent prognostic marker for cardiovascular and all-course mortality within this clinical population (64).

The impairments in $\dot{V}O_{2peak}$ in T2D might be influenced by cardiovascular limitations at a systemic level, such as impaired left ventricular filling (68, 69), and limitations in peripheral vasodilation and/or microvascular function in the lower limbs (5, 18, 19, 25, 27, 32, 49, 52, 65). Regarding peripheral O_2 delivery constraints, Kiely et al. (26) initially reported reduced peak leg haemodynamic and vasodilatory responses during an incremental calf plantar-flexion exercise in uncomplicated T2D. More recently, Gildea et al. (18), reported a significant reduction in $\dot{V}O_{2peak}$ accompanied by a greater reliance in fractional oxygen extraction during ramp incremental cycling exercise, in a similar cohort of individuals with T2D compared with healthy controls. This was depicted by an increased near-infrared spectroscopy (NIRS)-derived rate of muscle deoxygenation (i.e., deoxygenated haemoglobin and myoglobin, [HHb + Mb]) which is suggestive of lower microvascular blood flow responses likely due to maldistribution of active muscle blood flow in T2D (18).

Exercise training is an important therapeutic modality in T2D because it elicits the most effective increases in exercise tolerance and cardiorespiratory fitness (11). In this regard, short-term (8-12 weeks), traditional endurance training interventions, involving ~150 min of continuous exercise per week, often termed moderate-intensity continuous training (MICT) despite exercise intensity not being prescribed relative to 'metabolic thresholds', have been shown to significantly increase $\dot{V}O_{2peak}$ in uncomplicated T2D by ~18% (ranging from 8 to 27%) (10, 21, 31, 37, 70). However, adherence to these time-oriented MICT guidelines is poor (61), with "lack of time" regularly cited as one of the key barriers (58). With this in mind, more recently, attention has been given to the intensity of exercise, with time efficient, low-volume high-intensity interval training (HIIT) interventions (involving ~75 min per week of intermittent brief periods of vigorous exercise) eliciting similar improvements in $\dot{V}O_{2peak}$ of ~16% (ranging from 7 to 25%) in T2D (15, 34, 37, 51, 67, 70). However, while low volume HIIT and MICT interventions are effective at inducing improvements in cardiorespiratory fitness in T2D, the time course of effects and the mechanisms underlying the increases in $\dot{V}O_{2peak}$ following these exercise training interventions in T2D are presently unknown. Accordingly, the primary aim of the present study was to assess the time course and mechanisms of adaptations in cardiorespiratory fitness subsequent to a 12 week MICT vs HIIT intervention in uncomplicated T2D. To shed light on whether peripheral microvascular function influences the changes in $\dot{V}O_{2peak}$ in T2D, the rates of muscle deoxygenation were assessed. We hypothesised that both training interventions would enhance $\dot{V}O_{2peak}$ by reducing the rates of muscle deoxygenation early in training.

Methods

89 *Participants*

90 Participants were recruited from the Diabetes Outpatient Clinics of St. Columcille's and St.
91 Vincent's University Hospitals (Dublin). Participant's eligibility was initially checked following
92 chart review. Specifically, participants were included if they had a clinical history of diabetes <
93 11 yr, were untrained and had HbA_{1c} levels of <10%. Participants were excluded if they were
94 treated by exogenous insulin, were smokers, had a disease contraindicating physical training, or
95 demonstrated evidence of renal, liver or cardiovascular disease.

96

97 The overall process of recruitment and allocation to experimental groups is shown in Fig 1. Three
98 hundred individuals with T2D were eligible for inclusion (by prior chart review) and were briefly
99 informed about the study initially by hospital consultants when they attended their outpatient
100 clinics. If individuals were interested they were then directed to the study investigators who were
101 present in the waiting area of the clinics. Fifty-nine individuals expressed interest in participating
102 in the study. These individuals completed a 12-lead electrocardiogram treadmill stress test at St.
103 Columcille's Hospital. Twelve of these 59 participants failed the treadmill exercise stress test
104 while 12 other participants who passed the exercise stress test decided to opt out from the study
105 before completing the pretraining laboratory assessments. Thus, 35 participants completed the
106 baseline laboratory assessments and were given opaque sealed envelopes randomly allocating
107 them to one of the 3 intervention groups (MICT, initially $n = 13$; HIIT, initially $n = 10$ or Control,
108 initially $n = 12$;). Eight participants dropped out of the study for personal reasons unrelated to the
109 experiment (Control, $n = 3$; HIIT, $n = 3$; MICT, $n = 2$). Participants in the Control group were
110 offered re-randomisation to one of the exercise training groups after the intervention period of
111 which 3 accepted (HIIT, $n = 2$; MICT, $n = 1$) and subsequently completed the respective training

intervention. The final study population consisted of 27 participants undergoing the intervention, of whom 3 underwent both Control and either HIIT or MICT. Thus, 30 completed responses from the study intervention were included for statistical analysis (Control, n = 9; HIIT, n = 9; MICT, n = 12). 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.

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 by 60-s of light cycling. The high-intensity bout was completed at a PO equivalent to 70% of the difference between participant's peak power output (PO_{peak}) and the PO at ventilatory threshold (VT) (70% Δ) achieved during the ramp exercise test (see *testing*). This

output was designed to elicit a target heart rate of ~90% HR_{max} during the high-intensity bouts, and participants were expected to exercise in the severe-intensity domain.

Continuous training: Each MICT session comprised of 50 minutes of cycling at a PO equivalent to ~80-90% VT as calculated from the ramp test (see *testing*). Therefore, the total monthly time commitment (including warm up) for the low-volume HIIT group was ~300 min while for the MICT group was ~660 min.

Testing

Initially, physical activity levels were assessed by the use of 5-day RT3 triaxial accelerometry (Stayhealthy Inc, CA) (Table 1). The threshold for sedentary or inactive behaviour (<1.5 metabolic equivalents or METs) was set as < 100 counts/min (4), counts/min between 101 and 1317 were considered light activity (1.5-3 METs); and counts/min >1317 corresponded to moderate-to-vigorous physical activity (>3 MET) (54). Then, prior to the commencement of, and every 3 weeks throughout the intervention, participants were required to attend the exercise testing facility in St. Columcille's Hospital on 2 separate occasions to complete a cycling ramp incremental test as well as 2-4 transitions to moderate- and high-intensity cycling exercise and high-intensity calf plantar-flexion exercise. In the current manuscript we report responses obtained during the cycling ramp incremental tests to exhaustion. For each participant all tests were performed at the same time of day. All exercise tests were carried out in an upright position on an electrically braked cycle ergometer (Excalibur Sport; Lode B.V., 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

158 the end of the intervention period (posttraining) fasting venous blood samples were collected to
159 assess glycosylated haemoglobin (HbA_{1c}).
160
161 *Ramp incremental cycling tests:* The test started with an initial workload of 10 W for 2 min (i.e.
162 'unloaded' cycling). This was followed by 10-25 W/min increments in power output based on
163 participants' activity levels. Pedalling rate was held constant at an individually selected cadence
164 between 60-75 revolutions per minute (rpm) and was maintained throughout all further testing.
165 Failure in a test was determined as a drop in cadence exceeding 10 rpm for >5 s. Peak workload
166 was the power output achieved at the point of failure. $\dot{V}O_{2peak}$ was the highest $\dot{V}O_2$ value (15-s
167 average) attained during the test. The first ventilatory threshold (VT) was determined by two
168 investigators as previously described (6).
169
170 *Measurements*
171 During exercise, participants wore a facemask to continuously collect expired air using an online
172 metabolic system (Innocor, Innovision A/S, Odense, Denmark) that measured airflow using a
173 pneumotachometer. Carbon dioxide analysis was performed by using a photoacoustic gas analyzer
174 and oxygen was analyzed using an oxygen sensor (Oxigraf Inc., USA) based on the principle of
175 laser diode absorption spectroscopy. The system was calibrated prior to each test as per
176 manufacturer's recommendations. Both the oxygen sensor and photoacoustic gas analyser require
177 multi-point calibration that is routinely performed by the manufacturer every 6-12 months.
178 Analysis of expired air allowed determination of pulmonary O_2 uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$),
179 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 defined as the highest HR attained within the last 15 s of termination of the test.

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

Muscle deoxygenation. The NIRS-derived signal was normalised whereby the unloaded exercise baseline value was adjusted to zero ('zero set'). Thus, the NIRS data are presented as a relative change from the baseline- to the end-exercise values. As such 0% represents the mean steady-state value of the last 30 s of the unloaded cycling and 100% represents the highest mean value of the last 30 s of any work rate. This was done given the uncertainty of the optical path length in the VL at rest and during exercise, so, data are presented as normalised delta units Δ[HHb+Mb]. Prior to analysis, NIRS data were averaged to give 1 s intervals. The second-by-second [HHb+Mb] data was averaged by applying a five-point moving average and then normalised to the peak amplitude of the response (%Δ[HHb+Mb]). The [HHb+Mb] response dynamics were expressed in relation to relative power output (%PO) prior to curve fitting. Therefore, individual profiles were plotted as a function of %PO and characterised by a linear function with two terms to establish the slope of increase of deoxygenation ($slope_1$), plateau as maximal exercise was approached ($slope_2$), and the break point (*BP*) located between the increasing deoxygenation and its plateau. The double linear function was applied using TableCurve 2D (Systat Software, USA) as:

$$y = a + b * x - c * (x-d) * f$$

$$f = if(x<d, 0, 1)$$

where *a* and *b* represent the y-intercept and slope of the first linear function ($slope_1$), *d* is the time delay or break point (*BP)* where the segments intersect, with the slope of the second linear function ($slope_2$) being calculated from the parameter estimates of *b* and *c* ($slope_2 = b - c$).

$\Delta\dot{V}O_2/\Delta PO$

The rate of change of $\dot{V}O_2$ relative to PO during ramp incremental exercise reflects the capacity of aerobic metabolism to adjust to the non-steady state conditions incurred during a ramp incremental protocol. Initially, the mean response time (MRT) of $\dot{V}O_2$ during the ramp incremental exercise was estimated using the approach recently described by Iannetta et al. (23). Briefly, we determined the average steady-state $\dot{V}O_2$ corresponding to 2-3 separate bouts of moderate-intensity constant-power outputs (performed on a separate visit), and we then compared the ramp-derived power output associated with that $\dot{V}O_2$ to the constant-power output which elicited that $\dot{V}O_2$. The difference between these power outputs was then converted to the time (taking into account the slope of the ramp protocol) to retrieve the time-interval corresponding to MRT. The breath by breath $\dot{V}O_2$ data were averaged over 15 s intervals and plotted as a function of work rate after accounting for the MRT to reflect the increase in aerobic metabolism ($\Delta\dot{V}O_2$) for each increase in power output (ΔPO). From this the $\Delta\dot{V}O_2/\Delta$PO slope was calculated over the same range of PO as used to determine the first %Δ[HHb+Mb]/%PO slope (i.e parameter *b* or $slope_1$) as described above.

Statistical Analysis

Physical characteristics and activity levels at baseline among groups were compared using a one-way ANOVA. Peak physiological responses and NIRS-derived muscle deoxygenation responses

during the intervention were compared using a two-factor [time (pretraining, week 3, week 6, week 9, posttraining) vs. group (HIIT, MICT, Control)] mixed ANOVA. Body mass and HbA_{1c} results were also compared using a two-factor [time (pretraining, posttraining) vs. group (HIIT, MICT, Control)] mixed ANOVA. Differences were detected using a Student-Newman-Keuls *post hoc* test. Correlations between pretraining $\dot{V}O_{2peak}$ or % change in $slope_1$ with the percentage change in $\dot{V}O_{2peak}$ were established using the Pearson product–moment correlation coefficient (Pearson *r*). A power analysis indicated that eight participants per group were required to detect a ~ 16% improvement in $\dot{V}O_{2peak}$ with a power of 0.80 and alpha of 0.05 for an ANOVA calculation design based on 3 groups. This was estimated using means and standard deviations from previously published data on participants with similar baseline physical characteristics and activity levels as in the current study following short term HIIT and MICT interventions (21, 34, 67). Significance was set at $P < 0.05$. All values are expressed as mean ± standard deviation (SD).

Results

Physical characteristics and activity levels.

Participants' physical characteristics at baseline are presented in Table 1. All three groups were well matched according to age, time since diabetes diagnosis, body mass, body mass index, HbA_{1c} and activity levels. There was a significant time x group interaction ($P < 0.001$) for body mass so that posttraining body mass was reduced ($P = 0.001$) in the MICT group (pre = 92.1 ± 20.6 kg, post = 89.7 ± 20.1 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, $P <$ 0.001) was reduced in the MICT (pre = 6.8 ± 0.5%, post = 6.6 ± 0.5%) 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 and work done

The mean exercise adherence was 94 ± 6% (range 31-36 sessions) and 96 ± 6% (range 31-36 sessions) in the HIIT and MICT groups respectively. The average training intensity (PO) increased significantly ($P < 0.05$) after each testing session (i.e., every 3 weeks) in the MICT group (weeks 1–3, 82 ± 32 W; weeks 4–6, 100 ± 39 W; weeks 7–9, 110 ± 42 W; weeks 10-12, 119 ± 44 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 total work done per training session (including the warm up) was ~165 kJ for the HIIT and ~326 kJ for the MICT groups. No adverse training effects were observed throughout the intervention period in either exercising group.

Peak physiological responses during ramp exercise

Peak physiological responses throughout the training period are summarised in Table 2, while individual $\dot{V}O_{2peak}$ ($ml.kg^{-1}.min^{-1}$) responses are shown in Fig 2. For absolute $\dot{V}O_{2peak}$ as well as $\dot{V}O_{2peak}$ normalised to body mass, there was a significant time x group interaction ($P < 0.001$, statistical power = 0.84 and 0.99 respectively), so that $\dot{V}O_{2peak}$ did not increase in the control group, but it significantly increased after 3 weeks of MICT and HIIT, with no further significant changes thereafter. The percentage change in $\dot{V}O_{2peak}$ ($ml.kg^{-1}.min^{-1}$) from pretraining to posttraining was not significantly different in the MICT (27 ± 21%) and HIIT (14 ± 8%) groups ($P = 0.14$), but it was larger from pretraining to week 6 in the MICT (25 ± 12%) than the HIIT (11 ± 8%) group ($P < 0.01$). The percentage changes in $\dot{V}O_{2peak}$ (relative to both, pretraining and posttraining) are illustrated in Fig 3. Importantly, pretraining $\dot{V}O_{2peak}$ was significantly correlated with the

293 percentage change in $\dot{V}O_{2peak}$ among exercising participants (r = 52, $P = 0.02$) (Fig 4). HR_{max} did
294 not change from pre- to post-intervention in any of the groups. Consequently, peak O_2 pulse
295 significantly increased after 3 weeks of MICT and HIIT with no further changes thereafter, while
296 it did not change in the control group (time x group interaction, $P < 0.01$). In addition, PO_{peak} was
297 higher at week 3 than pretraining in both the HIIT and MICT groups. Further changes in PO_{peak}
298 were observed in the MICT group from week 6 to 9 and from week 9 to posttraining; whereas in
299 the HIIT group PO_{peak} further increased from week 3 to 6. PO at VT was significantly increased
300 at week 3, and between week 3 and 6 in both exercising groups. In contrast, PO_{peak} or PO at VT
301 was not changed throughout the 12 week period in the control group. There was a main effect of
302 group ($P < 0.01$) for RER values so that they were larger in the HIIT compared with the other 2
303 groups. Finally, there was a main effect of time ($P < 0.05$) for $\dot{V}CO_{2peak}$, $\dot{V}E_{peak}$ and MRT without
304 a group x time interaction ($P = 0.07$, $P = 0.71$ and $P = 0.81$ respectively). Specifically, $\dot{V}CO_{2peak}$,
305 $\dot{V}E_{peak}$ were larger at all time points than pretraining while MRT was larger at week 9 compared
306 with pretraining.
307
308 *Muscle deoxygenation [HHb + Mb] responses during ramp exercise*
309 Group mean parameter estimates from the double linear model of the Δ[HHb+Mb] profile as a
310 function of normalised power output (%PO) are summarised in Table 3. Individual representative
311 profiles of the modelled [HHb+Mb] response dynamics as a function of %PO are displayed in Fig
312 5. Due to a technical error with the NIRS data, results from 4 participants (2 participants from the
313 MICT and 2 from the control group) were excluded from the analyses. There was a significant
314 time x group interaction ($P = 0.04$) for the slope of the first linear regression function ($slope_1$) used
315 to establish the dynamic adjustment of [HHb+Mb]. In both exercising groups $slope_1$ was

significantly reduced at week 3 with no further changes observed thereafter; whereas no changes in $slope_1$ were observed in the control group. The percentage change in $slope_1$ from pretraining to posttraining was not significantly different in the MICT and HIIT groups. The percentage changes in $slope_1$ (relative to both, pretraining and posttraining) are illustrated in Fig 3. In addition, in all participants, the percentage change in $slope_1$ was significantly correlated with the percentage change in $\dot{V}O_{2peak}$ at week 3 ($r = -0.51$, $P < 0.01$), week 6 ($r = -0.41$, $P = 0.03$) and posttraining ($r = -0.40$, $P = 0.04$) but not at week 9 ($r = -0.25$, $P = 0.21$). However, within each group or among the 2 exercising groups together, the percentage change in $slope_1$ was not significantly correlated with the percentage change in $\dot{V}O_{2peak}$ at any time point. The slope of the second Δ[HHb+Mb]/%PO regression function ($slope_2$) and the break point (% PO_{peak}) did not change throughout the 12 week period in any of the groups.

$\Delta\dot{V}O_2/\Delta PO$

The rate of change in $\dot{V}O_2$/PO during the ramp incremental test was not significantly different between groups or among groups throughout the 12 week period of the intervention (Table 2).

Discussion

To our knowledge this is the first study to explore the time-course effects of low-volume HIIT and MICT interventions on $\dot{V}O_{2peak}$ and muscle deoxygenation responses during a ramp incremental exercise test in uncomplicated T2D. The main findings were that both HIIT and MICT significantly improved $\dot{V}O_{2peak}$ by week 3 of the intervention and that these effects were likely linked to improvements in microvascular O_2 delivery, as suggested by the less steep slope in the O_2 extraction signal during the ramp incremental test. These benefits in $\dot{V}O_{2peak}$ and muscle

deoxygenation followed a time course that was not different between groups and were maintained for the remainder of both exercise interventions without further improvement. This rapid improvement in cardiorespiratory fitness is of great clinical relevance, as it significantly reduces the risk for adverse cardiovascular outcomes and all-cause mortality (53).

In the present study a single incremental exercise test was performed at each time point. While performing an additional incremental test and/or verification ride at each time point would have been benefitial to add confidence in the outcome, the training-induced significant increases in peak O_2 pulse suggest that the training response following MICT and HIIT was captured as opposed to participants providing more effort as they became more used to exercise.

Time-course effects on $\dot{V}O_{2peak}$

After the 12-week intervention, in the present study both MICT and HIIT significantly increased $\dot{V}O_{2peak}$ by 27% and 14% respectively. Such improvements are in keeping with the literature pertaining to short-term exercise training in individuals with uncomplicated T2D subsequent to MICT (10, 21, 31) and low-volume HIIT (15, 34, 51, 67). The tendency for the overall larger percentage increase in $\dot{V}O_{2peak}$ herein for the MICT group (27% vs 14%, $P = 0.14$) can partly be attributed to the ~16% lower initial baseline $\dot{V}O_{2peak}$ of the MICT group, despite random assignment, given that pretraining $\dot{V}O_{2peak}$ was significantly correlated to the percentage increase in $\dot{V}O_{2peak}$ in both training groups. Our findings are consistent with those from a recent multi-centre comparative study (across 18 studies) of $\dot{V}O_{2peak}$ trainability between interval and continuous training modalities in both healthy ($n = 272$) and clinical populations ($n = 405$) where no significant differences were revealed between MICT and low-volume HIIT in $\dot{V}O_{2peak}$ (66).

Only a small number of previous studies compared the effects of HIIT and MICT on $\dot{V}O_{2peak}$ in individuals with uncomplicated T2D (37, 60, 70) and results are equivocal. For instance, Winding et al. (70) reported a 20% increase in $\dot{V}O_{2peak}$ after 11 weeks of HIIT (10 x 60 s cycling at 95% PO_{peak}) which was greater than the 8% increase in $\dot{V}O_{2peak}$ observed after MICT (8% increase; 40 mins cycling at 50% PO_{peak}). Similarly, Mitranun et al. (37) reported a 25% increase in $\dot{V}O_{2max}$ following 12 weeks of HIIT (4-6 x 1 minute intervals at 80-85% $\dot{V}O_{2max}$ with 4 min active recovery at 50-60% $\dot{V}O_{2max}$) compared to a 14% increase after MICT (20-30 min at 60-65% $\dot{V}O_{2max}$); however, the 2 interventions therein were matched for exercise energy expenditure, resulting in a similar time commitment (HIIT: 26 mins vs MICT: 30 mins), thereby countering the time efficacy attraction of HIIT. On the contrary, also employing energy-matched HIIT and MICT interventions, Terada et al. (60) did not observe significant benefits in $\dot{V}O_{2peak}$ subsequent to 12 weeks of training in either group. It is likely that differences in the age range, initial fitness and physical activity levels, or the duration and severity of diabetes among participants in the different studies as well as differences in study protocols are factors that likely contributed to the response variation following these training modalities.

A novel and clinically relevant finding herein is that $\dot{V}O_{2peak}$ increased within 3 weeks of training in both the MICT and HIIT groups (17% and 8 % respectively), accounting for ~60% of the total change in $\dot{V}O_{2peak}$ in both groups. Despite an additional 10% and 6% numerical increase between week 3 and posttraining following MICT and HIIT respectively, no further significant changes were observed in any of the training groups. It is likely that interindividual variability in response precluded these increases to attain statistical significance. A levelling off in the increase in $\dot{V}O_{2peak}$, despite an adjustment in intensity, has also been reported in healthy individuals during short-term

low-volume HIIT interventions (1, 2). Interestingly, Astorino et al. (1) showed that subsequent to 10 low-volume HIIT sessions (8-10 x 60 s cycling at 90-100% PO_{peak}), 10 additional sprint interval training sessions (8-12 "all-out" 30 s sprints) further increased $\dot{V}O_{2max}$ in young active individuals, whereas 10 additional high-volume HIIT sessions (5-7 x 150 s cycling at 70-80% PO_{peak}) did not. The findings by Astorino and colleagues (1) suggest that in order to further increase $\dot{V}O_{2max}$ beyond the initial few weeks of training, a modification in the structure, rather than volume, of the HIIT sessions might be needed. Among studies investigating time course of effects on cardiorespiratory fitness in healthy individuals following short-term aerobic continuous training interventions mixed results have been reported. When training intensities ≥70% $\dot{V}O_{2max}$ were employed, studies showed progressive linear increases in $\dot{V}O_{2max}$ (22, 38, 40), no changes until posttraining (17) or changes at posttraining in additions to changes at one additional time point (41, 63); whereas employing lower training intensities (50-60% $\dot{V}O_{2max}$) a plateau beyond the mid-point of the training interventions has been reported (16, 44). It should be noted that only one of these interventions employed training intensities relative to 'metabolic thresholds' (63) but therein, exercise training intensity progressed from moderate-intensity (< VT) to severe-intensity (>VT2) throughout the intervention.

Muscle deoxygenation responses

In order to explore if peripheral microvascular function affected the changes in $\dot{V}O_{2peak}$ in T2D following both training interventions, the present study investigated the rates of NIRS-derived fractional O_2 extraction within the vastus lateralis. The profile of % Δ[HHb+Mb], characterised by a 'double-linear model' (62) offers an insight into the dynamic balance between regional oxygen delivery and $\dot{V}O_2$ at the level of the microvasculature (57). In the first segment therein, a

linear increase in %Δ[HHb+Mb] relative to changes in work rate occurs, representing the increasing reliance on O_2 extraction relative to metabolic demand, which culminates at a 'breakpoint' (Δ[HHb+Mb] – *BP*), from which a "plateau-like" response ensues despite the continued increase in work rate. That the initial slope of this first linear increase in %Δ[HHb+Mb] herein was significantly reduced in both training groups after 3 weeks with no further significant changes thereafter, while the rate of increase in $\dot{V}O_2$ relative to PO (i.e. $\Delta\dot{V}O_2/\Delta PO$) remained unchanged, suggests that exercise-induced improvements in microvascular O_2 delivery contributed, at least partly, to reducing the dependence on fractional O_2 extraction during ramp exercise. Additionally, the training-induced reductions in the MRT of the $\dot{V}O_2$ response during the ramp tests observed herein may also suggest an enhanced muscle oxidative capacity, given that cardiorespiratory fitness has been shown to be associated with this parameter (36), and are consistent with reductions observed in individuals with a prior myocardial infarction following a short-term MICT intervention (59). That the reductions in MRT were not significantly different until week 9 despite a numerical reduction from week 3 onwards can likely be attributed to the large variation in MRT responses herein. This large variation was influenced, at least partly, by the different ramp slopes utilized by participants in the present study (9).

Indeed an impaired peripheral O_2 delivery extant during maximal exercise in this clinical population has been documented. Specifically reductions in maximum leg haemodynamic and vasodilatory responses during an incremental calf plantar-flexion exercise (26) as well as alterations in the profile of muscle fractional O_2 extraction at the interface of the capillary to myocyte within the vastus lateralis muscle in individuals with uncomplicated T2D during ramp incremental cycle exercise (18) have been reported. Therein, Gildea et al. (18) observed that T2D

induced a greater reliance on NIRS-derived O_2 extraction for a given PO compared with healthy controls despite a similar rate of increase in $\dot{V}O_2$ relative to PO (i.e. $\Delta\dot{V}O_2/\Delta PO$). Similarly, in rodent models with T2D, greater microvascular deoxygenation responses at any given absolute PO were observed compared with controls (7), which were associated with a lower oxygen delivery and $\dot{V}O_2$ at the level of the microvasculature, the determining factor for microvascular partial pressure of O_2 and thereby, lower O_2 diffusion to the muscle mitochondria (7).

In the present study the BP (as $\%PO_{peak}$) did not change throughout the intervention even if the slope of muscle deoxygenation ($slope_1$) was reduced. The fact that the onset of $slope_1$ did not occur at the same time point (relative to $\%\ PO_{peak}$) between or within participants throughout the intervention (see representative responses in the MICT and HIIT groups in Fig 5) likely influenced this.

Although the mechanisms responsible for the enhanced profile of muscle fractional O_2 extraction following the exercise interventions were not directly explored in the present study, improvements in vascular function likely contributed to the early improvements given that functional endothelial improvements have been elicited within as little as 2 weeks of MICT and resistance training in T2D (56). Other mechanisms potentially at play, include structural adaptations within the vasculature (12, 33) and increased capillary-to-myocyte interface for tissue perfusion and substrate delivery (39), potentially by increasing the proportion of red blood cell-flowing capillaries in muscle which is reduced in T2D, at least in rats (47). However, these structural adaptations have been reported beyond 8 weeks of training, so, it is likely that they influenced the non-significant changes observed in the latter part of the interventions and/or helped maintain the early

adaptations. On the other hand, in addition to the enhanced peripheral adaptations observed herein, it is possible that central adaptations (i.e. peak stroke volume and cardiac output) also influenced the increases in $\dot{V}O_{2peak}$. For instance, recent evidence suggests that short-term HIIT increases left ventricular stroke volume via increases in left ventricular end-diastolic volume, during submaximal exercise intensities in uncomplicated T2D and that these effects are independent of changes in total blood volume (67). On the other hand, in healthy untrained older men, peak cardiac output (and stroke volume) responses were increased, accompanied with simultaneous increases in $\dot{V}O_{2max}$, within 3 weeks of a 12-week MICT intervention (41). Further studies are needed to elucidate the time-course of effects on central adaptations following training in T2D and how these adaptations influence changes in cardiorespiratory fitness.

Limitations

A number of limitations of the present study must be acknowledged. First, even if in the present study mixed groups of men and women were included in each study arm, sex-related effects on the magnitude of responses to HIIT and MICT in T2D are likely small given that 12-weeks of MICT in individuals with T2D (21), as well as 6 weeks of HIIT in individuals with risk factors for T2D (48), showed no difference in response between men and women. Second, we also acknowledge that the muscle deoxygenation findings herein relate to the evaluation of a single muscle, the VL. Therefore, interpretation of this data is limited to the examined region, with potential structural (vascularity and fibre type) (24), and functional (fibre recruitment, vascular control and blood flow (8, 29, 35) differences acknowledged. In addition, NIRS signals have temporal and spatial heterogeneity among muscles and within deep and superficial muscle segments (28, 45, 55) which likely extend to the vastus lateralis herein. Third, we did not take into

account the MRT of the $\dot{V}O_2$ during the ramp incremental tests when calculating the exercise training intensities, and hence, power outputs corresponding to the VT may have been slightly overestimated. This is particularly relevant for the MICT group who trained at an intensity close to VT (i.e. ~80-90% VT). Despite this, $\dot{V}O_2$ kinetics analyses carried out at 80% VT on a separate visit (data not shown) revealed that only 2 participants of the MICT group demonstrated a small $\dot{V}O_2$ 'slow component', hence, the majority of participants in the MICT group likely exercised within the moderate-intensity domain. Finally, in the present study we did not control for baseline $\dot{V}O_{2peak}$ values among groups, as all participants were untrained with similar objectively measured activity levels. However, baseline $\dot{V}O_{2peak}$ values expressed as $ml.kg^{-1}.min^{-1}$ (although not $\dot{V}O_{2peak}$ values expressed as L/min or PO_{peak} values) were indeed higher ($P < 0.05$, one-way ANOVA) in the HIIT compared with the other groups, and given that these values influenced the training-induced changes in $\dot{V}O_{2peak}$ in our exercising participants (Fig 4), baseline $\dot{V}O_{2peak}$ values among groups should therefore be controlled in future studies.

Perspective and significance

Exercise adherence in individuals with T2D is low, with lack of time and fear of having an acute adverse health event often cited as barriers for not being more active. In addition, those living with T2D consistently demonstrate a decreased cardiorespiratory fitness or exercise tolerance which is an independent prognostic marker for mortality. In the present study the time-efficient HIIT in parity with MICT achieved rapid (i.e. within 3 weeks) clinically significant benefits in cardiorespiratory fitness which were accompanied with simultaneous reductions in fractional O_2 extraction of the active musculature. This suggests that augmenting the initial diminished capacity to increase peripheral O_2 delivery to meet the increasing O_2 demands during exercise, serves to

positively impact muscle oxidative metabolism and thus, exercise tolerance in uncomplicated T2D. Importantly, the training volume and time commitment herein was ~50% lower in the HIIT compared with the MICT group, while no adverse events were reported. Thus, physicians and exercise practitioners should consider low-volume HIIT as an attractive exercise modality that could be better suited to the time availability and motivational level of novice exercisers with T2D.

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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., A.M'D., J.R., D.O'S., S.G. and M.E. approved final version of manuscript.

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Figure captions

Figure 1: Participant flow chart diagram.

Figure 2: Individual time course of changes in peak oxygen uptake ($\dot{V}O_{2peak}$) in the moderate-intensity continuous training (MICT, n = 12), high-intensity interval training (HIIT; n = 9) and non-exercising control (n = 9) groups. Thin lines are individual participants and thick lines represent the mean change in each group.

Figure 3: Mean time course of changes in peak oxygen uptake ($\dot{V}O_{2peak}$) and in the first %Δ[HHb+Mb]/%PO slope ($slope_1$) relative to the baseline or pretraining (panels A and C respectively) and as a function of the total change (panels B and D respectively) in the moderate-intensity continuous training (MICT, n = 12 for panels A & B; n = 10 for panels C & D) and high-intensity interval training (HIIT, n = 9) groups. Within panel A group differences did not reach statistical significance at wk 3 (P = 0.07), wk 9 (P = 0.22) or wk 12 (P = 0.14). ***** significantly different from HIIT (P < 0.05).

Figure 4: Relationships between pretraining peak oxygen uptake ($\dot{V}O_{2peak}$) and total changes in $\dot{V}O_{2peak}$ across the 12-week intervention period in participants from the moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT) groups. The Pearson r (correlation) value and a line of best fit are shown for all data.

753 **Figure 5:** Representative time course of changes in profiles of the modelled [HHb+Mb] response
754 dynamics expressed as a function of relative power output (PO%) during ramp incremental
755 exercise for individuals in the moderate-intensity continuous training (MICT) and high-intensity
756 interval training (HIIT) groups. Double linear regression models are superimposed on the data.
757 Note the larger first %Δ[HHb+Mb]/%PO slope ($slope_1$) of the double linear regression at the
758 pretraining time point in participants in the MICT and HIIT groups. The slopes within the control
759 group were not affected throughout the intervention.
760

Table 1. *Physical characteristics and activity levels.*

	MICT	HIIT	Control
n	12	9	9
Sex (male, female), *n*	7, 5	6, 3	5, 4
Age, yr	53 ± 10	52 ± 10	54 ± 9
BMI, kg/m^2	30.4 ± 5.8	28.7 ± 3.0	30.5 ± 3.6
Time since diabetes diagnosis, yr	6.9 ± 3.7	6.6 ± 3.5	6.6 ± 3.3
HbA_{1c}, %	6.8 ± 0.5	7.3 ± 0.5	6.8 ± 1.0
Fasting glucose, mmol/L	7.6 ± 1.2	9.3 ± 3.3	7.9 ± 2.0
Fat layer of VL, mm	7.7 ± 3.9	6.4 ± 2.6	8.6 ± 3.2
Resting SBP, mmHg	121 ± 16	124 ± 13	130 ± 12
Resting DBP, mmHg	75 ± 9	72 ± 6	73 ± 7
Resting HR, beats/min	75 ± 11	73 ± 9	75 ± 11
Diabetes medication			
Diet only, *n*		1	1
Metformin, *n*	9	7	6
Sulfonylurea, *n*	2	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
Habitual physical activity			
Inactive, h/day	17.5 ± 2.0	17.4 ± 2.9	17.9 ± 1.9
Light, h/day	5.7 ± 1.6	5.8 ± 2.6	5.4 ± 1.1
MVPA, h/day	0.7 ± 0.7	0.7 ± 0.3	0.7 ± 0.8

Data are mean ± SD. BMI, body mass index; HbA_{1c}, glycosylated haemoglobin; VL, vastus lateralis; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; DPP-4, Dipeptidyl-peptidase 4; GLP-1, Glucagon-like peptide 1; MVPA, moderate-to-vigorous physical activity.

Table 2 *Physiological responses during the ramp incremental test during the intervention for the MICT, HIIT and control groups.*

	Pretraining	Week 3	Week 6	Week 9	Posttraining
PO_{peak}, W					
MICT	155 ± 54	178 ± 63*	185 ± 64*	194 ± 65*†	195 ± 68*†‡
HIIT	187 ± 51	204 ± 52*	216 ± 52$^{*\dagger\#}$	220 ± 50$^{*\dagger\#}$	217 ± 55*†
Control	148 ± 49	149 ± 52	146 ± 55	151 ± 51	153 ± 50
$\dot{V}O_{2peak}$, L/min					
MICT	2.01 ± 0.69	2.31 ± 0.71*	2.46 ± 0.77$^{*\#}$	2.37 ± 0.75*	2.41 ± 0.78*
HIIT	2.31 ± 0.51	2.50 ± 0.56*	2.54 ± 0.52*	2.63 ± 0.60*	2.59 ± 0.54*
Control	1.86 ± 0.52	1.94 ± 0.63	1.89 ± 0.56	1.94 ± 0.64	1.92 ± 0.54
$\dot{V}O_{2peak}$, $mL.kg^{-1}.min^{-1}$					
MICT	22.1 ± 4.4	25.9 ± 5.5*	27.4 ± 5.1$^{*\#}$	27.0 ± 5.5$^{*\#}$	27.6 ± 5.1$^{*\#}$
HIIT	26.4 ± 4.0	28.5 ± 4.2$^{*\#}$	29.2 ± 3.5$^{*\#}$	30.2 ± 4.4$^{*\#}$	30.0 ± 4.0$^{*\#}$
Control	21.5 ± 3.6	22.1 ± 4.4	21.6 ± 4.0	22.2 ± 4.2	22.0 ± 3.4
HR_{max}, beats/min					
MICT	157 ± 14	158 ± 14	158 ± 15	160 ± 17	158 ± 16
HIIT	162 ± 13	165 ± 13	162 ± 13	165 ± 13	162 ± 15
Control	162 ± 12	157 ± 15	157 ± 13	158 ± 16	157 ± 18
Peak O_2 pulse, ml/beat					
MICT	12.8 ± 4.1	14.9 ± 4.1*	15.7 ± 4.3$^{*\#}$	15.1 ± 4.4*	15.5 ± 4.5*
HIIT	14.4 ± 3.3	15.2 ± 3.6*	15.8 ± 3.4*	16.1 ± 4.1*	16.3 ± 4.0*
Control	11.3 ± 3.2	12.4 ± 3.4	12.2 ± 2.9	12.2 ± 3.5	12.2 ± 3.0
$\dot{V}CO_{2peak}$, L/min [a]					
MICT	2.30 ± 0.82	2.59 ± 0.73	2.74 ± 0.80	2.71 ± 0.79	2.77 ± 0.98
HIIT	2.69 ± 0.59	2.97 ± 0.75	2.98 ± 0.78	3.22 ± 0.80	3.01 ± 0.63
Control	1.86 ± 0.52	1.94 ± 0.63	1.89 ± 0.56	1.94 ± 0.64	1.92 ± 0.54
$\dot{V}E_{peak}$, L/min [a]					
MICT	76 ± 28	86 ± 27	88 ± 25	90 ± 25	89 ± 21
HIIT	84 ± 18	92 ± 20	92 ± 27	96 ± 24	97 ± 25
Control	69 ± 15	72 ± 22	72 ± 31	71 ± 26	73 ± 21
RER					
MICT	1.14 ± 0.10	1.13 ± 0.05	1.12 ± 0.08	1.13 ± 0.06	1.16 ± 0.09
HIIT [b]	1.16 ± 0.05	1.22 ± 0.06	1.18 ± 0.07	1.22 ± 0.06	1.19 ± 0.06
Control	1.13 ± 0.07	1.12 ± 0.10	1.13 ± 0.11	1.11 ± 0.09	1.11 ± 0.06
MRT, s [c]					
MICT	78 ± 46	67 ± 39	52 ± 43	42 ± 35	49 ± 25
HIIT	78 ± 37	58 ± 25	59 ± 50	40 ± 29	49 ± 20
Control	76 ± 37	78 ± 50	78 ± 53	71 ± 51	72 ± 27
PO @ VT, W					
MICT	91 ± 32	111 ± 42*	123 ± 45$^{*\dagger\#}$	132 ± 47$^{*\dagger\#}$	131 ± 44$^{*\dagger\#}$
HIIT	115 ± 32	129 ± 34$^{*\#}$	142 ± 37$^{*\dagger\#}$	145 ± 34$^{*\dagger\#}$	148 ± 43$^{*\dagger\#}$

Control	83 ± 25	83 ± 20	87 ± 27	82 ± 26	90 ± 27

Data are mean (SD). PO, power output; $\dot{V}O_2$, oxygen consumption; HR, heart rate; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, minute ventilation; RER, respiratory exchange ration; MRT, mean response time; VT, ventilatory threshold. [*]Significantly different from week 0 ($P < 0.05$); [†] significantly different from week 3 ($P < 0.05$); [‡] significantly different from week 6 ($P < 0.05$); [#]significantly different from control ($P < 0.05$); [a] significantly different at pretraining than all other timepoints ($P < 0.05$); [b] significantly different from MICT & Control ($P < 0.05$); [c] significantly different at week 9 compared with pretraining ($P < 0.05$).

Table 3 *Parameter estimates for the % [HHb+Mb] profile for all groups plotted as a function of normalised PO(%) as well as the rate of increase in $\dot{V}O_2$ relative to PO (i.e. $\Delta\dot{V}O_2/\Delta PO$) during ramp incremental test throughout the intervention period.*

	Pretraining	Week 3	Week 6	Week 9	Posttraining
$Slope_1$					
MICT	1.96 ± 0.60	1.40 ± 0.19*#	1.41 ± 0.32*	1.36 ± 0.29*#	1.37 ± 0.22*#
HIIT	1.89 ± 0.63	1.35 ± 0.49*	1.43 ± 0.39*	1.28 ± 0.24*#	1.31 ± 0.12*#
Control	1.80 ± 0.49	1.83 ± 0.45	1.80 ± 0.38	1.83 ± 0.53	1.85 ± 0.25
$Slope_2$					
MICT	0.21 ± 0.31	0.15 ± 0.20	0.11 ± 0.24	0.12 ± 0.17	0.07 ± 0.57
HIIT	-0.1 ± 0.56	0.15 ± 0.17	0.19 ± 0.23	0.14 ± 0.19	-0.08 ± 0.47
Control	0.00 ± 0.53	0.18 ± 0.55	0.07 ± 0.27	0.04 ± 0.28	-0.08 ± 0.63
BP, % PO					
MICT	72.2 ± 14.3	75.5 ± 14.9	73.4 ± 17.2	75.3 ± 14.5	78.6 ± 10.2
HIIT	77.4 ± 13.4	75.4 ± 15.6	74.9 ± 14.1	74.0 ± 17.7	78.7 ± 7.9
Control	74.5 ± 16.3	72.4 ± 11.1	70.8 ± 19.7	71.7 ± 11.8	71.4 ± 15.2
$\Delta\dot{V}O_2/\Delta PO$, $mL.min^{-1}.W^{-1}$					
MICT	9.1 ± 1.4	9.9 ± 1.5	10.3 ± 1.6	10.1 ± 1.8	9.6 ± 1.6
HIIT	9.5 ± 1.1	9.2 ± 1.5	9.5 ± 0.6	9.7 ± 0.8	9.8 ± 0.9
Control	9.2 ± 1.1	9.4 ± 1.1	9.0 ± 1.8	9.1 ± 2.1	9.1 ± 1.3

Data are mean (SD). $Slope_1$ and $slope_2$ are the slopes of the double linear regression before and after the break point (BP) respectively. PO, power output; $\dot{V}O_2$, oxygen consumption. The $\Delta\dot{V}O_2/\Delta PO$ slope was calculated over the same range of PO as used to determine the first %Δ[HHb+Mb]/%PO slope ($slope_1$).

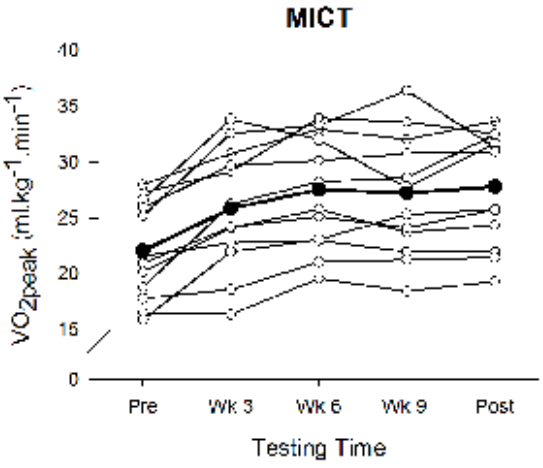
* Significantly different from week 0 ($P < 0.05$) # significantly different from control ($P < 0.05$).

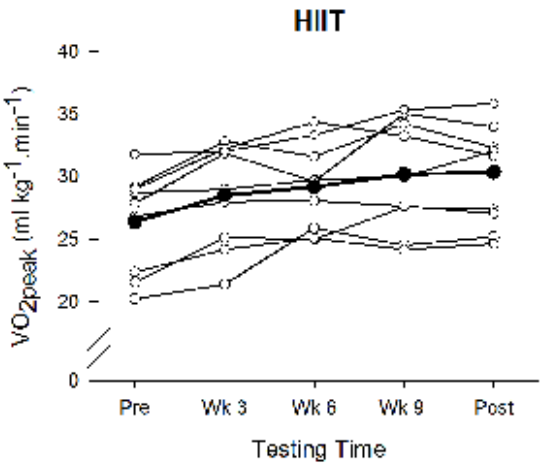
Fig 1

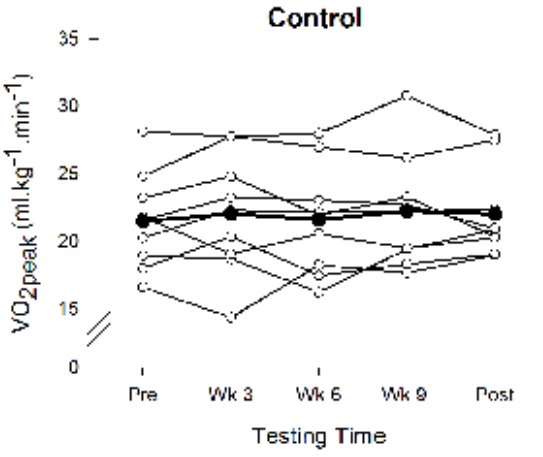

Enrolment
Pre-screened
(n = 300)
Screened/assessed for eligibility
(n = 59)
Excluded (n = 24)
- Not meeting inclusion criteria (n = 12)
- Declined to participate (n = 12)
Randomized
(n = 35)
Allocation
Allocated to Control intervention
(n = 12)
Allocated to MICT intervention
(n = 13)
Allocated to HIIT intervention
(n = 10)
Follow-up
Discontinued intervention (n = 3)
- Due to personal reasons
Discontinued intervention (n = 2)
- Due to personal reasons
Discontinued intervention (n = 3)
- Due to personal reasons
Re-allocated to training (n = 3)
- MICT (n = 1)
- HIIT (n = 2)
Analysis
Analyzed (n = 9)
Analyzed (n = 12)
Analyzed (n = 9)

789

Fig 2

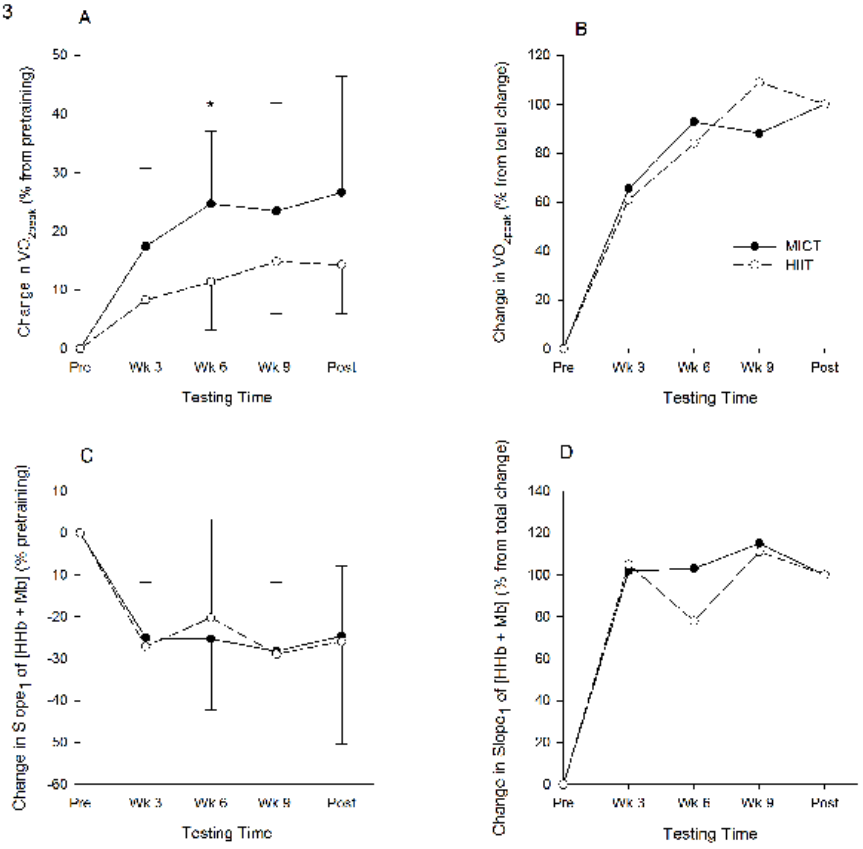

MICT
40
35
30
25
20
15
0
VO2peak (ml.kg-1.min-1)
Pre
Wk 3
Wk 6
Wk 9
Post
Testing Time


HIIT
40
35
30
25
20
0
VO2peak (ml kg-1.min-1)
Pre
Wk 3
Wk 6
Wk 9
Post
Testing Time


Control
35
30
25
20
15
0
VO2peak (ml.kg-1.min-1)
Pre
Wk 3
Wk 6
Wk 9
Post
Testing Time

790

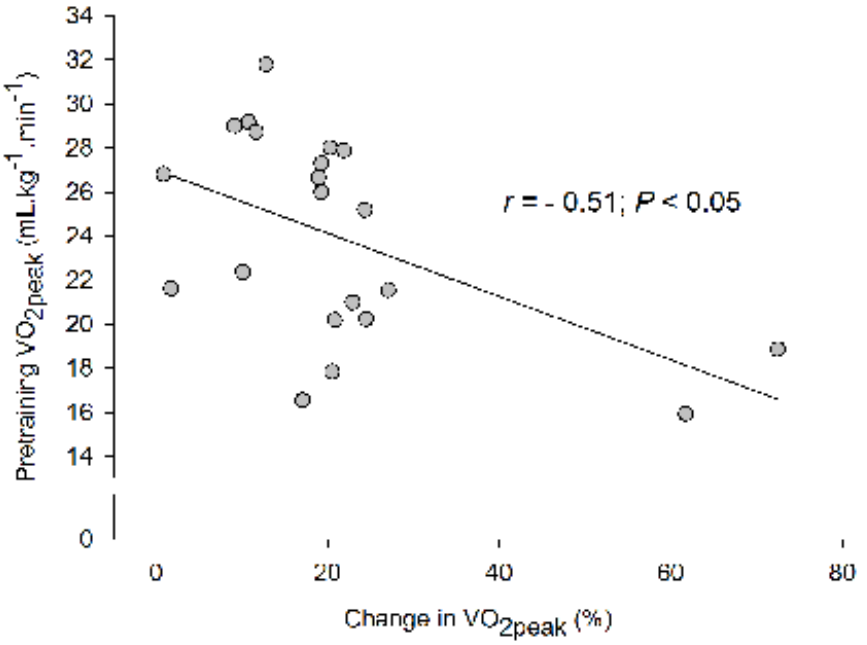
Fig 3


A
B
C
D
Change in VO2peak (% from pretraining)
Change in VO2peak (% from total change)
Change in Slope1 of [HHb + Mb] (% pretraining)
Change in Slope1 of [HHb + Mb] (% from total change)
Pre
Wk 3
Wk 6
Wk 9
Post
Testing Time
MICT
HIIT
*

791

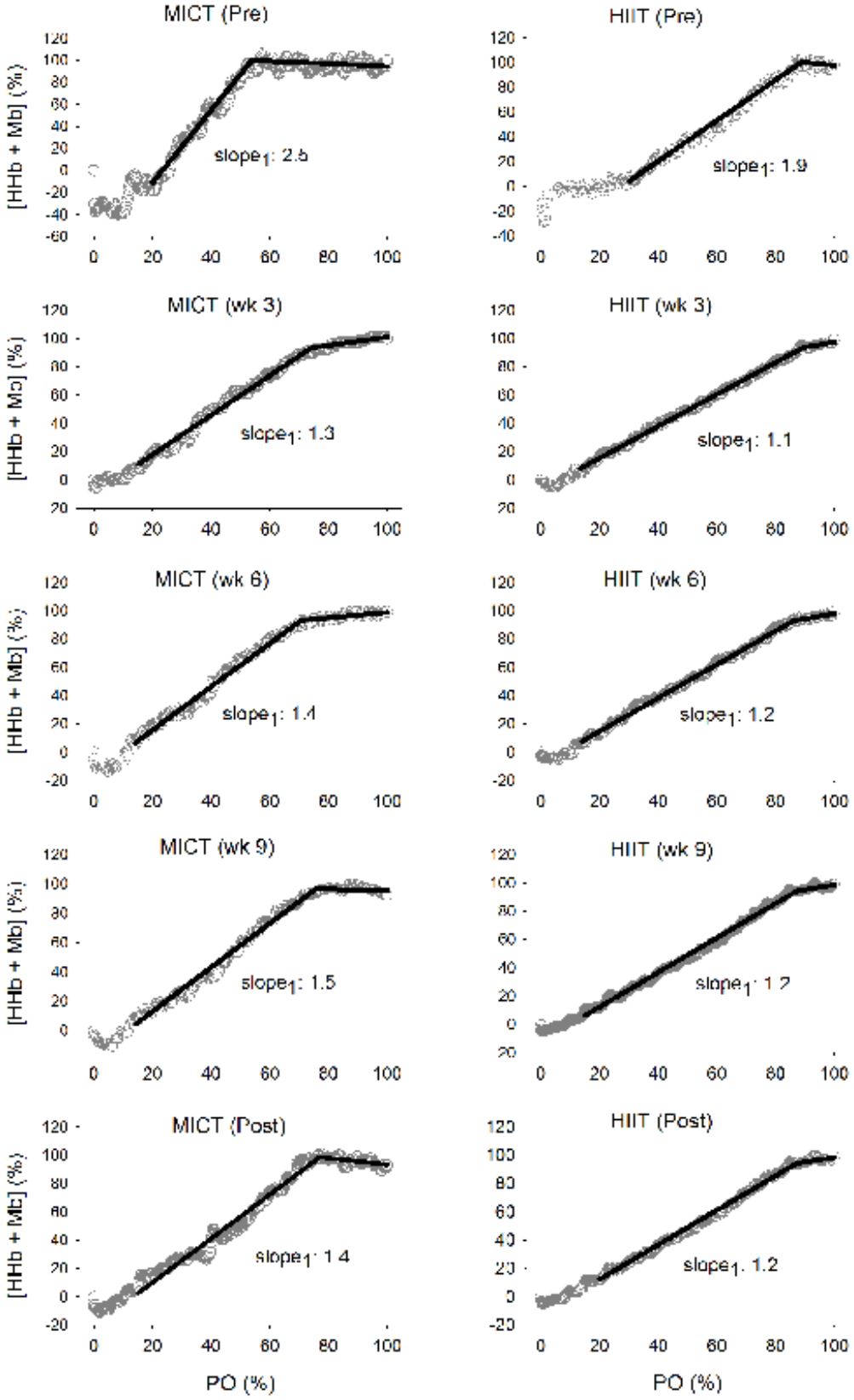
792

Fig 4


Pretraining VO_{2peak} ($mL.kg^{-1}.min^{-1}$)
34
32
30
28
26
24
22
20
18
16
14
0
0
20
40
60
80
Change in VO_{2peak} (%)
r = - 0.51; P < 0.05

793

Fig. 5


MICT (Pre)
HIIT (Pre)
MICT (wk 3)
HIIT (wk 3)
MICT (wk 6)
HIIT (wk 6)
MICT (wk 9)
HIIT (wk 9)
MICT (Post)
HIIT (Post)
[HHb + Mb] (%)
slope1: 2.5
slope1: 1.9
slope1: 1.3
slope1: 1.1
slope1: 1.4
slope1: 1.2
slope1: 1.5
slope1: 1.2
slope1: 1.4
slope1: 1.2
PO (%)

794