Effects of high-intensity interval vs moderate-intensity continuous training on the time course adaptations in cardiovascular fitness and oxygen uptake kinetics in type 2 diabetes.

Thesis submitted for the degree of Doctor of Philosophy in Physiology at the University of Dublin, Trinity College.

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I. DECLARATION

I declare that this thesis is entirely of my own work with the exception of the testing of 5 participants at week 0 and week 3 which was completed by Dr Norita Gildea and Dr Joel Rocha, the completion of the majority of the exercise stress tests with the study participants by Dr Norita Gildea and Dr Mehmoona, the collection of blood samples by Dr Joel Rocha and Dr Noreen Boyle and the recruitment of 21 of the participants who completed the intervention by Dr Norita Gildea. This thesis has not been previously submitted for a degree in this or any other university. Trinity College Dublin may lend or copy this thesis on request.

Signature: ________________________________

Date: ___________________________

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III. Abstract

Individuals with type 2 diabetes mellitus (T2DM) present with significant impairments in the dynamic and peak responses of pulmonary oxygen uptake ($\dot{V}O_2$) during exercise. Both low-volume high-intensity interval training (LVHIIT) and moderate-intensity continuous training (MICT) have been shown to be effective at increasing maximal exercise capacity ($\dot{V}O_{2max}$) in individuals with T2DM, however, the mechanisms and time course of adaptations have not yet been investigated. While MICT has been shown to be effective at accelerating the rate of increase of $\dot{V}O_2$ at the onset of submaximal steady-state exercise (i.e. $\dot{V}O_2$ kinetics), the time course and mechanisms of adaptation are unclear. Furthermore, the effect of LVHIIT on $\dot{V}O_2$ kinetics in T2DM has yet to be investigated. Accordingly, the primary aims of this thesis were to compare the effects of 12 weeks of MICT vs 12 weeks of LVHIIT on the mechanisms and time course of adaptation in a) $\dot{V}O_{2max}$ and b) $\dot{V}O_2$ kinetics to different submaximal exercise transitions in people with uncomplicated T2DM.

Three experiments were carried out. *Experiment 1* compared the effects of 12 weeks of MICT with LVHIIT on the central and peripheral mechanisms and time course adaptation in $\dot{V}O_{2max}$ in people with uncomplicated T2DM. It was hypothesised that both exercise interventions would improve $\dot{V}O_{2max}$ by inducing changes in central (via increases in cardiac output) and peripheral (via increases in muscle fractional oxygen extraction, estimated using changes in deoxygenated haemoglobin and myoglobin concentration, [HHb+Mb]) mechanisms. Thirty-one participants with T2DM (18 men, mean ± SD, age: 53 ± 9 yr, body mass index: 30.1 ± 4.5 kg.m^{-2}) were randomly assigned to MICT (*n* = 13, 8 men, 50 min of moderate-intensity cycling), LVHIIT (*n* = 9, 6 men, 10 x 1 min at ~90% maximal heart rate interspersed by 1 min of 'unloaded' cycling) or to a non-exercising control (CON) group (*n* = 9, 5 men). Exercising groups trained 3 times/week with intensity adjusted every 3 weeks. $\dot{V}O_{2max}$ significantly increased after 3 weeks of MICT (+17%; $P < 0.05$) and LVHIIT (+8%; $P < 0.05$) with no further significant changes thereafter (total increases in $\dot{V}O_{2max}$ after 12 weeks of MICT and LVHIIT were 24% and 13% respectively). In terms of central adaptations to training, both MICT and LVHIIT significantly increased peak cardiac output within 3 and 9 weeks of training respectively, with no further changes thereafter. Regarding peripheral adaptations, after 3 weeks of training

there was a significant decrease in the slope of the first linear component of the Δ [HHb+Mb] % vs Δ % peak power output (PO_{peak}) profile (data was curve fitted using a double-linear model) in both the LVHIIT and MICT groups with no further changes observed thereafter, which is indicative of a reduction in the over reliance on O_2 extraction due to an improved microvascular O_2 delivery. No changes in physical fitness were observed in the CON group.

The subsequent 2 experiments focused on the effects of MICT and LVHIIT on the time course and mechanisms of adaptation in $\dot{V}O_2$ kinetics responses during different submaximal exercise transitions in T2DM. *Experiment 2* investigated the effects of 12 weeks of MICT and LVHIIT on $\dot{V}O_2$ and muscle deoxygenation ([HHb+Mb]) kinetics during rest to moderate-intensity (80% of each participant's ventilatory threshold, VT) cycling exercise transitions. A secondary aim was to explore the effects of heavy-intensity (50% Δ, PO equivalent to 50% between the VT and PO_{peak}) 'priming' exercise (PE) on subsequent moderate-intensity $\dot{V}O_2$ kinetics responses throughout the exercise training interventions. Unlike the CON group, both LVHIIT and MICT significantly accelerated $\dot{V}O_2$ kinetics after only 3 weeks of training with no further improvements thereafter. In addition, the lack of adjustment in [HHb+Mb] profiles with training resulted in a significant reduction in the 'overshoot' of the Δ[HHb+Mb]/$\Delta\dot{V}O_2$ ratios observed at baseline in the MICT and LVHIIT groups only, thus, reflecting a superior matching of microvascular O_2 delivery to utilisation. At week 0 PE significantly accelerated $\dot{V}O_2$ kinetics and significantly reduced the overshoot of the Δ [HHb + Mb]/$\Delta\dot{V}O_2$ ratio during a subsequent bout of moderate-intensity exercise in all groups. However, there was no effect of PE on any of the $\dot{V}O_2$ parameters observed in the LVHIIT and MICT groups beyond 3 weeks of training while the overshoot remained apparent in the control group. This finding further strengthens the evidence that both LVHIIT and MICT improved submaximal exercise capacity by improving the ability of the microvasculature to deliver or redistribute O_2 to the exercising muscle resulting in a decreased reliance on O_2 extraction for a given workload.

Since everyday functional activities involve transitions between exercise intensities, *Experiment 3* investigated the effects of 12 weeks of MICT and LVHIIT on $\dot{V}O_2$ and muscle deoxygenation ([HHb+Mb]) kinetics during heavy-intensity (50% Δ) cycling exercise initiated from an elevated baseline (i.e. work-to-work transitions). In addition, as in *Experiment 2*, the effects of PE on these responses were also assessed. Both LVHIIT and MICT accelerated the overall $\dot{V}O_2$ kinetics response during heavy-intensity exercise after 3 weeks of training through a speeding of the time constant of the primary $\dot{V}O_2$ ($\tau\dot{V}O_{2P}$) response and a reduction in amplitude of the slow component ($\dot{V}O_{2SC}$). The significant reduction in $\tau\dot{V}O_{2P}$ with MICT and LVHIIT in the presence of an unaltered [HHb + Mb] response profile indicates a likely improvement in O_2 delivery; whereas, the significant reduction in the $\dot{V}O_{2SC}$ amplitude after just 3 weeks of MICT and LVHIIT is indicative of exercise induced adaptations in the intrinsic properties of the skeletal muscle and alterations in motor unit recruitment patterns. PE significantly reduced the $\tau\dot{V}O_{2P}$ as well as $\dot{V}O_{2SC}$ amplitude during a subsequent bout of heavy-intensity exercise initiated from an elevated baseline at week 0 in all groups. However, there was no effect of PE on any of the $\dot{V}O_2$ parameters observed beyond 3 weeks of training only in the LVHIIT and MICT groups.

Taken together, the findings of this thesis show that both MICT and LVHIIT improve maximal exercise capacity and accelerate the dynamic response of $\dot{V}O_2$ during rest to moderate and moderate to heavy-intensity submaximal exercise transitions in T2DM by a similar magnitude and within a similar timeframe. Moreover, the reduction in the reliance on O_2 extraction during maximal and submaximal exercise indicates that both interventions induced an improvement in peripheral microvascular blood flow that is, at least in part, responsible for the improvements in exercise capacity observed. Importantly, LVHIIT induced these benefits with a time commitment that was more than 50% less than MICT (60 vs. 150 min per week), and given that 'lack of time' is consistently presented as one of the primary barriers to exercise participation, it is likely that high-intensity interval training can be an effective intervention to increase exercise adherence rates in people living with T2DM.

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V. List of abbreviations and symbols.

% PO	percentage power output
Δ	delta; a difference or change in value
≈	approximately
<	less than
>	greater than
1RM	1 repetition maximum
2-hr OGTT	2 hour oral glucose tolerance test
50% Δ	value equivalent to half of the difference between peak workload and workload at ventilatory threshold
70% Δ	value equivalent to 70% of the difference between peak workload and workload at ventilatory threshold
α	alpha
A	asymptotic amplitude of a mathematically modelled response
a.u.	arbitrary units
ABI	ankle: brachial index
ACSM	American College of Sports Medicine
ADA	American Diabetes Association
Akt	protein kinase B
AMP-K	adenosine monophosphate activated protein kinase
ANOVA	analysis of variance
ATP	adenosine triphosphate
$a\text{-}vO_2$	arteriovenous oxygen difference
$a\text{-}vO_{2max}$	maximum arteriovenous oxygen difference
β	beta
BA	brachial artery
BBS	Borg breathlessness scale
BMI	body mass index
BP	blood pressure
cm	centimetre
CO_2	carbon dioxide
CON	control
$counts.min^{-1}$	counts per minute

CP	critical power
CS	citrate synthase
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DP	dorsalis pedis artery
ECG	electrocardiograph
EMG	electromyography
EST	exercise stress test
FG	fasting glucose
Fig	figure
FMD	flow mediated dilation
g	gram
G	change in $\dot{V}O_2$ per unit change in external work (i.e. $\Delta \dot{V}O_2/\Delta PO$)
GET	gas exchange threshold
GLUT4	glucose transport type 4
$h.day^{-1}$	hours per day
H^+	hydrogen ion
Hb	haemoglobin
HbA_{1c}	glycated haemoglobin
HC	hip circumference
HDL	high density lipo-protein
[HHb + Mb]	deoxyhaemoglobin and myoglobin
Δ[HHb +Mb]	changes in the deoxyhaemoglobin and myoglobin concentration
[HHb + Mb]-BP	Deoxyhaemoglobin and myoglobin break point
[HHb + Mb]TD	Time Delay of the [HHb + Mb] kinetics response
[HHb + Mb] τ	time constant of the [HHb + Mb] kinetics response
τ' [HHb + Mb]	effective time constant of the [HHb + Mb] kinetics response
Δ [HHb]/$\Delta \dot{V}O_2$	haemoglobin and myoglobin deoxygenation to oxygen uptake ratio
HIIT	high-intensity interval training
$hr.day^{-1}$	hours per day

HR	heart rate
HR_{max}	maximal heart rate
HRpeak	peak heart rate
hz	hertz
IDF	International Diabetes Federation
IGT	impaired glucose tolerance
IRS	insulin receptor substrate
kg	kilogram
$kg.m^{-2}$	kilogram per metre squared
L	litre
$L.min^{-1}$	litres per minute
LDL	low density lipo-protein
LED	light emitting diode
LVC	leg vascular conductance
LVHIIT	low-volume high-intensity interval training
m	metre
$m.s^{-1}$	metres per second
MAP	mean arterial pressure
max	maximum
$MET.hr^{-1}. wk^{-1}$	MET hours per week
METs	metabolic equivalents
$mg.dL^{-1}$	milligram per decilitre
MICT	moderate-intensity continuous training
Min	minute
mL of $O_2.100ml^{-1}$	millilitres per 100 millilitres of oxygen
$mL.min^{-1}.W^{-1}$	millilitre per minute per watt
$ml^{-1}.kg^{-1}.min^{-1}$	millilitre per kilogram per minute
mm	millimetre
mM	millimolar
mmHg	millimetre of mercury
$mmol.L^{-1}$	millimoles per litre
$mmol/mol^{-1}$	millimoles per mol
MOD A	‘unprimed’ moderate-intensity exercise
MOD B	‘primed’ moderate-intensity exercise

MRT	mean response time
MVC	maximum voluntary contraction
n	number of participants
N_2O	nitrous oxide
NADH: O2	nicotinamide adenine dinucleotide oxidoreductase
NIRS	Near-infrared spectroscopy
NO	nitric oxide
O_2	oxygen
O_2 Hb	oxyhaemoglobin
P	probability (statistics)
PAD	peripheral arterial disease
PCr	phosphocreatine
PDH	pyruvate dehydrogenase
PE	priming exercise
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PDK1	3-phosphatidylinositol (3, 4, 5)-triphosphate
Phase I	cardiodynamic phase of the $\dot{V}O_2$ kinetics response
Phase II	primary phase of the $\dot{V}O_2$ kinetics response
Phase III	attainment of steady state of the $\dot{V}O_2$ kinetics response
Pi	inorganic phosphate
PI3-K	phosphatidylinositol 3-kinase
PIL	participant information leaflet
PIP_2	phosphatidylinositol (3, 4)-bisphosphate
PIP_3	phosphatidylinositol (3, 4, 5)-trisphosphate
Pmvo2	microvascular O_2 partial pressure
$P_{MV}O_2$	microvascular PO_2
PO	power output
PO_{peak}	peak power output
PT	posterior tibial artery
Q	cardiac output
Q_{max}	maximal cardiac output
Q_m	microvascular blood flow
r	correlation coefficient

RCP	respiratory compensation point
RER	respiratory exchange ratio
RI	ramp incremental test
RPE	rating of perceived exertion
RPM	revolutions per minute
RST	repeated sprint training
RVU	rebreathing valve unit
s	second
S_1	Slope 1 of the %Δ [HHb] vs %ΔPO profile
S_2	Slope 2 of the %Δ [HHb] vs %ΔPO profile
SBP	systolic blood pressure
SD	standard deviation
SF_6	sulfur hexafluoride
SS	steady state
SV	stroke volume
t	time
τ'	effective time constant
τ	time constant
T2DM	Type 2 diabetes mellitus
TC	total cholesterol
TCD	Trinity College Dublin
TD	time delay
TG	triglyceride
TOI	total oxygenation index
TTF	time to failure
$\dot{V}CO_2$	carbon dioxide output
$\dot{V}_e$	expired minute ventilation
VL	vastus lateralis
VM	vector magnitude
$\dot{V}O_2$ kinetics	oxygen uptake kinetics
$\dot{V}O_2$	oxygen uptake
$\dot{V}O_2b$	oxygen uptake at baseline
$\dot{V}O_{2max}$	maximal oxygen uptake
$\dot{V}O_{2MRT}$	mean response time of oxygen uptake kinetics response

$\dot{V}O_{2P}$	primary phase of the VO_2 kinetics response
$\dot{V}O_{2peak}$	peak oxygen uptake
$\dot{V}O_{2SC}$	oxygen uptake 'slow-component'
$\tau\dot{V}O_{2P}$	time constant of the primary phase of the VO_2 kinetics response
VT	ventilatory threshold
W	Watts
$W.min^{-1}$	watts per minute
WC	waist circumference
W: H	waist to hip ratio
W-to-W	work-to-work exercise transition
yr	year

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1. Introduction.

1.1. Overview.

The increasing global prevalence and incidence of type 2 diabetes mellitus (T2DM) is one of the major healthcare challenges of modern times. The accelerated rise in T2DM worldwide is a result of the rising levels of obesity in addition to the behavioural shift towards a more sedentary lifestyle. Currently, particular concern is drawn to the low levels of physical activity in T2DM (Steeves *et al.* 2015) and the apparent T2DM-induced exercise intolerance, characterised by impairments in maximal and submaximal exercise capacity (Green *et al*. 2015), factors that correlate strongly with all-cause mortality (Wei *et al.* 2000).

Moderate-intensity continuous aerobic training (MICT) has been shown to improve peak exercise responses and the rate of increase in pulmonary oxygen uptake, $\dot{V}O_2$ ($\dot{V}O_2$ kinetics) in T2DM (Brandenburg *et al.* 1999; MacAnaney *et al.* 2012). However, the mechanisms and time course of adaptation of these improvements in maximal and submaximal exercise capacity in response to MICT in T2DM remain unclear. There is growing interest in investigating whether exercise interventions of a shorter duration but higher-intensity, such as low volume high-intensity interval training (LVHIIT) can induce benefits of a similar magnitude to those seen with MICT in T2DM. Recent studies have shown that LVHIIT in T2DM is effective at improving exercise capacity, mitochondrial function and vascular function in the short-term (Little *et al.* 2011; Madsen *et al*. 2015). However, a comparison of the time course and mechanisms of adaptations in maximal and submaximal exercise capacity in response to LVHIIT in T2DM has yet to be completed.

This introduction will firstly describe the underlying pathophysiology and clinical management of T2DM. It will then focus on the characteristic exercise intolerance observed in this population and the potential underlying mechanisms of this intolerance. The possible role of priming exercise (PE) or heavy-intensity warm up on subsequent submaximal exercise in T2DM will also be described; and finally, the current roles of MICT and LVHIIT in reducing exercise intolerance in T2DM will be examined.

1.2. Type 2 diabetes mellitus.

Type 2 diabetes mellitus (T2DM) is a complex metabolic condition with an increasing national and global prevalence. The estimated global diabetic population has risen from 108 million in 1980 to 422 million in 2014 (NCD Risk Factor Collaboration, 2016). Currently, in Ireland, there are an estimated 208,000 people between the ages of 20-79 years living with T2DM, with this figure predicted to increase to approximately 280,000 by the year 2030 (International Diabetes Federation, 2015). The characteristic clinical traits of T2DM are chronic hyperglycaemia and impaired glycaemic control as a result of a chronic perturbation of blood glucose homeostasis. The diagnostic criteria for T2DM are outlined by the American Diabetes Association (ADA) as follows (Colberg *et al.* 2010):

1) Fasting glycated haemoglobin (HbA_{1c}) ≥ 6.5% (48 $mmol/mol^{-1}$),

2) Fasting plasma glucose ≥ 126 $mg.dL^{-1}$ (7.0 $mmol.L^{-1}$),

3) 2-hour plasma glucose ≥ 200 $mg.dL^{-1}$ (11.1 $mmol.L^{-1}$) during an oral glucose tolerance test using 75 g of glucose,

4) Presenting with a combination of the typical symptoms associated with hyperglycaemia such as polyuria, polydipsia, and unexplained weight loss

5) Presenting with a hyperglycaemic crisis with a random plasma glucose of 200 $mg.dL^{-1}$ (11.1 $mmol.L^{-1}$) or higher.

Normal glucose homeostasis depends on the tight matching of glucose appearance in the blood stream through ingestion of substrates and hepatic glucose output and glucose disappearance, with skeletal muscle responsible for 80% of glucose uptake (DeFronzo *et al.* 1981). However, glucose entry into the muscle cell requires the involvement of a carrier protein to facilitate movement across the cell membrane (Ryder *et al.* 2001). This is accomplished through the insulin-dependent translocation of glucose transporter 4 (GLUT4) from the intracellular pool to the plasma membrane. The insulin-dependent mobilisation of GLUT4 is initiated by the binding of insulin to its receptor; insulin receptor substrate (IRS), followed by a specific intracellular signalling cascade and the activation of phosphatidylinositol 3-kinase (PI3-K), which is essential in the regulation of glucose transport into the muscle cell (Fig. 1.1). However, it is important to note that regular skeletal muscle contractions during exercise also initiate the translocation of GLUT 4 from the intracellular pool to the cell membrane independently of insulin. This is achieved through increases in the activity of adenosine monophosphate-activated protein kinase (AMP-K).

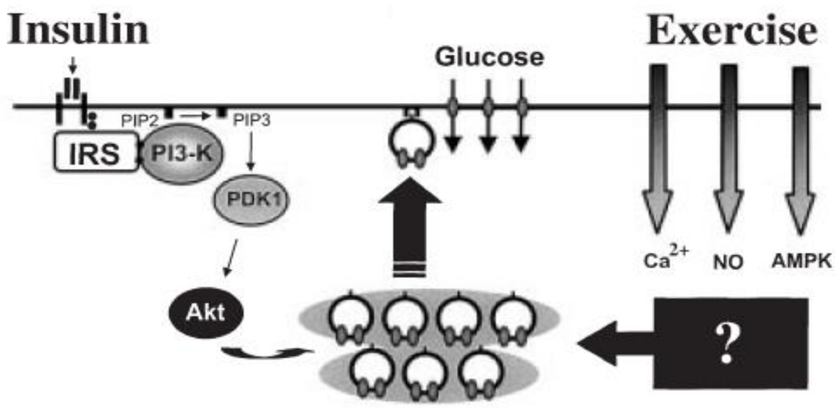

Figure 1.1. Illustration of insulin- and exercise-stimulated glucose transport into the skeletal muscle cell. This is accomplished by the translocation of GLUT4 from the intracellular pool to the plasma membrane. Insulin-stimulated glucose transport is dependent upon the activation of phosphatidylinositol 3-kinase (PI3-K). The activation of PI3-K results in the conversion of phosphatidylinositol (3, 4)-bisphosphate (PIP_2) to phosphatidylinositol (3, 4, 5)-trisphosphate (PIP_3) which in turn causes the activation of 3-phosphoinositide-dependent protein kinase 1 (PDK1) and protein kinase B (Akt) leading to GLUT4 translocation to the cell membrane. Exercise-stimulated glucose transport is PIK-3 independent and it is thought that exercise increases the activity of AMP activated protein kinase (AMP-K) which increases GLUT4 translocation to the cell membrane (adapted from Ryder *et al.* 2001; Hemmings & Restuccia, 2012).

The primary action of the hormone insulin is the regulation of glucose uptake and its disposal in skeletal muscle and adipose tissue (Lambadiairi *et al*. 2015). In addition, insulin has an important vasodilatory function that improves nutrient flow into the tissues and increases microvascular vessel recruitment during post-prandial periods to enhance substrate disposal (Vincent *et al.* 2002; Newman *et al.* 2007). Insulin is secreted from the β-cells of the pancreas and there is a growing body of evidence to suggest that β-cell dysfunction is the primary mechanism leading to the development of T2DM. Several underlying mechanisms have been suggested as the cause of β-cell dysfunction such as chronic hyperglycaemia, chronic low grade inflammation caused by obesity, high levels of saturated fats in the circulation, chronic oxidative stress resulting in mitochondrial damage in the pancreas and insulin resistance (Cerf, 2013).

Chronic hyperglycaemia contributes to β-cell dysfunction by causing β-cell exhaustion which leads to impaired insulin responses to episodes of hyperglycaemia and also during periods of hypoglycaemia (Cerf, 2013). Furthermore, it has been suggested that over-stimulation of the β-cells increases the production of reactive oxygen and nitrogen species which in turn inhibits electron transport chain activity within the pancreatic mitochondria. This results in reduced energy production and the formation of advanced glycation end-products (Drews *et al.* 2010; Cerf, 2013). Moreover, hyperglycaemia results in extended periods of chronic low grade inflammation and oxidative stress which can lead to cellular damage and apoptosis within the pancreas. In fact, it has been observed that people with T2DM can exhibit a 40-60% loss of β-cell mass (Butler *et al.* 2003; Pandey *et al.* 2015).

In addition to β-cell dysfunction, there is ample evidence to indicate that insulin resistance significantly contributes to the development of T2DM (Chiasson & Rabasa-Lhoret, 2004). Both β-cell dysfunction and insulin resistance result from the interaction between a person's genetic disposition to develop T2DM and a variety of other risk factors such as body composition, low physical activity level, poor diet and obesity (Khan, 2003).

Insulin resistance is the desensitisation of tissues, especially skeletal muscle, to insulin resulting in a significant reduction in glucose uptake, a reduction in nutrient flow to the peripheral tissues and an increasingly hyperglycaemic state in the body (Bird and Hawley, 2012). Insulin resistance has been strongly linked to obesity with several studies identifying it as the primary risk factor for its development (Hall *et al*. 2002; Chiasson & Rabasa-Lhoret, 2004). Moreover, obesity causes increased levels of circulating free fatty acids and triglycerides which compete with glucose for substrate oxidation and subsequently inhibit the cellular uptake of glucose resulting in persistent hyperglycaemia. Furthermore, the nutrient overload and insulin demand associated with obesity results in islet inflammation within the pancreas and β-cell exhaustion. In addition, the chronic low grade systematic inflammation associated with obesity has been shown to induce insulin resistance (Arnetz *et al.* 2014; Pandey *et al*. 2015).

1.3. Clinical Management of T2DM.

People diagnosed with T2DM are exposed to a heightened risk of developing other significant co-morbidities. For instance, people living with T2DM have an increased risk of developing vascular complications such as peripheral neuropathies, nephropathies, retinopathies and peripheral vascular disease (Utsunomiya *et al.* 2012). Furthermore, T2DM results in a two-fold increase in the risk of developing cognitive impairment and/or vascular dementia (Feil *et al.* 2012). Those living with T2DM experience a four-fold increase in the risk of experiencing a significant cardiovascular event such as a stroke or myocardial infarction compared with those without the condition (Arnetz *et al.* 2014). In addition, those with T2DM typically have a worse prognosis following a cardiovascular event than those without T2DM (Pandey *et al.* 2015). In fact, it has been estimated that approximately 65 - 75% of diabetes related deaths are caused by cardiovascular disease (Tanasecu *et al.* 2003; Vamos *et al.* 2012; Pandey *et al.* 2015).

The clinical management of T2DM focuses on achieving optimal glycaemic control and the prevention and treatment of diabetic co-morbidities. Lifestyle modifications have been identified as one of the cornerstones of the management of T2DM alongside pharmacological interventions (ADA, 2016). Targeting the modifiable risk factors of T2DM such as obesity, low levels of physical activity and poor diet through lifestyle modification has been reported to prevent the onset of T2DM in at risk populations (Pan *et al.* 1997; Tuomilehto *et al*. 2001; Knowler *et al.* 2002).

1.3.1 Pharmacological management of T2DM

Frontline management of uncomplicated T2DM typically involves lifestyle modification in combination with at least one appropriately prescribed anti-diabetic medication. If this management strategy improves glycaemic control to a significant extent (typically if consecutive fasting blood glucose levels < 5.6 mmol/L^{-1} or fasting HbA_{1c} levels of < 48 mmol/mol^{-1} are reported), then pharmacological therapy may be removed in preference to lifestyle modifications alone. However, if consistent HbA_{1c} levels > 59 mmol/mol^{-1} persist following the initial intervention then multiple anti-diabetic medications may be prescribed to improve glycaemic control. Commonly prescribed anti-diabetic medications include the following:

Metformin: Prescribed to reduce blood glucose levels. It achieves this by increasing insulin sensitivity and by increasing the activation of AMP-K in the liver which increases hepatic glucose uptake and inhibits gluconeogenesis (Chaudhury *et al.* 2017).

Sulfonylureas: Reduce blood sugar levels by increasing insulin levels in the pancreas by closing pancreatic cell potassium channels. They also reduce the breakdown of lipids into fatty acids and reduce hepatic insulin clearance (Proks *et al.* 2002). Sulfonylureas are frequently used in conjunction with metformin to increase pancreatic β-cell insulin secretion in a glucose-independent manner (Niswender, 2010).

Glucagon like Peptide-1 Receptor Agonists: Utilised to improve glycaemic control by stimulating insulin secretion while also suppressing glucagon secretion and slowing gastric emptying (Chaudhury *et al*. 2017).

Thiazolidinedione: Facilitates glucose uptake by enhancing insulin sensitivity. Also aids in the preservation of β-cell function and reduction of insulin resistance by reducing chronic inflammation and preventing fatty acid accumulation (Reusch *et al.* 2003; Chaudhury *et al*. 2017).

In addition to pharmacological therapies, regular exercise has been established as a key cornerstone in the management of T2DM. A combined statement by the ADA and American College of Sports Medicine (ACSM) states that in order to achieve the exercise-induced health benefits, those with T2DM should be aiming to complete at least 150 minutes of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity per week with an additional 2-3 sessions of moderate-intensity resistance training per week (Colberg *et al*. 2016). Despite these recommendations, people with T2DM do not exercise sufficiently, with many citing lack of time as one of the primary perceived barriers to regular exercise participation (Thomas *et al*. 2004). For instance, a study of people living with T2DM in Britain found that the top three barriers to exercise participation were cultural issues regarding participation in exercise, lack of time and lack of awareness around the benefits of exercise in T2DM (Lawton *et al.* 2006). In an American individuals with T2DM lack of time was the most commonly reported barrier to exercise participation (Dutton *et al.* 2005). More recently a small study of Irish people living with T2DM identified lack of time as being one of the primary barriers to exercise participation (Egan *et al.* 2013). Another barrier to regular exercise participation is the fact that people with T2DM perceive exercise as harder; and demonstrate a reduced tolerance to maximal and submaximal exercise (Huebschmann *et al.* 2009; Green *et al.* 2015).

1.4. Exercise intolerance in T2DM.

1.4.1. Peak aerobic exercise capacity in T2DM.

Peak exercise capacity as determined by peak oxygen consumption ($\dot{V}O_{2peak}$) in people with T2DM has been consistently reported to be between 12-30% lower than those without the condition (Baldi *et al.* 2003; Regensteiner *et al.* 2009; Green *et al.* 2015). This has a significant impact in these individuals as a lower $\dot{V}O_{2peak}$ is associated with a reduced quality of life and an increased risk of all-cause mortality and morbidity (Regensteiner *et al.* 1995; Wei *et al.* 2000). The mechanisms of this reduced $\dot{V}O_{2peak}$ remain to be elucidated, though it is likely that a combination of central and peripheral factors are involved.

1.4.1.1. Peak cardiac output.

The Fick equation states that $\dot{V}O_2$ is the product of oxygen delivery (i.e. Cardiac Output (Q)) and oxygen extraction by the exercising tissues (i.e. arteriovenous oxygen difference (a-vO_2 diff)). In regards to O_2 delivery, it appears that uncomplicated T2DM does not affect peak Q responses (Q_{peak}). For instance, using the CO_2 rebreathing technique, Baldi *et al.* (2003), reported no significant differences in Q_{peak} between participants with and without T2DM, although participants with T2DM showed a significant reduction in peak a-vO_2 diff. An important limitation of this study, however, was that peak values for Q and a-vO_2diff were extrapolated from submaximal estimates of Q (Baldi *et al.* 2003). Consistent with the findings of Baldi *et al.* (2003), Regensteiner *et al.* (2009) reported no differences in Q_{peak} during maximal exercise between premenopausal women with and without T2DM when measured at the end of exercise by both direct Fick and thermodilution methods (Regensteiner *et al.* 2009). In addition, Regensteiner *et al.* (2009) reported no differences in a-vO_2diff between groups during peak exercise using both methods. In contrast, Roy *et al.* (1989) observed a significant reduction in Q_{peak} in individuals with

T2DM compared with healthy controls during peak exercise (Roy *et al.* 1989), however, individuals with T2DM had a confirmed cardiac autonomic dysfunction.

1.4.1.2. Peak muscle deoxygenation responses.

Recent advances in the use of near infrared spectroscopy (NIRS) over the last 20 years has allowed for the non-invasive monitoring and quantification of the oxygenation of human tissue (Elwell, 1995). Briefly, NIRS is based on the ability of light of the near-infrared region of the spectrum (wavelength 700-1000 nm) to pass through living tissue such as skin, muscle and bone (Boushel & Piantadosi, 2000). During the measurement of tissue deoxygenation using NIRS, near infrared light is transmitted from the emitting optode through the area of interrogation in a spherical pattern at an established intensity and at two or more wavelengths surrounding the isosbestic point to a light detecting photodiode which measures the intensity of the existing light. The penetration depth of the emitted light is considered to be approximately half the distance between the two optodes (Kalliokoski *et al.* 2006; Bakker *et al*. 2012).

Compounds that absorb light from the near infrared range within the tissues are referred to as chromophores (Jobsis, 1977) with the primary chromophores of interest in human muscle tissue being oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (HHb). Determining the concentration of these two chromophores within the tissues can therefore provide inferences into the oxygenation state of the tissue are under interrogation. Both HbO_2 and HHb have a unique absorption spectrum (760 nm and 850 nm respectively), with the isosbestic point for both being 798 nm (Chance *et al.* 1982; Mancini *et al*. 1994). However, the absorption spectrum of myoglobin and haemoglobin within skeletal muscle overlap, thus making them indistinguishable by NIRS, therefore the measurements of skeletal muscle oxygenation through the NIRS derived signal reflect the oxygen saturation of both myoglobin and haemoglobin (Grassi *et al*. 2003).

The muscle deoxygenation responses (i.e., deoxygenated haemoglobin and myoglobin, [HHb+Mb]) during ramp exercise tests were initially characterised using a sigmoid model (Ferreira *et al.* 2007; Boone *et al.* 2009; DiMenna *et al.* 2010). The sigmoid model can be described in three regions (Fig. 1.2). The first region shows a blunted initial [HHb + Mb] response and is reflective of a greater increase in muscle blood flow rather than muscle oxygen uptake at the onset of exercise. The second phase can be described as the 'slope' region of the response and reflects the increasing reliance on O_2 extraction as higher worker rates are reached. Finally, the third region indicates a plateau of [HHb + Mb] and is thought to represent the limits of O_2 extraction within the skeletal muscle microvasculature (Ferreira *et al.* 2007).

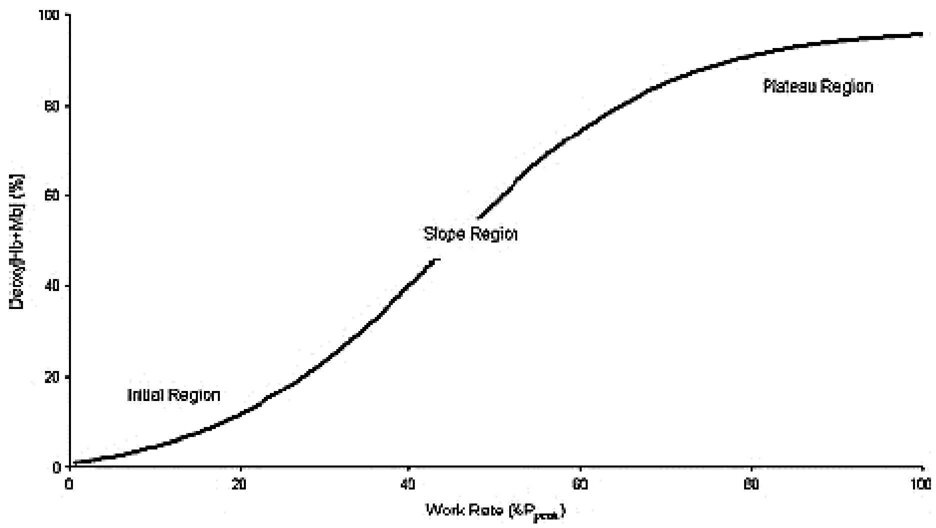

Figure 1.2. Representative plot of the sigmoid model showing the distinct initial, slope and plateau regions. (Taken from Ferreira *et al.* 2007).

However, recent work by Spencer *et al.* (2012a), has suggested that the sigmoid model is more a 'fit of convenience' and may not be physiologically accurate in capturing the [HHb] response during ramp exercise. For instance, there is a suggestion that the initial phase on the sigmoid model significantly underestimates the reliance on O_2 extraction at lower exercise intensities. Furthermore, the final phase of the sigmoid model may significantly overestimate the reliance on O_2 extraction during higher intensities. Therefore, Spencer *et al*. (2012) proposed employing a 'double-linear' model that comprises of 2 linear sections and a breakpoint, whereby the slope of the first line (S_1) represents the rate of [HHb+Mb] during the middle part of the exercise test as the [HHb+Mb] signal begins a systematic increase above baseline (Fig. 1.3). A steeper S_1 is thought to reflect a higher dependency on O_2 extraction for a given increase in workload. The second line (S_2) represents the plateau at which O_2 extraction reaches its limit. A large S_1 is thought to indicate an over reliance on fractional O_2 extraction during exercise (Spencer *et al.* 2012). The breakpoint between the two lines has been suggested to correlate with the maximal lactate steady state and is also thought to be influenced by alterations in neuromuscular activity (Bellotti *et al*. 2013; Boone *et al.* 2015).

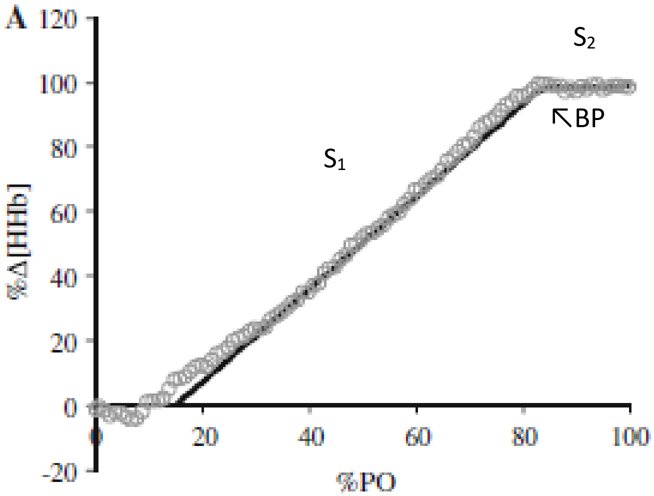

Figure 1.3. Representative plot of the bilinear model proposed by Spencer *et al.* (2012a) whereby S_1 represents the rate of muscle deoxygenation during the middle part of the exercise; S_2 represents the plateau at which O_2 extraction has reached its limit; BP represents the breakpoint between the 2 slopes (adapted from Spencer *et al.* 2012a).

Indeed, when Spencer *et al.* (2012a) compared the suitability of the sigmoid model and the double-linear model in characterising [HHb + Mb] profiles during ramp exercise, they found that the double-linear model was a more suitable fit in 85% of cases. Similarly, Murias *et al.* (2013) reported that the double-linear model was a more suitable model compared to the sigmoid profile in 90% of cases when they compared [HHb + Mb] profiles between males and females during ramp exercise.

Recent work has shown that individuals with uncomplicated T2DM display an over reliance in fractional oxygen extraction, reflected by an increased rate of muscle deoxygenation in the vastus lateralis muscle (i.e., [HHb+Mb]) during a ramp incremental exercise test (RI) (Gildea *et al.* 2016). Gildea *et al.* (2016), reported a significant reduction of a magnitude of 17% in peak exercise capacity in individuals with T2DM compared to age-matched controls which was accompanied by a significantly larger initial slope of the double linear model (S_1) used to establish the dynamic adjustment of [HHb+Mb] vs $\%PO_{peak}$ during RI in participants with T2DM (T2DM = 1.35 ± 0.17 a.u.; healthy control = 1.08 ± 0.35 a.u.). These results are indicative of a greater reliance on oxygen extraction for a given increase in $\dot{V}O_2$, suggesting that an impairment in peripheral O_2 delivery may, at least in part, cause a reduction in peak exercise capacity in T2DM (Gildea *et al.* 2016).

In this regard, leg blood flow responses have been shown to be significantly impaired in T2DM following maximal incremental tests of isolated muscle groups (Kiely *et al.* 2014). Kiely *et al.* (2014), reported a 15%, albeit non-significant, lower maximal plantar flexion force during a graded intermittent incremental test in participants with uncomplicated T2DM compared with age-matched controls which was accompanied with a significant reduction in the peak hyperaemic and vasodilatory response in the group with T2DM (Kiely *et al.* 2014). These results suggest that reductions in peripheral blood flow responses likely influence the impaired peak exercise capacity in T2DM.

1.4.2. Submaximal exercise performance in T2DM.

There is substantial evidence showing that submaximal exercise performance is also impaired in T2DM (Regensteiner *et al.* 1998; Bauer *et al.* 2007; MacAnaney *et al.* 2011; O'Connor *et al.* 2012). This includes observations of increased ratings of perceived exertion (RPE) and significantly slowed pulmonary $\dot{V}O_2$ and leg blood flow kinetics responses during submaximal exercise in people with T2DM compared with healthy controls (Regensteiner *et al* 1998; Kingwell *et al.* 2003; Lalande *et al.* 2008; Huebschmann *et al.* 2009; MacAnaney *et al.* 2011; O'Connor *et al.* 2012).

1.4.2.1. Pulmonary oxygen uptake kinetics.

In response to the instantaneous increase in adenosine triphosphate (ATP) demand at the onset of exercise, there is an exponential increase in $\dot{V}O_2$ towards a steady-state. This exponential response is represented by the pulmonary oxygen uptake kinetics response ($\dot{V}O_2$ kinetics) which reflects the ability to oxygenate the body in response to the initiation of muscular exercise (Whipp *et al.* 1982).

In order to discuss the $\dot{V}O_2$ kinetics response, it is important to firstly define the exercise intensities employed to elicit the response. The moderate-intensity domain encompasses exercise performed at an intensity below the gas exchange threshold (GET) or ventilatory threshold (VT) whereby VT typically occurs at 50-65% of maximal oxygen uptake ($\dot{V}O_{2max}$) as measured by a RI test (Poole *et* *al.* 2016). The heavy-intensity exercise domain is deemed to lie between VT and the so called ‘critical power’ (CP). CP is represented by the asymptote of power in the power-duration relationship and is considered to be the highest metabolic rate that can be sustained through predominantly oxidative metabolism (Jones *et al.* 2008; Poole *et al.* 2016; Jones & Vanahatalo 2017). Furthermore, CP may also be referred to as the maximal lactate steady-state as it is the highest work rate that can be maintained without a progressive increase in lactate accumulation or phosphocreatine (PCr) breakdown (Pringle *et al.* 2002; Poole *et al.* 2016). CP has been suggested to lie equidistant between an individual’s power output at VT and maximal power output as measured during a RI test or at approximately 70-80% $\dot{V}O_{2max}$ (Pringle *et al*. 2002; Poole *et al.* 2016). Finally, the severe-intensity domain includes any exercise intensities above CP whereby there is a progressive increase in lactate accumulation and $\dot{V}O_2$ without attainment of a steady-state (Poole *et al.* 2016; Jones & Vanhalato 2017) (Fig. 1.4).

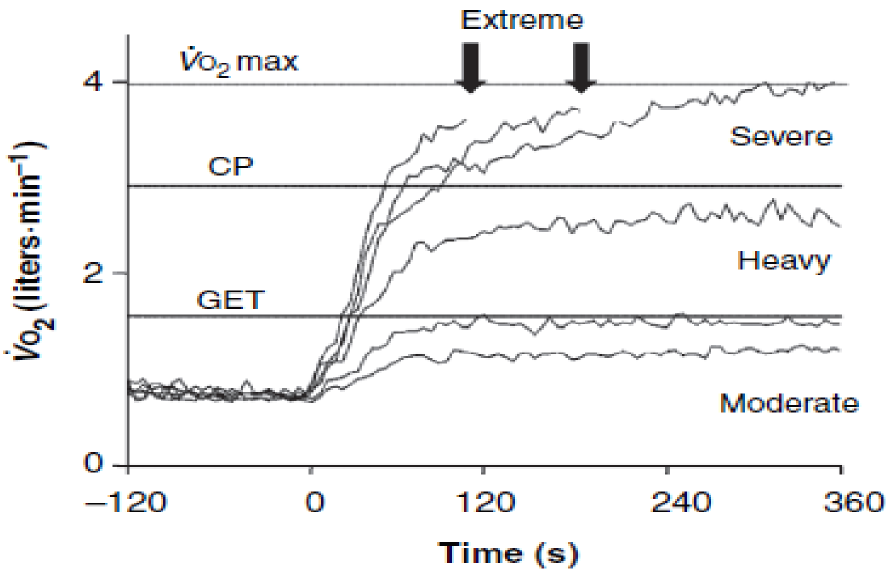

Figure 1.4. Schematic illustration of exercise intensity domains and their associated $\dot{V}O_2$ responses. Moderate intensity, <gas exchange threshold GET; heavy intensity, between GET and critical power (CP); severe intensity, between CP and $\dot{V}O_{2max}$ (taken from Poole & Jones 2005).

The response profile of $\dot{V}O_2$ kinetics to a stepwise increase from baseline to a moderate-exercise intensity can be broken down into three distinct phases (Fig. 1.5). Each of these phases has its own time delay (TD) which is the time after exercise onset when the phase commences, amplitude (A) which measures the magnitude of the $\dot{V}O_2$ response during each phase and time constant (τ) which reflects the time taken to reach 63% of the steady state amplitude of the phase.

Phase I or the cardio-dynamic phase is the rapid increase in $\dot{V}O_2$ at the onset of exercise and is representative of the O_2 exchange associated with the initial increase in cardiac output at the start of exercise and resulting increase in pulmonary blood flow (Whipp *et al.* 1982; Gerbino *et al*. 1996; Murias *et al*. 2011). Phase I typically lasts 10-20 s (Grassi *et al.* 1996). Phase II or the primary component ($\dot{V}O_{2P}$) is the rapid exponential increase in $\dot{V}O_2$ to a steady state and reflects the arrival at the lung of venous blood from the working muscles. It is therefore thought to closely reflect $\dot{V}O_2$ kinetics at the level of the exercising muscles (Grassi *et al.* 1996). Furthermore, the overall time course of the $\dot{V}O_{2P}$ is closely associated with leg blood kinetic responses and microvascular capillary blood flow responses during exercise transitions (Ferreira *et al.* 2005; DuManoir *et al.* 2010). Therefore, it is likely that $\dot{V}O_{2P}$ is regulated by the combination of O_2 delivery and distribution to the working muscle fibres and by the availability of substrates for mitochondrial oxidative phosphorylation, in addition to the timely activation of mitochondrial enzymes (Grassi *et al.* 2001; Hughson *et al*. 2001; Poole *et al.* 2008; Murias *et al.* 2011). In fact, mitochondrial function and oxidative capacity have been suggested to be the location of the main rate limiting factors for oxygen uptake kinetics during submaximal exercise in healthy individuals (Poole *et al.* 2008).

Phase III at intensities below VT occurs as $\dot{V}O_2$ plateaus and reflects the plateau of cardiac output to constant load exercise (Jones & Poole, 2005). However, during exercise performed above VT an additional elevation in $\dot{V}O_2$ that is superimposed onto Phase II is observed approximately 90-120s after the onset of exercise. This additional increase in $\dot{V}O_2$ is known as the $\dot{V}O_2$ slow component ($\dot{V}O_{2SC}$) (see Fig. 1.5). Depending on the intensity of the exercise, the $\dot{V}O_{2SC}$ will either result in a delayed attainment of a $\dot{V}O_2$ steady-state at exercise intensities between VT and CP (Gaesser & Poole, 1996), or drive $\dot{V}O_2$ towards its maximal value at exercise intensities between CP and $\dot{V}O_{2max}$ (Poole *et al.* 1988).

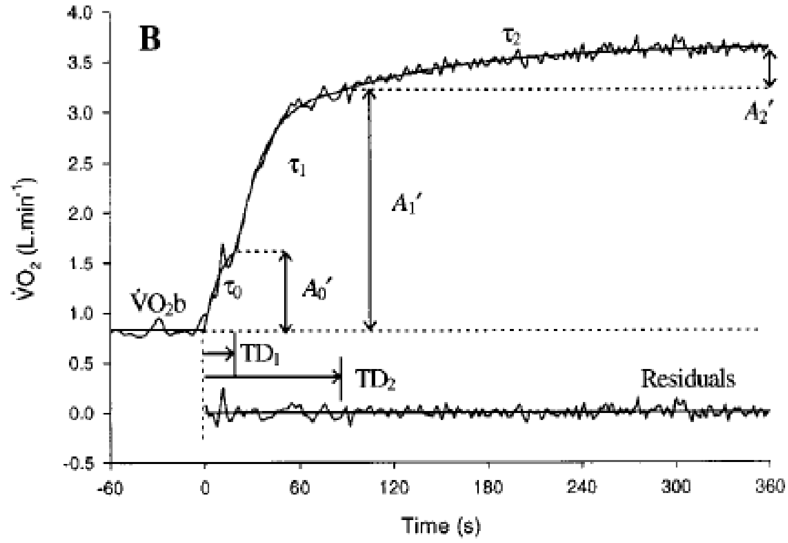

Figure 1.5. Representative model of the $\dot{V}O_2$ kinetics response from the onset of moderate- and heavy-intensity exercise. The three-exponential terms, each with a τ (time constant); TD, (time delay) and A, (amplitude), correspond to the Phase I, Phase II and slow component portions of the response. Subscript numbers represent the specific phase (0 = phase I, 1 = phase II and 2 = $\dot{V}O_{2SC}$). The dotted line represents the steady state of $\dot{V}O_2$ (i.e. phase III) below the level of the lactate threshold that is achieved after 2-3 mins of moderate-intensity exercise. $\dot{V}O_2b$ is the baseline $\dot{V}O_2$ value (adapted from Burnley *et al*. 2000).

It has been proposed that additional muscle fibre recruitment is the underlying mechanism of the $\dot{V}O_{2SC}$, with estimates that 86% of the $\dot{V}O_{2SC}$ can be accounted for by the working muscles (Poole *et al*. 2008). Indeed, the higher order muscle fibre types recruited at higher exercise intensities are believed to have significantly slower $\dot{V}O_2$ kinetics than those recruited during lighter intensities (Pringle *et al*. 2002; DiMenna *et al.* 2010). For instance, Krustrup *et al.* (2004) reported similar levels of creatine phosphate and glycogen depletion during heavy-intensity exercise in both Type I and Type II muscle whereas glycogen depletion was only observed in Type I fibres during moderate-intensity (Krustrup *et al.* 2004). Moreover, Rossiter *et al.* (2002), observed that the rise of the $\dot{V}O_{2SC}$ was accompanied by a related increase in phosphocreatine (PCr) metabolism during a transition from rest to exercise in the heavy-intensity domain which further suggests an increase in the recruitment of higher order glycolytic fibres during heavy-intensity exercise (Rossiter *et al.* 2002). Taken together these findings indicate that recruitment of additional muscle fibres contributes significantly to the rise of the $\dot{V}O_{2SC}$.

1.4.2.2. Pulmonary oxygen uptake kinetics in T2DM.

In contrast to age-matched healthy individuals, young and middle-aged people with T2DM exhibit a significantly slower $\dot{V}O_2$ kinetic response during moderate-intensity exercise (see Fig. 1.6) (Regensteiner *et al.* 1998; Brassard *et al.* 2006; Bauer *et al.* 2007; Nadeau *et al*. 2009; MacAnaney *et al.* 2011; O'Connor *et al*. 2015). Evidence from the literature indicates that the time constant of $\dot{V}O_{2P}$ ($\tau\dot{V}O_{2P}$) in T2DM is 34-36% slower than in healthy controls (Green *et al.* 2015) (Fig 1.6). The implication of an attenuated $\dot{V}O_2$ kinetics response in people with T2DM (< 60 yrs) is significant. A longer $\tau\dot{V}O_{2P}$ results in a longer period of time relying on substrate level phosphorylation to meet the increasing ATP demand. This results in increased PCr breakdown, increased H^+ accumulation, increased lactate accumulation and increased free P_i accumulation, all of which contribute to an increased sensation of fatigue and therefore exercise intolerance (Jones & Poole, 2005; Wilkerson *et al.* 2011).

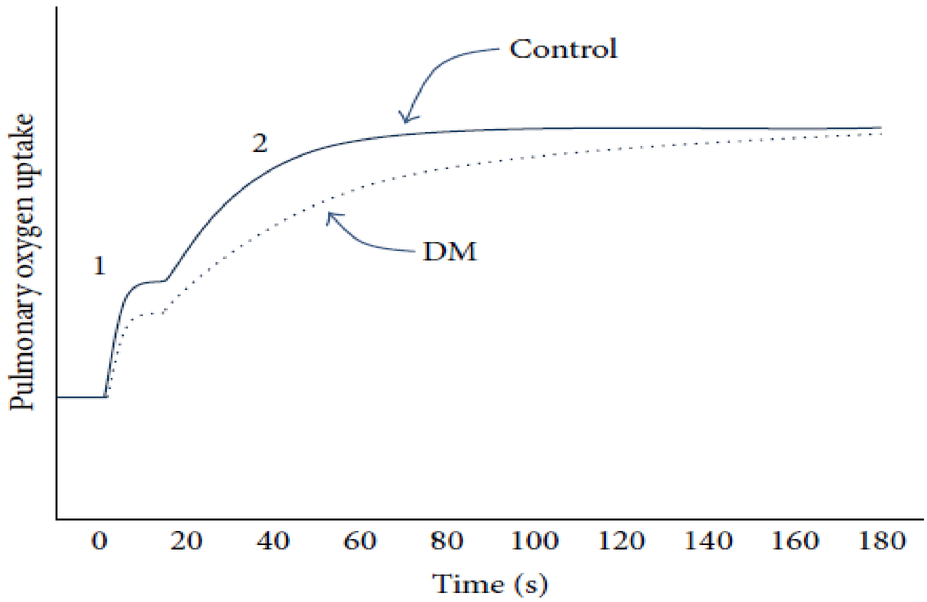

Figure 1.6. Representative model of the slowed $\dot{V}O_2$ kinetic response in people with T2DM (dotted line) compared to healthy age-matched controls (solid line). Phase I kinetics are represented by '1' and $\dot{V}O_{2P}$ by '2' (from Green *et al*. 2015).

Early investigations by Regensteiner *et al.* (1998), reported a significant attenuation of $\tau\dot{V}O_{2P}$ during cycling exercise during 3 different absolute intensities (cycling at 20W, 30W and 80W) in middle-aged women with T2DM compared with overweight and lean controls (T2DM vs overweight vs lean; 20W: 42.6 ± 23.8 s vs 18.4 ± 9.9 s vs 21.s ± 8.9 s; 30W: 36.8 ± 6.2 s vs 27.8 ±

8.9 s vs 28.5 ± 5.3 s; 80W 55.7 ± 20.6 s vs 43.3 ± 11.3 s vs 42.8 ± 7.5 s) (Regensteiner *et al.* 1998). More recently, MacAnaney *et al.* (2011) further extended these findings by reporting a significant slowing of $\tau\dot{V}O_{2P}$ at submaximal relative exercise intensities (50% VT and 80% VT) during cycling exercise in middle-aged women with T2DM compared to age-matched overweight and lean controls without T2DM (T2DM vs overweight vs lean; 50% VT: 34.2 ± 15.7 s vs 15.4 ± 7.3 s vs 20.2 ± 9.7 s; 80% VT: 39.1 ± 9.1 s vs 24.8 ± 8.8 s vs 26.8 ± 10.4 s). However, they did not observe any differences in $\tau\dot{V}O_{2P}$ during heavy-intensity cycling exercise (50% Δ, the midpoint between VT and $\dot{V}O_{2peak}$: 22.1 ± 12.2s vs 21.1 ± 6.2 s vs 24.1 ± 12.2 s) (MacAnaney *et al.* 2011).

1.4.2.3. Sex-related and menopausal-related effects on pulmonary oxygen uptake kinetics in T2DM.

Although these initial studies reported predominantly on female participants, O'Connor *et al.* (2012) reported that both middle-aged men and women with T2DM displayed impairments in $\dot{V}O_2$ kinetics during moderate-intensity cycling exercise at 80% VT of a similar magnitude when compared with age-matched healthy controls ($\tau\dot{V}O_{2P}$ men, T2DM vs healthy, 44 ± 12 s vs 35 ± 10 s; $\tau\dot{V}O_{2P}$ women, T2DM vs healthy, 43 ± 10 s vs 34 ± 10 s) (O'Connor *et al.* 2012). Given that the majority of women in the study by O'Connor *et al.* (2012) were post-menopausal, more recently, Kiely *et al.* (2015) investigated whether menopausal status influenced $\dot{V}O_2$ kinetics in women with T2DM. It is well known that oestrogen provides a cardio-protective effect (known as the so-called 'female advantage') that reduces the risk of cardiovascular disease and enhances endothelial function in healthy pre-menopausal women compared to age-matched men (Perregaux *et al.* 1999). However, the female advantage appears to be attenuated by T2DM so that vasodilatory responses during exercise and therefore, O_2 delivery and $\dot{V}O_2$ kinetics may be impaired to a greater extent in pre-menopausal women with T2DM compared with post-menopausal women and men with T2DM. Nevertheless, Kiely *et al.* (2015), reported that both pre- and post-menopausal women with T2DM (age range: 30-60 yr) exhibited a similar magnitude of impairment in $\dot{V}O_2$ kinetics during moderate-intensity cycling exercise at 80% VT when compared with age- and menopausal status matched healthy women ($\tau\dot{V}O_{2P}$: premenopausal healthy vs T2DM, 29.1 ± 11.2 s vs. 43.0 ± 12.2 s; $\tau\dot{V}O_{2P}$: postmenopausal healthy vs T2DM, 33.0 ± 9.1 s vs.

41.8 ± 17.7 s) (Kiely *et al.* 2015). This study suggests that there doesn't appear to be an effect of menopausal stage on $\dot{V}O_2$ kinetics in women with uncomplicated T2DM.

1.4.2.4. Age-related effects on pulmonary oxygen uptake kinetics in T2DM.

There is a significant slowing of the $\dot{V}O_2$ kinetics response in healthy older adults (Scheuermann *et al.* 2002). This is due to various factors such as reduced muscle O_2 supply (Proctor *et al.* 1998), decreased skeletal muscle capillarity (Coggan *et al.* 1992), reduced endothelial function (McGuire *et al.* 2001; Hepple *et al.* 2003) and decreased mitochondrial enzyme activity (Coggan *et al.* 1992). Recent studies by Wilkerson *et al.* (2011) and O'Connor *et al.* (2015), have suggested that the T2DM-induced impairments in $\dot{V}O_2$ kinetics are not apparent in older individuals with T2DM (> 60 yr). Initially, Wilkerson *et al.* (2011) observed similar $\dot{V}O_2$ kinetics responses ($\tau\dot{V}O_{2P}$: T2DM = 43 ± 17 s, healthy = 41 ± 12 s) during moderate intensity exercise (50% peak power output) in men with T2DM compared with age-matched healthy controls (65 ± 5 yr vs 62 ± 6 yr). The authors suggested that this finding was due to the relatively long disease duration of participants with T2DM (9.3 ± 3.8 yr) and the subsequent development of adaptive responses in skeletal muscle O_2 extraction capabilities. In this regard, Wilkerson *et al.* (2011), reported that the ratio between the dynamic adjustment of muscle deoxygenation ([HHb+Mb]), as measured by near-infrared spectroscopy (NIRS), and $\dot{V}O_2$ was significantly elevated (i.e., Δ [HHb]/$\Delta\dot{V}O_2$ ratio >1.0) in the group of people with T2DM, which is indicative of a greater proportional contribution of O_2 extraction to satisfy a given increase in $\dot{V}O_2$ (Wilkerson *et al.* 2011). Although this is suggestive of adaptive responses in the skeletal muscle, the NIRS data relates to only the vastus lateralis muscle of the quadriceps. In addition, the lack of skeletal muscle biopsies makes it difficult to attribute the observed results to the skeletal muscle alone. Further limitations in this study may lie in the small sample size (12 T2D v 12 controls) and the lack of objective baseline physical activity measurement. Although participants were recruited only if they self-reported completing less than 2 sessions of low-moderate physical activity per week for the preceding 3 months prior to the study, no objective measure of baseline physical activity is mentioned.

More recent work by O'Connor *et al*. (2015) also reported similar $\tau\dot{V}O_{2P}$ values during moderate-intensity exercise (work load equivalent to 80% VT) in a group of older men with T2DM (age: 64.2 ± 3 yr; $\tau\dot{V}O_{2P}$: 41.1 ± 8.5 s) and without T2DM (age: 64.2 ± 2 yr; $\tau\dot{V}O_{2P}$: 40.5 ± 7.8 s) (O'Connor *et al.* 2015). However, the disease duration of the participants in the study by O'Connor *et al.* (2015) was substantially shorter (4.1 ± 2.7 yr) than that reported by Wilkerson *et al.* (2011). Therefore, it appears that advanced age per se rather than disease duration, is the primary influence for the similar $\dot{V}O_2$ kinetics responses observed during submaximal exercise in older male individuals with and without T2DM. However, the study by O'Connor *et al.* (2015) is limited by its small control group which did not numerically match the group with T2DM in both the middle-aged (CON *n* = 11 vs T2DM *n* = 15) and older groups (CON *n* = 10 vs T2DM *n* = 18).

1.4.3. Mechanisms of sub-maximal exercise intolerance in T2DM.

The mechanisms underlying the slowing of $\dot{V}O_2$ kinetics in young and middle-aged individuals with uncomplicated T2DM appear to be related to an impairment in central and peripheral O_2 delivery, a reduction in local O_2 extraction by the exercising muscle or a combination of both factors. In terms of O_2 delivery there appears to be an impairment in muscle blood flow and systematic vasodilation in addition to abnormalities in microvascular blood flow distribution and delivery during exercise in T2DM (Bauer *et al.* 2007; Lalande *et al*. 2008; Green *et al.* 2015). On the other hand, T2DM induces a lower mitochondrial content and oxidative capacity in the skeletal muscle which may result in a reduced oxygen extraction ability of skeletal muscles. (Kelley *et al.* 2002; Ritov *et al.* 2005; Bauer *et al.* 2007).

1.4.3.1. Impairments in O_2 delivery.

Both MacAnaney *et al.* (2011) and O'Connor *et al.* (2012) reported normal Q responses during submaximal steady-state cycling exercise in both men and women with T2DM, suggesting that any T2DM-induced impairment in O_2 delivery is more likely to lie within the peripheral vasculature rather than being of a central origin (MacAnaney *et al.* 2011; O'Connor *et al.* 2012). Supporting this, Bauer *et al.* (2007), reported a significant lengthening of the microvascular blood flow response (Q_m) in a group with T2DM (43.6 ± 12.9 s vs 32.0 ± 9.7 s), that also demonstrated a significant slowing of $\dot{V}O_2$ kinetics ($\tau\dot{V}O_{2P}$: 43.8 ± 9.6 s vs 34.2 ± 8.2 s) compared to age matched healthy controls. Q_m was estimated using the Fick equation using changes in fractional oxygenation extraction as a surrogate for a-vO_2diff such that Q_m (t) = $\dot{V}O_{2P}$ (t) / [HHb + Mb] (t) where t = time. Moreover, steady-state femoral artery blood flow responses during submaximal cycling (Kingwell *et al.* 2003) and knee extension exercise (Lalande *et al.* 2008) as well as limb vascular conductance (LVC) kinetics during higher-intensity plantar flexion exercise have been shown to be impaired in T2DM (MacAnaney *et al.* 2011; Kiely *et al.* 2014).

In the first study that explored the vasodilatory kinetics responses in T2DM MacAnaney *et al*. (2011) reported a significant lengthening of the second growth phase of the LVC kinetics response during high-intensity plantar-flexion (70% maximal voluntary contraction; MVC) exercise in the upright tilt position in women with uncomplicated T2DM compared to overweight and lean healthy controls (τLVC: 64.2 ± 29.2 s vs 22.4 ± 13.4 s vs 21.8 ± 9.3 s). To minimise the baroreceptor-mediated changes in muscle sympathetic nerve activity associated with upright tilting of participants a follow-up study by the same group explored the same vasodilatory kinetic responses during a high-intensity (70% MVC) and low-moderate intensity (30% MVC) plantar flexion exercise performed in the supine position in larger separate groups of men and women with T2DM (Kiely *et al.* 2014). Kiely *et al.* (2014), reported a marked lengthening of the second growth phase of LVC kinetics in T2DM compared with healthy controls (τLVC males; 29.2 ± 26.6 s vs 13.6 ± 11.1 s; females: 44.3 ± 21.6 s vs 17.9 ± 10.1 s) during supine high-intensity (70% MVC) plantar flexion exercise which was of similar magnitude for men and women. However, Kiely *et al.* (2014) reported no diabetes-related differences in LVC when exercise was performed at 30% MVC. This is suggestive that other compensatory mechanisms are utilised by individuals with T2DM to augment LVC responses to increases in metabolic demand at lower exercise intensities (Kiely *et al.* 2014).

Despite the above-mentioned evidence suggesting that O_2 delivery is impaired in T2DM, some studies have reported unaltered blood flow responses in T2DM (Womack *et al.* 2009; Pak *et al.* 2010; Poitras *et al* 2015a; Poitras *et al* 2015b). Differences in muscle groups studied (i.e., upper limb vs lower limb), muscle contraction types or co-morbidities in participants with and without T2DM are likely factors underlying these disparities among studies. For instance, Poitras *et al* (2015a), reported no compromise to femoral artery blood flow during low to moderate-intensity rhythmic isometric quadriceps exercise in individuals with T2DM (Poitras *et al.* 2015a) while a second study by the same group found that there was no T2DM-induced impairment in forearm blood flow during 10 minutes of repeated maximal hand grip exercise (Poitras *et al.* 2015b). Similarly, Womack et al. (2009) reported unaltered brachial artery and skeletal muscle capillary blood flow responses during low- and high-intensity hand grip exercise in middle-aged men and women with uncomplicated /T2DM (Womack *et al.* 2009).

While it is tempting to suggest that a peripheral impairment in O_2 delivery may be responsible for the characteristic exercise impairment observed in T2DM, there are too many disparities in the above mentioned evidence to make a definitive conclusion. The relatively small sample sizes of the studies and the seemingly intensity dependent nature of the impairment make it difficult to apply these findings to everyday life. In addition, all of the studies discussed above only looked at isolated muscle groups. Since everyday functional activities and movements are global and involve multiple muscle groups the relevance of these findings to real world situations may be lacking.

1.4.3.2. Impairments in O_2 extraction.

The second part of the Fick equation ($\dot{V}O_2$ = Q x a-vO_2 diff), relates to the contribution of oxygen extraction and utilisation (a-vO_2 diff) to overall oxygen consumption. The a-vO_2 diff is determined by the availability of O_2 to the working muscles and the capacity of the skeletal muscle mitochondria to extract and utilise O_2 during exercise (Baldi *et al.* 2003). There is evidence that indicates that mitochondrial function, structure and oxidative capacity are impaired in people with T2DM (Kelley *et al*. 2002; Ritov *et al.* 2005).

For instance, Kelley *et al.* (2002), reported significant impairments in mitochondrial structure and function at rest in middle-aged participants with uncomplicated T2DM compared to age-matched lean and obese controls. The authors observed that the activity of NADH:O_2 oxidoreductase (representative of electron-transport chain activity) was ~ 40% lower in those with T2DM and that citrate synthase activity was significantly reduced compared to the healthy controls (Kelley *et al.* 2002). Furthermore, mitochondrial size and area were reduced by approximately 30% and 35% respectively in the group with T2DM. Further work by Ritov *et al*. (2005) reported a significant negative effect of obesity and T2DM on mitochondrial function. The authors observed that electron transport chain activity at rest was reduced by seven- and three-fold in middle-aged participants with uncomplicated T2DM and obesity respectively in comparison with lean subjects. In addition, there was a significant T2DM-induced reduction in mitochondrial protein content, mitochondrial DNA content and in the number and size of sub-sarcolemmal mitochondria (Ritov *et al.* 2005).

1.5. Priming exercise; an acute intervention for exercise intolerance.

Reports from healthy populations have shown that a prior bout of heavy-intensity (> VT) 'priming exercise' (PE) is effective at manipulating the $\dot{V}O_2$ kinetics of subsequent bout of moderate- or heavy- intensity exercise (Gurd *et al.* 2005; Gurd *et al.* 2006; Poole *et al.* 2008x; Murias *et al.* 2011; Spencer *et al.* 2012). For instance, during heavy-intensity exercise which elicits the emergence of the $\dot{V}O_{2SC}$, PE has been shown to reduce the mean response time (MRT) of $\dot{V}O_2$ kinetics through a reduction in the amplitude of the $\dot{V}O_{2SC}$ and an increase in the amplitude of the primary component without influencing the time constant of the primary component in healthy young active participants (Burnley *et al.* 2000; Rossiter *et al*. 2001; Burnley *et al.* 2002; Fukuoka *et al.* 2015). However, when $\dot{V}O_2$ is slowed during unprimed exercise due to an impairment in O_2 delivery limitation to active muscles, such as when tilting the body from an upright to a supine or prone position thereby reducing muscle perfusion pressure, PE significantly reduces $\dot{V}O_2$ MRT by significantly speeding $\tau\dot{V}O_{2P}$ during the subsequent heavy-intensity exercise (Rossiter *et al.* 2001; Jones *et al.* 2006; Di Menna *et al.* 2010).

Similarly, during moderate-intensity exercise, it appears that a prior bout of PE enhances the subsequent $\tau\dot{V}O_{2P}$ in individuals who show a prolonged $\tau\dot{V}O_{2P}$ (~ 30 s) during the unprimed condition whereas individuals with faster initial $\tau\dot{V}O_{2P}$ (~ 25 s) do not display any change in $\dot{V}O_2$ kinetics following PE (DeLorey *et al.* 2004; Gurd *et al.* 2005). For instance, DeLorey *et al.* (2004), compared the effects of PE on subsequent $\tau\dot{V}O_{2P}$ during moderate-intensity exercise (80% lactate threshold) between young (25 ± 3 yr) and older (68 ± 3 yr) male healthy participants. The older participants displayed a significantly longer $\tau\dot{V}O_{2P}$ than the younger group during the first 'unprimed' bout ($\tau\dot{V}O_{2P}$: older = 38 ± 5 s, younger = vs 26 ± 7 s). Post-priming, there was a significant shortening of $\tau\dot{V}O_{2P}$ in the older group (pre-PE = 38 ± 5 s, post-PE = 30 ± 7 s), whereas, no effect of priming on the $\tau\dot{V}O_{2P}$ parameter was observed in the younger group (pre-PE = 26 ± 7 s, post-PE 25 ± 5 s). Furthermore, there was a significant slowing of the [HHb + Mb] response post-priming in the older group alone (DeLorey *et al.* 2004). Taken in combination these results suggest that in those with slower $\dot{V}O_2$ kinetics, PE significantly improved the matching of O_2 delivery and O_2 utilisation therefore resulting in faster $\dot{V}O_2$ kinetics post-priming. Thus, this suggests that when $\tau\dot{V}O_{2P} < \sim 25$ s PE does not manipulate any parameter of the subsequent $\dot{V}O_2$ kinetics response during moderate-intensity exercise. A possible reason for this may be that with faster $\dot{V}O_2$ kinetics, cellular energetics may be the most influential rate limiting factor in the determination of $\dot{V}O_2$ kinetics rather than the matching of O_2 delivery and utilisation.

In this regard, Gurd *et al.* (2005) investigated the influence of initial $\tau\dot{V}O_{2P}$ length during moderate-intensity cycling exercise on the effects of PE. The authors in this study divided the participants into 2 groups depending on their initial $\tau\dot{V}O_{2P}$ during the first 'unprimed' bout. Those with a $\tau\dot{V}O_{2P} > 30$ s were placed in the 'slow' group (mean $\tau\dot{V}O_{2P}$; 45 ± 11 s) and those with a $\tau\dot{V}O_{2P} < 30$ s (mean $\tau\dot{V}O_{2P}$; 26 ± 5.1 s) were placed in the 'fast' group. Interestingly, both groups displayed a significantly faster $\tau\dot{V}O_{2P}$ post PE. However, the magnitude of the improvement was significantly higher in the 'slow' group compared to the 'fast' group (~33.2 % vs ~22.3 %). Furthermore, the mean response time of [HHb + Mb] in the slow group was significantly longer after PE which suggests that an improvement in muscle perfusion and the matching O_2 delivery and utilisation was the underlying factor for the improvement in $\tau\dot{V}O_{2P}$. On the other hand, a significant speeding of the [HHb + Mb] was observed in the fast group as a result of a significantly reduced [HHb + Mb] TD which is suggestive of an enhancement of $\tau\dot{V}O_{2P}$ due to an earlier activation of mitochondrial phosphorylation in the 'fast' group. Similar results were reported by Nederveen *et al.* (2017) who observed that there was no speeding of $\dot{V}O_2$ kinetics after PE in young male individuals with initially 'fast' $\dot{V}O_2$ kinetics ($\tau\dot{V}O_{2P}$: pre PE = 21 ± 2 s; post PE = 21 ± 2 s) whereas a 25% reduction in the length of $\tau\dot{V}O_{2P}$ in individuals with 'slow' $\dot{V}O_2$ kinetics ($\tau\dot{V}O_{2P}$: pre PE = 32 ± 7 s post-PE = 24 ± 2 s) was reported (Nederveen *et al.* 2017).

1.5.1. Physiological mechanisms of priming exercise and its effect in T2DM.

Current evidence suggests that the underlying mechanisms of the positive effects of PE on subsequent moderate-intensity exercise include an increased O_2 availability at the onset of exercise (Gurd *et al.* 2005; Nederveen *et al*. 2017) and an improved matching of O_2 delivery and utilisation due to improved microvascular blood flow (Murias *et al*. 2011; Spencer *et al*. 2013) and it is mostly observed in participants showing a slow $\tau\dot{V}O_{2P}$. Mechanisms inducing faster $\dot{V}O_2$ kinetics during heavy-intensity exercise post-PE include increased motor unit recruitment (Burnley *et al.* 2002; Di Menna *et al.* 2008), increase substrate availability for oxidative phosphorylation (Behnke *et al*. 2002; Faisal *et al.* 2009; Fukuoka *et al.* 2015) and increased O_2 availability (Rossiter *et al.* 2001; Jones *et al.* 2006).

Recently, Gildea *et al.* (2016) investigated the effect of PE on $\tau\dot{V}O_{2P}$ kinetics during moderate-intensity exercise in middle-aged individuals with uncomplicated T2DM. Gildea *et al.* (2016) reported a significant reduction in $\tau\dot{V}O_{2P}$ during a subsequent bout of moderate-intensity cycling exercise following PE in the group of participants with uncomplicated T2DM. Furthermore, a strong tendency ($P < 0.10$) was reported for a reduction in the Δ [HHb + Mb]/$\Delta\dot{V}O_2$ ratio (pre-PE: 1.18 ± 0.17 a.u. post-PE: 1.05 ± 0.15 a.u.) during the 'primed' exercise bout. Also during the 'primed' bout the ratio was not significantly different from 1.0. This is to the results observed by Murias *et al.* (2011) among healthy untrained individuals with initial 'slow' $\dot{V}O_2$ kinetics ($\tau\dot{V}O_{2P} > 25$ s) (Murias *et al.* 2011), and suggests that PE speeds $\dot{V}O_2$ kinetics in T2DM by ameliorating the matching of O_2 utilisation and delivery (Gildea *et al.* 2016).

During heavy-intensity exercise in healthy active individuals (i.e. when O_2 delivery to active muscles is not impaired) $\dot{V}O_2$ kinetics are mainly manipulated by PE via a reduction in the amplitude of the $\dot{V}O_{2sc}$. For instance, Burnley *et al.* (2001), observed a significant reduction in the $\dot{V}O_{2SC}$ in 9 active healthy young volunteers following PE. They reported that the $\dot{V}O_{2SC}$ was decreased due to an increased phase II amplitude following PE which the authors suggested was indicative of a priming related increase in muscle fibre recruitment (Burnley *et al.* 2001). Furthermore, a later study by Burnley and colleagues (2002), again reported a significant reduction in the $\dot{V}O_{2SC}$ following PE, which was accompanied by an increase in the amplitude of $\dot{V}O_{2P}$ and was accompanied by a significant increase in electromyography (EMG) activity at the onset of the primed exercise bout, which suggests an increased muscle fibre recruitment in response to PE (Burnley *et al.* 2002). Neither Burnley *et al.* (2001) nor Burnley *et al.* (2002), reported a reduction in $\tau\dot{V}O_{2P}$ post-PE.

When a limitation in $\tau\dot{V}O_{2P}$ presents during unprimed exercise as a consequence of O_2 delivery, such as when tilting the body from upright to the supine position, PE accelerates $\tau\dot{V}O_{2P}$ in a subsequent bout of heavy-intensity exercise (Rossiter *et al.* 2001; Jones *et al.* 2006). Similarly, in a group of individuals with uncomplicated T2DM, Rocha *et al.* (2016) reported a strong tendency towards a decrease in $\tau\dot{V}O_{2P}$ (P =0.06) during a subsequent bout of heavy-intensity exercise following a bout of heavy PE with an overall significant decrease in the $\dot{V}O_2$ MRT (Rocha *et al.* 2016).

More recent studies have investigated the effects of PE on $\dot{V}O_2$ kinetics during transitions from a moderate-intensity to severe-intensity cycle exercise (work-to-work transition, w-to-w) in primarily young active participants (Di Menna *et al.* 2008). Di Menna *et al.* (2008) observed a significantly lengthened $\tau\dot{V}O_{2P}$ in unprimed severe-intensity cycling transitions initiated from a moderate-intensity baseline (w-to-w) in comparison to those observed following the unprimed on-transition from an unloaded baseline. Priming exercise had no effect on the $\tau\dot{V}O_{2P}$ in the subsequent w-to-w transition. However, PE significantly increased the amplitude of phase II $\dot{V}O_2$ kinetics and reduced the amplitude of the $\dot{V}O_{2SC}$ (Di Menna *et al.* 2008). Furthermore, there was a reduction in EMG activity, such that the end-exercise value (min 6) of EMG activity was no longer different from the minute 2 value after PE, whereas during the unprimed w-to-w, there was a significant increase in ΔEMG throughout the exercise period.

In regard to T2DM, Gildea *et al.* (2018) recently reported a significant reduction in the $\dot{V}O_2$ MRT following PE when participants with uncomplicated T2DM performed exercise transitions from an elevated baseline to a heavy-intensity bout (w-to-w). This was achieved through a significant reduction in the amplitude of the $\dot{V}O_{2SC}$. However, even if there was no significant effect of priming exercise on $\tau\dot{V}O_{2P}$, the magnitude of the difference in $\tau\dot{V}O_{2P}$ pre- and post- PE was substantially higher in the individuals with T2DM ($\tau\dot{V}O_{2P}$ T2DM pre-PE = 54 ± 14 s, post-PE = 42 ± 17 s) compared to their age-matched controls ($\tau\dot{V}O_{2P}$ healthy controls pre-PE = 42 ± 11 s, post-PE = 41 ± 11 s) (Gildea *et al.* 2018). The study by Gildea *et al.* (2018) is in line with the findings of Di Menna *et al.* (2010) who showed that PE significantly accelerated τVO_{2P} during a subsequent w-to-w exercise bout when healthy participants adopted a supine cycling posture (i.e. when muscle perfusion pressure was reduced leading to a compromised O_2 delivery).

These above-mentioned studies suggests that PE is an effective means of manipulating the parameters of $\dot{V}O_2$ kinetics during moderate- and heavy intensity exercise in addition to heavy-intensity exercise initiated from an elevated baseline. However, the effects of exercise training on the priming effect on moderate-intensity exercise and heavy-intensity exercise initiated from an elevated baseline are unknown in T2DM.

1.6. Exercise in the management of T2DM.

There is very robust evidence supporting the several health benefits of physical activity in T2DM. Structured exercise interventions have been reported to have significant benefits for people with T2DM in terms of improving maximal exercise capacity (Boule *et al.* 2003; Karstoft *et al.* 2013), glycaemic control (Stolinski *et al.* 2008; Balducci *et al.* 2012; Karstoft *et al.* 2013), vascular and endothelial function (Maiorana *et al.* 2001; Madsen *et al.* 2015) and body composition, promoting weight loss (Karstoft *et al.* 2013; Mitarun *et al.* 2014) and reducing the risk of the development of diabetic complications.

1.6.1. High-intensity interval training.

People with T2DM struggle to achieve the 150 minutes of moderate-intensity exercise per week recommended by the ADA (Steeves *et al.* 2015; Colberg *et al* 2016). Therefore, new time efficient exercise protocols that may potentially elicit similar benefits to traditional exercise interventions have been proposed. One such intervention is high-intensity interval training (HIIT) which comprises of short bursts of high-intensity vigorous activity interspersed by periods of rest or low-intensity exercise (Gibala *et al*. 2012) (Fig. 1.7).

Many HIIT programmes can be completed in half the time of other continuous moderate-intensity protocols, and they are thought to be more enjoyable than moderate-intensity interventions (Bartlett *et al.* 2011), therefore potentially promoting exercise adherence. A recent cross-over study of sedentary but otherwise healthy adults observed that 62% of participants preferred HIIT over MICT although only after a single session (Jung *et al.* 2014). Moreover, a recent study in young healthy adults reported that enjoyment of HIIT increased over a 6 week training period while enjoyment of MICT showed no such improvement (Heisz *et al.* 2016).

Short-term HIIT interventions of 2 to 6 weeks in healthy non-diabetic populations have been suggested to cause significant improvements in maximal exercise capacity (Rakobowchuk *et al.* 2008), mitochondrial oxidative capacity (Burgomaster *et al.* 2008), endothelial function (Rakobowchuk *et al.* 2008) and submaximal endurance performance as measured by time-to-exhaustion tests (Gibala *et al.* 2006).

For instance, Rakobowchuk *et al.* (2008) reported similar significant improvements in endothelial function as measured by flow-mediated dilation (FMD) and peak oxygen uptake responses ($\dot{V}O_{2peak}$) following 6 weeks of either moderate-intensity training (MICT) or HIIT in healthy participants. MICT (40-60 mins at 65% $\dot{V}O_{2peak}$) was performed 5 days per week while HIIT (4-6 30s ‘all out’ sprints interspersed by 4.5 mins recovery) was performed 3 days per week (Rakobowchuk *et al.* 2008). Results from muscle biopsies taken from the participants who took part in the study by Rakobowchuck *et al*. (2008) were reported by Burgomaster and colleagues (2008). They found that both HIIT and MICT induced similar significant increases in skeletal muscle carbohydrate and lipid oxidation of a similar magnitude (Burgomaster *et al*. 2008). Similarly, Gibala *et al.* (2006) reported significant improvements in exercise performance, as measured by a 30 km time trial, and in skeletal muscle oxidative capacity after just 6 sessions of HIIT or MICT completed over 2 weeks. MICT comprised cycling at an intensity corresponding to 65% $\dot{V}O_{2peak}$, whereas HIIT consisted of 4-6 30 s ‘all-out’ sprints interspersed by a 4 mins active recovery (Gibala *et al.*

2006). The duration of the MICT sessions was increased from 90-120 mins progressively throughout the 2 weeks while the number of all-out sprints progressed from 4 to 6. It is important to note that the benefits induced from HIIT training were achieved with a significantly shorter time commitment (HIIT: 135 mins vs MICT: 630 mins over 2 weeks) (Gibala *et al.* 2006).

Although these initial studies show promising results some important limitations may prevent these results from being applicable to other populations. Firstly, all three studies took place over a relatively short time period in a highly controlled laboratory environment and not in a community or gym setting. Therefore the sustainability and applicability of such interventions in a more general population is unknown. Secondly, the participants in the above mentioned studies were young healthy males and females (mean age 21-23.5 yrs) who may be more motivated to train at such high intensities. It is debatable whether clinical populations who are not conditioned to exercise would tolerate such high intensities. Thirdly, the small sample sizes used in the above mentioned studies (Gibala *et al.* 2006 n = 16; Rakobowchuk *et al*. 2008 n = 20; Burgomaster *et al*. 2008 n = 20) lend them open to selection bias and makes generalisation of their findings to a wider population difficult.

1.6.2. HIIT and T2DM.

There is growing interest in the use of HIIT in clinical and deconditioned populations as it may promote exercise adherence due to its time efficient nature while also inducing similar benefits to more traditional long duration moderate-intensity training interventions. For instance, Jung *et al.* (2014) reported that adherence to HIIT (10 x 60s at 90% HR_{peak} interspersed by 60s rest) was greater compared to MICT (50 mins at 65% HR_{peak}) in group of individuals with prediabetes over a period of 4 weeks (HIIT 89% adherence vs MICT 71%) (Jung *et al.* 2014).

However, there is a concern that deconditioned populations such as those with T2DM, may not tolerate the demands of ‘all-out’ sprint training as used in studies including healthy individuals (Gibala *et al.* 2006; Rakobowchuk *et al.* 2008; Burgomaster *et al.* 2008). Therefore, a less intense, but still time efficient model of HIIT known as low-volume high intensity interval training (LVHIIT) was proposed as a more suitable modality (Gibala *et al.* 2012). Typically, a

LVHIIT session consists of 10 x 60 s high-intensity (~90% HR_{max}) exercise bouts interspersed by a 60 s period of active or passive recovery (Fig. 1.7). Encouragingly, this model has been utilised in T2DM and has so far been shown to induce significant improvements in exercise performance (Little *et al.* 2011; Madsen *et al.* 2015; Francois *et al.* 2017a), glycaemic control (Little *et al.* 2011; Gillen *et al.* 2012; Madsen *et al.* 2015), vascular function (Madsen *et al.* 2015; Francois *et al.* 2017b) and mitochondrial oxidative capacity (Little *et al.* 2011) (Table 1.1).

Table 1.1. ***Summary table of studies investigating LVHIIT in T2DM.***

Study	Exercise protocol	Participants	Intervention	Outcome measures	Pre	Post	P value	Effect size
Little *et al.* (2011)	10 x 60 s at 90% HR_{max}, 1 min rest	T2DM *n* = 8 (mean age: 62.5 ± 7.6 yr)	LVHIIT 3 days per week for 2 weeks. No control	(mean ± SD) Peak power output (W)	111 ± 36	124 ± 37	0.03	0.36
				average 24hr blood glucose ($mmol.L^{-1}$)	7.6 ± 1.0	6.6 ± 0.7	0.01	1.16
Mitranun *et al.* (2014)	LVHIIT; 4-6 x 1min at 80% $\dot{V}O_{2peak}$, 4 min recovery at 50% $\dot{V}O_{2peak}$ MICT; 20-30 min at 60- 65% $\dot{V}O_{2peak}$	T2DM *n* = 45 (age range: 50-70 yr; m/f: 16/29)	LVHIIT (*n* = 14) & MICT (*n* = 14); 3 days per week for 12 weeks Control (*n* = 15); Normal daily routine	(mean ± SD) $\dot{V}O_{2\,max}$ ($mL.kg.min^{-1}$)	24.2 ± 1.6	30.3 ± 1.2	<0.05	4.47
				LVHIIT	23.8 ± 1.0	27.1 ± 1.2	<0.05	5.73
				MICT	24.4 ± 1.3	23.9 ± 1.0	NS	
				CON				
				HbA_{1c} ($mmol.mol^{-1}$)				
				LVHIIT	60 ± 2	54 ± 2	<0.05	3
				MICT	61 ± 2	59 ± 3	NS	
				CON	62 ± 2	65 ± 2	NS	
				FMD (%)				
				LVHIIT	5.4 ± 1.1	7.4 ± 0.9	<0.05	1.99
				MICT	4.8 ±1.6	6.1 ± 1.8	<0.05	0.76
				CON	5.1 ± 1.3	5.6 ± 1.8	NS	

Study	Exercise protocol	Participants	Protocol	Outcome Measures	Pre	Post	P value	Effect size
Madsen *et al.* (2015a)	10 x 60 s at 90% HR_{max}, 1 min rest	T2DM *n* = 10 (mean age: 56 ± 2 yr; m/f: 7/3) Healthy controls *n* = 13 (mean age: 52 ± 2 yr; m/f: 8/5)	T2DM LVHIIT; 3 days per week for 8 weeks. CON LVHIIT; 3 days per week for 8 weeks.	(mean (95% CI)) FMD (%)				
				T2DM	4.84 (3.34- 6.33)	5.66 (4.33-6.99)	<0.05	Not available
				CON	5.12 (3.32-6.92)	6.58 (4.71-8.45)	<0.01	Not available
Madsen *et al.* (2015b)	10 x 60 s at 90% HR_{max}, 1 min rest	T2DM n =10 (mean age: 56 ± 2 yr; m/f: 7/3) Healthy controls *n* = 13 (mean age: 52 ± 2 yr; m/f: 8/5)	T2DM LVHIIT; 3 days per week for 8 weeks. CON; 3 days per week for 8 weeks.	(mean ± SD) $\dot{V}O_{2\ max}$ (mL.min^{-1})				
				T2DM	1963 ± 118	2147 ± 105	<0.05	1.65
				CON	2291 ± 184	2410 ± 159	<0.05	0.69
				mean (95% CI) HbA_{1c}				
				T2DM	8.18 (6.32 – 10.03)	7.84 (5.92-9.77)	<0.05	Not available
				CON	5.89 (5.62 – 6.15)	5.90 (5.63 - 6.17)	NS	Not available
				mean (95% CI) 2hr end OGTT				
				CON	6.67 (5.64-7.71)	6.36 (5.25-7.47)	NS	Not available
				T2DM	15.34 (11.35-19.33)	13.41 (9.81-17.01)	<0.05	Not available

Study	Exercise protocol	Participants	Protocol	Outcome Measures	Pre	Post	P value	Effect size
				(Mean ± SD)				
Francois *et al.* (2017a)	Cardio-LVHIIT; 10 x 60 s at 85-90% HR_{max}, 1 min rest Resistance LVHIIT; 10 x 60 s at an RPE of 5-7 ('Hard'), 1 min rest	T2DM *n* = 53 (age range: 40-75 yr; m/f: 19/34)	2 days of cardio-LVHIIT and 1 day of resistance-LVHIIT per week for 12 weeks.	$\dot{V}O_{2\ peak}$ ($mL.kg.min^{-1}$)	19.6 ± 4.4	21.8 ± 5.1	<0.01	0.46
				FMD (mm)	0.020 ± 0.01	0.027 ± 0.01	<0.05	0.7
				mean 24hr glucose concentration ($mmol.L^{-1}$)	8.4 ± 1.4	7.7 ± 1.2	<0.01	0.54
				(Mean ± SD)				
Francois *et al.* (2017b)	Cardio-LVHIIT; 10 x 60 s at 85-90% HR_{max}, 1 min rest Resistance LVHIIT; 10 x 60s at an RPE of 5-7 ('Hard'), 1 min rest	T2DM *n* = 53 (age range: 40-75 yr; m/f: 19/34)	2 days of cardio-LVHIIT and 1 day of resistance-LVHIIT per week for 12 weeks.	PWV ($m.s^{-1}$)		+0.19 ± 1.0	NS	
				HbA_{1c} (%)	7.0 ± 0.72	6.8 ± 0.74	<0.01	0.27

Study	Exercise protocol	Participants	Protocol	Outcome Measures (mean ± SD)	Pre	Post	P value	Effect size
Winding *et al.* (2018)	LVHITT; 10 x 60 s at 95% PO_{peak}, 1 min rest MICT; 40 mins cycling at 50% PO_{peak} CON; No intervention	T2DM *n* = 32 (mean age: 56 yr)	3 days of MICT (*n* = 12) or LVHIIT (*n* =13) per week for 11 weeks	$\dot{V}O_{2\ peak}$ (mL.kg.min^{-1})				
				LVHIIT	28.4 ± 6.1	34.2 ± 6.3	<0.05	0.94
				MICT	27.8 ± 5.5	30.3 ± 7.5	<0.05	0.38
				CON	27.2 ± 9.1	26.3 ± 6.8	NS	
				HbA_{1c} (%)				
				CON	7.0 ± 1.2	6.9 ± 1.0	NS	
				MICT	6.9 ± 0.9	6.9 ± 0.8	NS	
				LVHIIT	6.8 ± 0.8	6.7 ± 0.8	NS	

T2DM, Type 2 diabetes mellitus MICT, Moderate intensity continuous training; LVHIIT, low-volume high-intensity interval training; CON, control; PO_{peak}, peak power output; $\dot{V}O_{2\ max}$, maximal oxygen uptake; $\dot{V}O_{2\ peak}$, peak oxygen uptake; CS, citrate synthase; FMD, flow mediated dilation; PWV, pulse wave velocity; m , male; f, female.

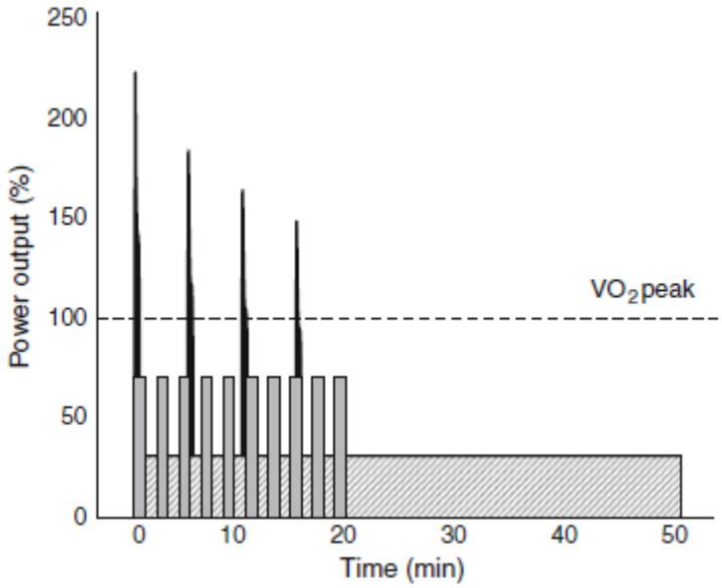

Figure 1.7. Schematic representation comparing typical exercise protocols. HIIT, black bars; 4 'all-out' sprints interspersed by ~4 mins rest; LVHIIT, grey bars; 10 x 60 s at ~ 85% peak power output interspersed by 60 s recovery; MICT, elongated grey bar; 50 mins at 35% peak power output (Taken from Gibala *et al.* 2014).

1.6.3. Improving exercise intolerance in T2DM: LVHIIT vs MICT.

1.6.3.1. Peak exercise performance.

Structured exercise training is an effective means for increasing maximal aerobic capacity in people with T2DM (Brandenburg *et al.* 1999; Stolinski *et al.* 2008; Meex *et al.* 2010; Pheilix *et al.* 2010; MacAnaney *et al.* 2012; Balducci *et al.* 2012). For instance, Brandenburg *et al.* (1999) reported a significant 27% increase in $\dot{V}O_{2max}$ in overweight women with T2DM after 12 weeks of moderate-intensity aerobic training (aerobic circuit training 3 days per week for 50 mins at 70-85% HR_{max}), while MacAnaney *et al.* (2012), reported a significant 24% increase in $\dot{V}O_{2peak}$ after 12 weeks of combined aerobic and resistance training (35-40 mins of aerobic exercise at 70-80% heart rate reserve and 1-2 sets of 12 repetitions of 6 exercises at 60-70% 1RM) in 13 participants with uncomplicated T2DM (8 males, 5 females). Interestingly, recent work suggests that LVHIIT can induce benefits in $\dot{V}O_{2max}$ of a similar magnitude to longer duration MICT. For instance significant 7% and 11% increases in $\dot{V}O_{2max}$ were reported following 8 weeks (Madsen *et al.* 2015) and 12 weeks (Francois *et al.* 2017) of LVHIIT (10 x 60 s at ~90% HR_{max}) in individuals with uncomplicated T2DM. Moreover, recent work by Windig *et al.* (2018) reported that 11 weeks of LVHIIT (3 days per week, 10 x 60 s cycling bouts at 95% PO_{peak}) was more efficient than MICT (3 days per week, 40 mins cycling at 50% PO_{peak}) at increasing peak exercise capacity (20% ↑ vs 8% ↑)in individuals with T2DM (Windig *et al.* 2018). However, the time course and mechanisms of adaptation following LVHIIT in T2DM are unknown.

Regarding the effects of LVHIIT and MICT on the central determinants of $\dot{V}O_{2max}$ (i.e. Q_{max} and maximal a-vO_2 diff) in T2DM very little data is available. In one of the key studies among non-diabetic participants, Murias *et al.* (2010) reported significant changes in $\dot{V}O_{2max}$ in both older (68 ± 7 yr) and young (25 ± 5 yr) men after just 3 weeks of the 12 week MICT intervention (45 mins cycling at 70% $\dot{V}O_{2max}$, 3 days per week), with changes in Q_{max} accounting for 2/3 of the change in $\dot{V}O_{2max}$ in the older participants while the majority of the change in $\dot{V}O_{2max}$ was accounted for by a larger a-vO_2 $diff_{max}$ in younger participants, although Q_{max} was also significantly increased (Murias *et al.* 2010). In regard to LVHIIT, significant improvements in $\dot{V}O_{2max}$ accompanied by significant increases in Q_{max} have been shown in young healthy active males and females after 6 weeks of LVHIIT while no changes in a-vO_2 $diff_{max}$ were observed (Astorino *et al.* 2017). Given that the exercise impairment observed in T2DM is often comparable with that observed in ageing per se; it is likely that both LVHIIT and MICT may induce significant benefits in Q_{max} in individuals with T2DM but this is currently unknown.

1.6.3.2. Vascular Function.

Structured exercise training interventions have shown to be effective at enhancing vascular endothelial function in T2DM. Maiorana *et al.* (2001) reported a significant improvement in endothelial dependent vascular function as measured by flow mediated dilation (FMD) after 8 weeks of moderate-intensity aerobic training in 16 adults with T2DM as well as a significant increase in $\dot{V}O_{2peak}$ (Maiorana *et al.* 2001). In addition, Schreuder *et al.* (2014), reported a significant increase in $\dot{V}O_{2peak}$ in addition to an improvement in vascular function, as measured by FMD in the brachial artery, in 13 men with T2DM within 2 weeks of an 8 week combined moderate-intensity aerobic and resistance exercise intervention (Schreuder *et al.* 2014). Typically exercise intervention studies in T2DM report only pre- and post-training responses, therefore, the study by Schreuder *et al.* (2014), is the first to provide an important insight into the time course of adaptation in vascular function and $\dot{V}O_{2peak}$ during exercise training in T2DM. On the other hand, Madsen *et al.* (2015a) observed that 8 weeks of LVHIIT (3 sessions per week of 10 x 60 s high-intensity bouts interspersed with 60 s active rest) induced a significant improvement in FMD in the popliteal artery in a group of individuals with T2DM which was accompanied by a significant improvement in $\dot{V}O_{2max}$. Similarly, Francois *et al.* (2017a) reported a significant improvement in FMD in the brachial artery (range 21-35% increase) in 53 adults with uncomplicated T2DM (19 males, 34 females) after 12 weeks of LVHIIT in addition to a significant increase in $\dot{V}O_{2peak}$ post-training (Francois *et al.* 2017a). One of the key physiological mechanisms proposed as the reason for the increase in vascular function with MICT and LVHIIT is an increase in nitric oxide availability due to the high levels of shear stress in the vasculature during LVHIIT (Mitranun *et al.* 2014).

However, there is a dearth of studies comparing MICT and LVHIIT in terms of their effect on vascular function in T2DM. The initial investigation by Mitranun *et al.* (2014) suggests that LVHIIT may be more effective than MICT at inducing significant improvements in vascular function (measured with FMD in the brachial artery) in individuals with T2DM, however, the 2 exercise intervention groups in this study were matched for exercise energy expenditure resulting in a similar time commitment (LVHIIT 26 mins vs MICT 30 mins). In addition, the LVHIIT protocol (6 x 60 s high-intensity bouts at 85% $\dot{V}O_{2max}$ interspersed with 4 mins active rest) included significantly longer rest periods than those proposed for LVHIIT by Gibala *et al.* (2006).

1.6.3.3. Mitochondrial Function.

Mitochondrial dysfunction and the reduction in mitochondrial size and number has been well documented in T2DM (Kelley *et al.* 2002; Ritov *et al.* 2005). Importantly, evidence suggests that both MICT and LVHIIT can significantly augment mitochondrial function in T2DM (Toledo *et al*. 2007; Meex *et al*. 2010; Phelix *et al.* 2010; Little *et al.* 2011). For instance, Toledo *et al*. (2007), reported a 67% increase in mitochondrial density (P < 0.05), a 20% increase in mitochondrial DNA content (P < 0.05) and a significant increase in CS and

NADH oxidase activity (both of which are indicators of mitochondrial oxidative capacity) following 16 weeks of MICT in middle-aged men with T2DM (Toledo *et al*. 2007). Similarly, Meex *et al.* (2010) observed a significant 48% increase in mitochondrial function with MICT in addition to a significant increase in mitochondrial density and content after 12 weeks of combined resistance and aerobic training in 18 males with T2DM, which was accompanied by a significant 11.8% increase in $\dot{V}O_{2max}$ (Meex *et al.* 2010). In addition, Pheilix *et al.* (2010) reported that 12 weeks of combined resistance and MICT in 15 males with T2DM significantly increased mitochondrial density and resulted in a 30% increase in mitochondrial content together with a significant 11.5% increase in $\dot{V}O_{2max}$ (Pheilix *et al.* 2010).

In terms of LVHIIT, Little *et al.* (2011a) reported a significant increase in citrate synthase activity (a marker of mitochondrial oxidative activity) as well as a 10% increase in peak power after only 2 weeks of LVHITT (3 sessions per week comprising of 10 x 60 s cycling bouts at 90% HR_{max} interspersed by 60 s active rest) in participants with uncomplicated T2DM (Little *et al.* 2011a). In terms of the improvements in mitochondrial activity induced by LVHIIT observed by Little *et al.* (2011a), an increase in the activity of peroxisome-proliferator activated ϒ coactivator (PGC-1α) is likely to be the underlying mechanism. PGC-1α is thought to be the master regulator of mitochondrial biogenesis (Gibala *et al.* 2012) and exercise intensity is suggested to be the key determinant of PGC-1α activity (Egan *et al.* 2010). Indeed, studies involving LVHIIT on PGC-1α levels in healthy populations have indicated a ~50% increase in PGC-1α activity with LVHITT, which is associated with significant increases in mitochondrial content and oxidative activity (Little *et al.* 2011b; Hood *et al.* 2011; Gibala *et al.* 2012).

1.6.3.4. $\dot{V}O_2$ kinetics.

Strong evidence suggests that structured exercise training induces significant benefits in $\dot{V}O_2$ kinetics in T2DM. Initially, Brandenburg *et al.* (1999), reported a significant reduction in $\tau\dot{V}O_{2P}$ (pre = 47.7 ± 4.7 s post = 37.4 ± 15 s) during absolute moderate-intensity exercise (50W) in a group of women with uncomplicated T2DM following 12 weeks of MICT (3 x 50 mins sessions per week at 70-85% HR_{max}) which was accompanied by a significant 28% increase in $\dot{V}O_{2peak}$. More recently, MacAnaney *et al*. (2012), reported a significant reduction in $\tau\dot{V}O_{2P}$ during a relative moderate-intensity cycling exercise (80% VT) (pre = 40.5 ± 10.1 s, post = 33.4 ± 6.4 s) following 12 weeks of combined moderate-intensity aerobic and resistance exercise in a group of men and women with uncomplicated T2DM (MacAnaney *et al*. 2012).

It is likely that the underlying mechanism for the speeding of $\dot{V}O_2$ kinetics with exercise training in T2DM is, at least in part, due to improvements in peripheral blood flow and its distribution. Although this hypothesis has not yet been tested in T2DM, Murias *et al.* (2010) reported a significant improvement in $\dot{V}O_2$ kinetics in healthy older men within 3 weeks of a 12 week MICT intervention which was accompanied by a significant improvement in the matching of the dynamic adjustment of [HHb+Mb] to VO_2 at the onset of exercise (Δ [HHb + mb]/Δ$\dot{V}O_2$ ratios). Elevated Δ[HHb + mb]/Δ$\dot{V}O_2$ratios (>1.0) displaying an 'overshoot' relative to the subsequent steady-state were demonstrated in the older groups with slower $\dot{V}O_2$ kinetics, which were progressively reduced as $\tau\dot{V}$O2p was reduced with training. This reduction in Δ [HHb + mb]/Δ$\dot{V}O_2$ ratios is suggestive of an improvement in the matching of O_2 delivery and O_2 utilisation at the level of the skeletal muscle. As there is a mismatch in O_2 delivery and utilisation at the onset of exercise in T2DM (Gildea *et al.* 2016, 2018; Rocha *et al.* 2016), it is likely that exercise training may improve this balance within a similar timeframe as observed in the elderly men of the study by Murias *et al.* (2010), but this has not been tested yet.

There is a dearth of evidence investigating the effect of LVHIIT on $\dot{V}O_2$ Kinetics in T2DM. Studies in young healthy male participants carried out by McKay *et al.* (2009) and Williams *et al.* (2013), have indicated that as little as 2-4 weeks of LVHIIT can induce significant reductions in $\tau\dot{V}O_{2P}$ at submaximal intensities. Initially, McKay *et al.* (2009) reported similar significant reductions in $\tau\dot{V}O_{2P}$ (LVHIIT pre = 27 ± 6 s, post = 16 ± 5 s; MICT pre = 23 ± 8 s, post = 14 ± 2 s) at the onset of moderate-intensity exercise after 3 weeks of LVHIIT (8-12 x 60 s cycling at 120% peak power output interspersed by unloaded cycling recovery) or MICT (90-120 minutes of cycling 65% $\dot{V}O_{2max}$), in a group of young healthy males (McKay *et al.* 2009). Furthermore, Williams *et al*. (2013), reported a significant reduction in $\tau\dot{V}O_{2P}$ (pre = 24 ± 6 s, post = 14 ± 3 s) during moderate-intensity exercise after just 4 weeks of LVHIIT (3 sessions per week; 8-12 x 60s cycling at 110% peak power interspersed by 1 min of unloaded cycling) in healthy young males (Williams *et al*. 2013). Even if both McKay *et al.* (2009) and Williams *et al.* (2013) reported no change in [HHb + Mb] during submaximal exercise following the intervention period, Williams *et al.* (2013) observed that the overshoot in the Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio (i.e. Δ [HHb + Mb]/Δ$\dot{V}O_2$ >1.0) that was present pre-training was abolished after 2 weeks of training, and did not re-emerge at the end of the training period. This is indicative of an improvement in microvascular O_2 delivery and distribution, and suggests that the improvements observed in $\dot{V}O_2$ kinetics with LVHIIIT may have resulted from an improvement in microvascular blood flow during exercise rather than an enhanced oxidative capacity of the skeletal muscle mitochondria. Following a higher intensity HIIT protocol, Da Boit *et al.* (2014) reported that 2 weeks of repeated sprint training (RST; 4-6 30 second 'all-out' sprints interspersed by 4 minutes of active recovery) was as effective as 2 weeks of MICT (60-110 mins cycling at 90% VT) at inducing significant reductions in $\tau\dot{V}O_{2P}$ (RST pre = 54 ± 7 s, post = 40 ± 11 s; MICT pre = 50 ± 10 s, post = 39 ± 11 s) and the overall mean response time (RST pre = 86 ± 22 s, post = 68 ± 5 s; MICT pre = 89 ± 15 s, post = 69 ± 10 s) when transitioning from a moderate-intensity to a severe-intensity exercise in young healthy individuals (Da Boit *et al.* 2014).

1.7. Aims.

There is clear evidence that shows that traditional MICT is an effective intervention at increasing $\dot{V}O_{2peak}$ and speeding $\dot{V}O_2$ kinetics responses in people with T2DM. Similarly, a growing body of evidence suggests that time efficient LVHIIT interventions are as effective as MICT programs at inducing significant improvements in $\dot{V}O_{2peak}$ in T2DM and $\tau\dot{V}O_{2P}$ in non-clinical populations. However, the mechanisms and time course of adaptation in maximal and submaximal exercise capacity induced by MICT and LVHIIT in T2DM have not been explored.

Therefore, the specific aims of the experiments described in this thesis were as follows:

- *Experiment 1* aimed to compare the effects of 12 weeks of MICT vs LVHIIT on the mechanisms and time course (i.e., every 3 weeks) of adaptation in peak cardiorespiratory responses and fractional oxygen extraction profiles during ramp incremental exercise in people with uncomplicated T2DM

- The primary aim of *Experiment 2* was to compare the effects of MICT vs LVHIIT on the mechanisms and time course of adaptation in $\dot{V}O_2$ and [HHb + Mb] kinetics responses during moderate-intensity cycling exercise in people living with uncomplicated T2DM. The secondary aim of this experiment was to investigate the effect of LVHIIT and MICT on the influence of priming exercise on $\dot{V}O_2$ and [HHb + Mb] kinetics during moderate-intensity exercise across the same time points of the study.
- The primary aim of *Experiment 3* was to compare the effects of MICT vs LVHIIT on the mechanisms and time course of adaptation in $\dot{V}O_2$ and [HHb + Mb] kinetics responses during heavy-intensity cycling exercise responses initiated from an elevated baseline (W-to-W) in people with uncomplicated T2DM. The secondary aim of this experiment was to investigate the effect of LVHIIT and MICT on the influence of priming exercise on pulmonary $\dot{V}O_2$ and [HHb + Mb] kinetics during heavy-intensity exercise initiated from an elevated baseline across the same time points of the study.

Chapter 2: *Time course and mechanisms of adaptations in cardiorespiratory fitness and fractional oxygen extraction profiles during ramp incremental exercise with LVHIIT and MICT in type 2 diabetes.*

2.1. Introduction.

People with T2DM have been consistently shown to have a peak exercise capacity that is ~12-30% lower than that of age-matched healthy controls (Regensteiner *et al.* 1998; Baldi *et al.* 2003; O'Connor *et al.* 2012; Green *et al.* 2015). This has a significant impact on the lives of those with T2DM as a lower peak exercise capacity is associated with a reduced quality of life, an increased level of insulin resistance and an increased risk of all-cause mortality and morbidity (Regensteiner *et al.* 1995; Wei *et al.* 2000).

Moderate-intensity continuous training (MICT) and low-volume high-intensity interval training (LVHIIT) are effective means for increasing maximal aerobic capacity in people with T2DM (Brandenburg *et al.* 1999; McAnaney *et al.* 2012; Madsen *et al.* 2015; Francois *et al.* 2017). Training interventions comprising MICT lasting 12 weeks have yielded improvements in $\dot{V}O_{2max}$ of the magnitude of ~21-28% in men and women with uncomplicated T2DM (Brandenburg *et al.* (1999; McAnaney *et al.* 2012). More recently, 12 week interventions utilising LVHIIT in T2DM have produced improvements in $\dot{V}O_{2max}$ of the magnitude of ~9-11% (Madsen *et al.* 2015; Francois *et al.* 2017). Although both forms of training are effective at inducing improvements in $\dot{V}O_{2max}$ in T2DM, studies directly comparing the effects of LVHIIT and MICT are limited. Furthermore, data pertaining to the time course and mechanisms of training induced adaptations in $\dot{V}O_{2max}$ in T2DM in response to MICT and LVHIIT are unavailable.

According to the Fick equation changes in $\dot{V}O_{2max}$ must be mediated by changes in Q and a-vO_2diff. In healthy populations, Murias *et al.* (2010), reported a significant increase in $\dot{V}O_{2max}$ and Q_{max} (as measured by the acetylene (C_2H_2) open-circuit inert gas-wash in method) after just 3 weeks of a 12 week MICT intervention in both young and older healthy males with a further significant increase in Q_{max} observed after 9 weeks in both groups. Interestingly, 66% of the initial improvement in $\dot{V}O_{2max}$ in the older participants was due to an improvement in Q_{max} while in the younger participants, increases in $\dot{V}O_{2max}$ were as a result of improvements in oxygen utilisation as reflected by a significant increase in a-vO_2diff$_{max}$ (Murias *et al.* 2010). In regards to LVHIIT, Astorino *et al.* (2017) reported that 6 weeks of LVHIIT yielded significant increases in Q_{max} (measured with an impedance cardiograph device) as well as significant improvements in $\dot{V}O_{2max}$ with no changes in a-vO_2diff$_{max}$ in young healthy male and female participants (Astorino *et al.* 2017).

In addition to central mechanisms, $\dot{V}O_{2max}$ is constrained by peripheral O_2 uptake and utilisation. In this regard, Gildea *et al.* (2016), reported an over reliance in fractional oxygen extraction during ramp incremental exercise (RI) reflected as an increased rate of muscle deoxygenation (i.e., deoxygenated haemoglobin and myoglobin, [HHb + Mb]) in a group of individuals with uncomplicated T2DM suggesting lower microvascular blood flow responses which was accompanied by a significant reduction in $\dot{V}O_{2max}$. However, it is unknown if muscle deoxygenation rates are affected by LVHIIT or MICT in individuals with uncomplicated T2DM and what the time course of adaptation may be.

Thus, the primary aim of this experiment was to compare the effects of 12 weeks of MICT with LVHIIT on the mechanisms and time course of adaptation in cardiorespiratory fitness in people with uncomplicated T2DM. A further aim of this experiment was to examine the effects of LVHIIT and MICT on fractional oxygen extraction profiles during ramp incremental exercise. It was hypothesised that both LVHIIT and MICT would improve $\dot{V}O_{2max}$ within a similar timeframe and to a similar extent while a training-induced improvement in fractional extraction profiles during ramp exercise would be observed in both training groups.

2.2. Methodology.

2.2.1. Recruitment of Participants.

Participants with uncomplicated T2DM were recruited from the out-patient endocrinology clinics of St. Colmcille's Hospital, Dublin and St. Vincent's University Hospital, Dublin. Eligible individuals were identified by hospital consultants through a review of medical charts and were briefly informed about the study during a routine clinic visit. Individuals who were interested in the study were then directed to the study investigator in the waiting area of the clinic. The investigator provided information on the study including the participant information leaflet (PIL) which outlined all the testing procedures involved in the study (see Appendix 8.2). Seven days following this meeting the potential participant was contacted via telephone or e-mail to confirm whether or not they would like to participate in the study.

Ethical approval for this study was granted by the Faculty of Health Sciences Research Ethics Committee of the University of Dublin, Trinity College Dublin and by the St. Vincent's Healthcare Group Ethics and Medical Research Committee.

2.2.1.1. Exclusion Criteria.

In order to participate in the study individuals had to be aged between 18-70 years, have a fasting HbA_{1c} < 10% (< 86 $mmol/mol^{-1}$), have no history of peripheral arterial disease as determined by the ankle: brachial index and be completing < 2 hours of moderate-intensity exercise per week (i.e. untrained). Furthermore, individuals were excluded if they were being treated with insulin as this indicates a more advanced stage of T2DM.

Additional criteria for exclusion from the study included persistent proteinuria (urine protein > 200 mg/dL^{-1}) and/or elevated creatinine levels (> 1.2 mg/dL^{-}). In addition, the presence of diabetic complications and/or comorbid conditions including autonomic insufficiency/dysfunction, symmetrical neuropathy, abnormal cardiac function or evidence of ischaemic heart disease, angina or any other cardiac or pulmonary symptoms limiting exercise performance led to exclusion from the study.

2.2.2. Study Overview.

Those who agreed to participate were invited to attend a pre-screening assessment in St. Colmcille's Hospital, Dublin. During this visit the participant signed an informed consent form (see Appendix 7.2), completed a 12-lead ECG exercise stress test with a qualified physician and were assessed for the presence of peripheral arterial disease (PAD) using the Ankle: Brachial Index (ABI). Baseline physical activity levels were then confirmed by wearing a RT3 accelerometer (Stayhealthy Inc., CAL, USA) for 5 consecutive days. On a separate day a fasting blood sample was obtained in order to assess metabolic profiles.

Once the pre-screening had been satisfactorily completed the participants entered the study and were randomised into one of three groups using a random number generator created using Microsoft Excel; control (CON), moderate-intensity continuous exercise training (MICT) or low volume high-intensity interval training (LVHIIT). The study investigator was not blinded to the randomisation process. The MICT and LVHIIT groups trained 3 times per week for 12 weeks whereas the CON group received no intervention and continued with their normal daily routine. Prior to the commencement of training and every 3 weeks during training, each participant attended the exercise physiology laboratory of St. Colmcille's Hospital on 1 occasion in order to complete a ramp incremental test (RI) to determine $\dot{V}O_{2max}$. Exercise intensities for MICT and LVHIIT were individually prescribed from the results of the RI at each time point.

To allow for standardisation of testing conditions the participants were asked to abstain from consuming alcohol for 24 hours and caffeine for 12 hours prior to a testing session. They were also asked not to perform any strenuous exercise for 24 hours before each session. The compliance to these conditions was confirmed by self-report by the participant. Participants were tested at the same time of day. All premenopausal participants (*n* = 5) were tested during the mid-follicular phase (days 5 - 12) of the menstrual cycle which was determined by self-evaluation.

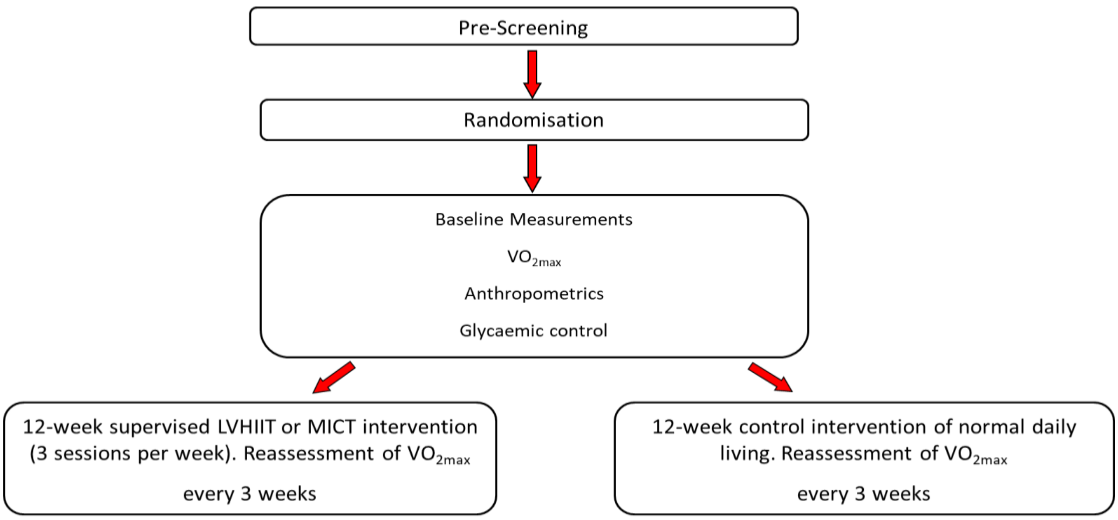

Figure 2.1. Study overview

2.2.3. Exercise training intervention.

Both the MICT and LVHIIT groups trained 3 times per week for 12 weeks in a community gym setting where they were supervised by gym instructors trained in the exercise protocols and by the study investigators. Prior to each exercise session each participant had their blood pressure recorded by the gym instructors or study investigators using an Omron M7 blood pressure monitor (Omron Healthcare Europe B.V., Hoofddorp, and The Netherlands). If a participant's SBP was > 170 mmHg or < 90 mmHg and/or DBP was > 90 mmHg or < 60 mmHg they were not permitted to train.

In addition, each participant was required to measure their blood glucose levels prior to training. To reduce the risk of hypo- and hyper-glycaemic episodes, participants were only permitted to train if their blood glucose level was between 5 - 15 $mmol.L^{-1}$.

2.2.3.1. Moderate-intensity continuous training.

Both exercise groups completed a 5 minute warm up and cool down before and after each session on any aerobic machine of their choice. Available machines included; elliptical trainers, treadmills, rowing ergometers and cycle ergometers. The main component of each training session was completed on a cycle ergometer (Precor 842i Upright Bike, Precor, Woodenville, WA, USA).

MICT was designed in order to achieve the ADA recommended guidelines for physical activity (Colberg *et al.* 2016). Each MICT session comprised of 50 minutes of cycling at an intensity equivalent of 80-100% VT as calculated from the maximal exercise test. At regular intervals throughout the session the participants were asked to record their power output, as displayed on the cycle ergometer display, heart rate as measured with a heart rate monitor (CardioSport Fusion 30, Healthcare Technology Ltd, Hampshire UK), and rating of perceived exertion (RPE) using the Borg scale (Borg, 1982) into an exercise diary provided to them (see Appendix 8.3).

The Borg Scale is a commonly used measurement tool for RPE that has been validated against measurements of physiological strain such as heart rate, VO_2 and power output (Faulkner *et al.* 2007). The Borg scale is used to assess levels of perceived local (i.e., the working muscles) and central (i.e., the work of breathing or cardiorespiratory sensations) fatigue, with sensations of local muscle fatigue predominantly reported during assessments of RPE during cycling exercise (Borg *et al*. 1985). Furthermore, the Borg scale is a psychophysiological index of physical strain based on a model that includes both subjective and objective feelings of exertion such as muscle pain, increased respiratory rates, sweating and increased temperature (Lewis *et al.* 2007; Zamuner *et al.* 2011).

2.2.3.2. Low-volume high-intensity interval training.

The LVHIIT group completed 10 x 60 s bouts of high-intensity cycling interspersed by 60 s of light cycling recovery. The high-intensity bout was completed at a PO equivalent to 70% of the difference between participant's PO_{peak} and the PO at VT (70% Δ) achieved during the ramp exercise test. This output was designed to elicit a target heart rate of 90% HR_{max} during the high-intensity bouts. The participants in the LVHIIT group were instructed to record the average PO, HR and RPE during each high-intensity bout into their exercise diary. The exercise diaries were reviewed weekly by study investigators to ensure exercise adherence and compliance.

For both training groups the prescribed HR and power output ranges were adjusted accordingly every 3 weeks following reassessment of $\dot{V}O_{2max}$. Both exercise interventions are summarised in Table 2.1. The control group received no intervention and were requested to continue with their routine care.

Table 2.1. ***Summary of exercise training programmes.***

Intervention	HR	Power Output	Warm up/Cool down (min)	Total session time (min)	Total time per week (min)
LVHIIT	~90% HR_{peak}	PO @ 70% Δ	5/5	30	90
MICT	~55-70% HR_{peak}	PO @ 80-100% VT	5/5	60	180
Control	Normal daily routine				

LVHIIT: low-volume interval training; MICT: Moderate intensity continuous training; HR: heart rate; PO: power output; VT: ventilatory threshold: PO @ 70% Δ, PO equivalent to 70% of the difference between participant's PO_{peak} and the PO at VT (70% Δ) achieved during the ramp exercise test.

2.2.4. Laboratory measurements.

2.2.4.1. Pre-screening.

2.2.4.1.1. Exercise stress test.

A standard 12 lead ECG was set up on the study participant. Then under the supervision of a physician, the participant completed an EST on a motorised treadmill using the Bruce protocol (Table 2.2). Briefly, the protocol began at a speed of 2.7 $km.hr^{-1}$ and an incline of 10% with both variables increasing every 3 minutes. The primary criterion for termination of the EST was achievement of 90% of age predicted maximum heart rate. In addition, the test was terminated if the participant reported any light-headedness, chest pain or excessive shortness of breath, any abnormal blood pressure response or abnormal ECG trace. Upon termination of the EST, the ECG trace throughout was reviewed and signed off by the attending physician. If the participant presented with an abnormal ECG trace or EST response they were referred on to the appropriate medical team for further investigations.

Table 2.2. ***Bruce protocol*.**

Stage	Velocity (km.h^{-1})	Gradient (%)
1	2.7	10
2	4.0	12
3	5.5	14
4	6.8	16
5	8.0	18

2.2.4.1.2. Physical activity levels.

Participants were required to be untrained (completing < 2 hours of moderate-intensity exercise per week), and to have not taken part in a structured exercise programme within the 6 months prior to study entry. Five-day physical activity levels were collected from each participant using a RT3-triaxial accelerometer (Stayhealthy Inc., CAL, USA). The RT3 has been found to be a valid measure of physical activity in adults and adolescents (Rowlands *et al*. 2004). The RT3 utilises piezoelectric sensors to detect movement in the anteroposterior, mediolateral and vertical planes to yield a vector magnitude (VM) and allows for measurement of the intensity, frequency, duration and volume of any physical activity completed by the wearer during waking hours (Hussey *et al.* 2007; Vanhelst *et al.* 2010).

Participants were required to wear the RT3 on their right hip during all waking hours apart from when they were entering water (e.g. swimming or showering), for 5 consecutive days. A pre-set mode was utilised, whereby the time sampling interval is set at 1 minute and accumulated activity counts on individual axes are converted to a digital representation for processing. Output is then expressed as mean counts per minute for each activity which is stored in the unit's memory chip (Eston *et al.* 1998).

Data from the RT3 were assessed for counts.min^{-1} for VM. Previously defined cut-off values were used to categorise the participant's level of physical activity: inactive (0-100 counts.min^{-1}), light (101-970 counts.min^{-1}), moderate (971-2333 counts.min^{-1}) and vigorous (>2334 counts.min^{-1}) (Rowlands *et al.* 2004). The accumulated physical activity counts obtained for 5 days were averaged to give a mean output for 1 day, with the total time spent in each category being expressed in hr.day^{-1}.

2.2.4.1.3. Ankle: Brachial index.

The Ankle: Brachial index has been shown to be a reliable non-invasive measure for PAD risk (Aboyans *et al.* 2012). Briefly, pneumatic cuffs (Hokanson, Bellvue, WA, USA) were placed around the arms approximately one inch above the antecubital fossa and the ankles (at the level of the malleoli) of the participant who was resting in a supine position. Then, using Doppler Ultrasound (Hokanson, Bellvue, WA, USA) at a frequency of 10 Hz the flow signal was detected in the artery of interest; either the Brachial (BA), posterior tibalial (PT) or dorsalis pedis (DP) artery. Once the artery was located, the cuff was inflated until the flow signal disappeared and then deflated slowly until the flow signal reappeared. The pressure at which the signal reappeared was deemed to be the systolic blood pressure in that artery. The measurement was repeated bilaterally for BA, PT and DP. To calculate ABI of both legs the highest of the two ankle pressures (PT or DP) on one side was divided by the highest of the 2 arm pressures and this calculation was then repeated for the other leg. A value of < 0.9 or > 1.4 is indicative of PAD (Aboyans *et al.* 2012) and any participants who presented with these values were excluded from the study.

2.2.4.1.4 Metabolic profile.

On a separate day and following a 12-hour fast, a fasting blood sample was obtained from the antecubital vein and sent to the biochemistry department of St. Vincent's University Hospital for analysis. Measurements of HbA_{1c} and fasting glucose were recorded from each blood sample at baseline (week 0) and after the intervention period (week 12).

2.2.4.2 Visit to exercise physiology laboratory.

2.2.4.2.1. Anthropometric measurements.

Body mass (kilogram) and height (metre) were measured using a Seca weighing scales and stadiometer (Seca, Hamburg, Germany). Body mass was measured to the nearest 0.1kg and height was measured to the nearest 0.1 cm. Participants were requested to remove their shoes during the measurement of body mass and height. Body mass index (BMI) was calculated by dividing the participant's body mass by their height squared (BMI = body mass (kg) / height (m^2)).

2.2.4.2.2. Maximal ramp incremental exercise test.

Each participant completed a ramp incremental test to volitional exhaustion on an upright electronically braked cycle ergometer (Excalibur Sport, LODE B.V., Groningen, The Netherlands). The ramp test consisted of 2 minutes cycling at 10 W followed by a continuous ramped increase in power output, of 15 $W.min^{-1}$ for females and 20 $W.min^{-1}$ for males until the participant could no longer maintain the target cadence for > 3 s. Cadence was kept constant at a self-selected RPM of between 60-70 RPM. Throughout the test breath-by-breath gas analysis was completed to continuously determine $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}_e$) and respiratory exchange ratio (RER) responses.

Within 5 minutes of completion of the ramp protocol, participants performed an additional cycling protocol to exhaustion at 85% of the peak power output achieved during the ramp test. This protocol was completed firstly, in order to confirm the attainment of $\dot{V}O_{2max}$ during the RI test, and secondly to allow for the measurement of peak cardiac output responses (Murias *et al*. 2010). Each participant was asked to raise their right hand once they felt that they were 30 s away from failure during the exhaustive cycling bout and recording of Q was commenced using the inert gas rebreathing technique (see below).

2.2.5. Laboratory equipment and measurement techniques.

2.2.5.1. Cardio-metabolic unit.

Breath-by-breath gas analysis was performed using a cardio-metabolic unit (Innocor, Innovision, Denmark) which allowed for the measurement of gas exchange and ventilatory variables (i.e. $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_e$, and RER). In preparation for data collection the participant wore a nose-clip and used a silicone mouth piece which was attached to a filter and subsequently to the rebreathing valve unit (RVU) of the cardio-metabolic unit which allowed for the collection of all expired gas (Fig. 2.1).

The cardio-metabolic unit was calibrated before each RI test according to the manufacturer's instructions. This involved calibration of the flow meter using a 3L syringe (Hans Rudolph, Kansas City, MO), flow-gas delay via a specific breathing technique performed by the investigator following a graphical tachymeter on the visual display unit, and finally the oxygen sensor, by exposing the sample line to atmospheric air. CO_2 calibration was performed every 6 months by the manufacturer.

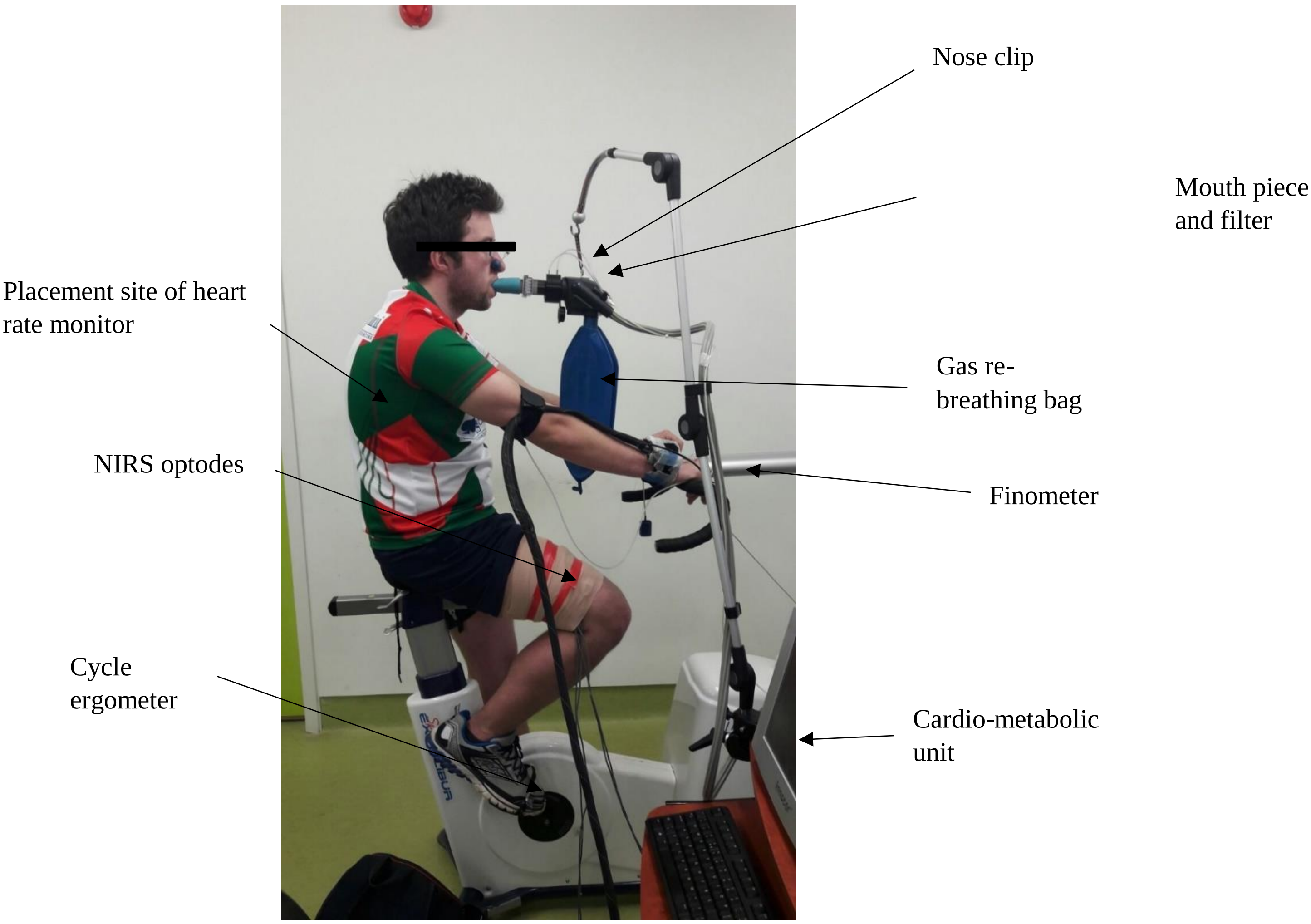

Figure 2.2. Illustration of the experimental set up utilised during the ramp incremental cycling protocol.

2.2.5.2. Heart rate.

A chest fitted heart rate monitor (Polar RS800CX, Polar Electro Oy, Finland) was used throughout the test with HR_{max} deemed to be the highest value achieved during the 15 s before termination of the exercise test.

2.2.5.3. Blood pressure.

Beat-to-to beat systolic (SBP) and diastolic blood pressure (DBP) were continuously monitored throughout the ramp incremental test using the volume clamp method at the level of the finger (Finometer, Finepress Medical Systems B.V. the Netherlands). The finometer is a valid and reliable method of measuring blood pressure. (Schutte *et al.* 2004). Peak SBP and DBP were expressed as the highest mean pressures obtained in the 15 s before the termination of the test. Mean arterial pressure (MAP) was then estimated from systolic and diastolic pressures (MAP: 0.33 SBP + 0.66 DBP).

2.2.5.4. Cardiac Output.

2.2.5.4.1. Modelflow method.

Beat-by-beat measures of Q were continuously measured using the pulse wave of the right finger arterial pressure (Finometer, Finepress Medical Systems B.V. the Netherlands) using the modelflow algorithm in order to estimate stroke volume and incorporating the variables of age, gender, height and weight to estimate the aortic cross-sectional area (Langewouters *et al.* 1984; Wesseling *et al.* 1993; Fasial *et al.* 2009). In order to minimise the effect of the Q measurement on cycling mechanics, participants were instructed to rest their right hand on the horizontal handle bar of the cycle ergometer and to avoid grasping the handlebar as it would interfere with data collection. Maximal Q was determined as the mean Q measured during the last 15 s of the 'confirmatory bout'. Importantly, Q values obtained from the model flow algorithm were highly correlated with the values yielded from the inert gas rebreathing method (number of measurements compared = 117, r = 0.93, P <0.001). Maximal values for a-vO_2 diff responses were derived from the Fick equation (i.e. a-$vO_2diff_{max} = \dot{V}O_{2max} / Q_{max}$).

2.2.5.5. Muscle Deoxygenation.

Local muscle deoxygenation was analysed throughout the incremental exercise test using a commercially available NIRS system (NIRO-200NX, Hamasatu Photonics, Hamasatu, Japan). NIRS is a non-invasive way of continuously and simultaneously monitoring oxygenation of the haemoglobin in the microvasculature and myoglobin in the skeletal muscle thus, reflecting the balance between oxygen consumption and delivery. Therefore, NIRS can serve as an indirect measure of oxygen extraction (DeLorey *et al.* 2003; Ferreira *et al.* 2007).

The underlying principles of NIRS have been outlined in detail by Elwell (1995) and their application during exercise by DeLorey *et al.* (2003). Briefly, tissue oxygenation is measured utilising one light-emitting diode (LED; 735, 810, and 850 nm) and two photodetectors spaced 0.8 cm apart. The inter-optode distance between the emission diode and light detectors was 3 cm. The diodes are pulsed in rapid succession and the light returning from the tissues is detected by the photodiodes for estimation of the following variables; deoxygenated haemoglobin and myoglobin concentration ([HHb + Mb]), oxygenated haemoglobin concentration ([O_2 Hb]) and the total oxygenation index (TOI) (Spencer *et al*. 2012). Measurement of [HHb + Mb] with NIRS is based on the diffusion approximation for a highly scattering semi-infinite homogeneous media and parameters are calculated using the modified Beer-Lambert law (Jacobs *et al.* 2013). The reduction in reflected light is measured as a function of the source detector separation distance and the effective light attenuation coefficient can be estimated. Assuming wavelength dependence of the decreased scattering co-efficient, the spectral shape of the absorption co-efficient can be calculated and tissue saturation estimated (Jacobs *et al.* 2013).

To prepare for the application of the NIRS, the vastus lateralis (VL) muscle of the right quadriceps was identified through palpation by the study investigator. VL is a dominant locomotor muscle during cycling (Okushima *et al.* 2016) and therefore, was chosen as the location of NIRS investigation. The area was shaved and cleaned using a sterile alcohol wipe before the NIRS optodes were placed on the area of interest using double sided tape (Fig. 2.2). The optodes are housed in optically dense plastic holders which were also covered in optically dense black rubber holders to minimise the intrusion of excess light. The optodes were covered in a cloth bandage to prevent excessive movement during exercise and to further prevent the entry of excessive light which may have interfered with the NIRS signal. Prior to the start of the ramp test the NIRS-derived signal was zero set while the participant was resting on the cycle ergometer.

The subcutaneous fat layer of the VL was measured using Doppler ultrasound (Zonare, Mindray technologies, Shenzhem, China). The same site used for placement of the NIRS probes was identified and three measures of the subcutaneous fat layer were taken and averaged.

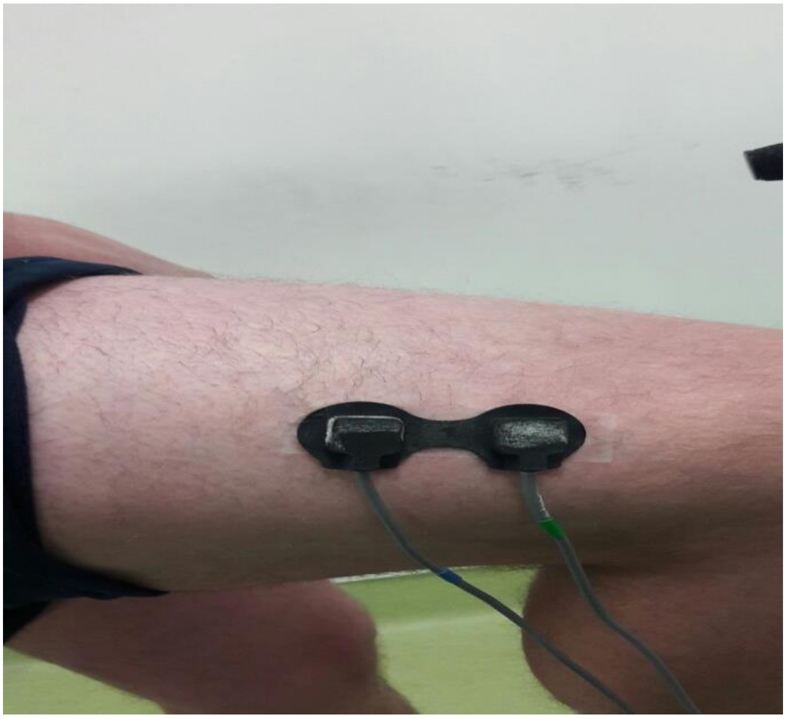

Figure 2.3. Illustration of the set-up of the NIRS set up.

Prior to the onset of exercise, the NIRS-derived signal was normalised such that the unloaded exercise baseline value was adjusted to zero ('zero set'), and thus the NIRS data are presented as a relative change from the baseline- to the end-exercise values. Given the uncertainty of the optical path length in the VL, Δ [HHb + Mb] data are presented as normalised Δ units.

The second-by-second [HHb + Mb] data from each test was smoothed with a 5 s moving average and these values were normalised to the maximum value achieved during the ramp test. Baseline [HHb + Mb] i.e. 0% [HHb + Mb] was taken as the average of the last 60 s of the 2-minute warm-up period. The highest value of the 5 s averages was deemed to be peak [HHb + Mb] i.e. 100% [HHb + Mb].The normalised [HHb + Mb] profile (%Δ[HHb + Mb]) for each participant was then plotted as a function of relative work rate (%PO_{peak}) on TableCurve 2D (v5.01.01, Systat Software, CA, USA).

Two linear portions of the %Δ [HHb+Mb] profiles were observed, with the first beginning (S_1) at the point where the %Δ [HHb+Mb] began a systematic increase above baseline (determined by visual inspection), followed by a second plateau section (S_2) in the %Δ [HHb+Mb]. The demarcation of the 2 linear segments is identified by a break-point (BP). This double-linear model was characterised using the following equation, based on the work of Spencer *et al.* (2012) (see Fig 2.X):

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, d is the time delay or 'breakpoint' (namely, the x value at the break point between the two segments) and the slope of the second linear function is calculated from the estimates of b and c (namely, parameter b-c).

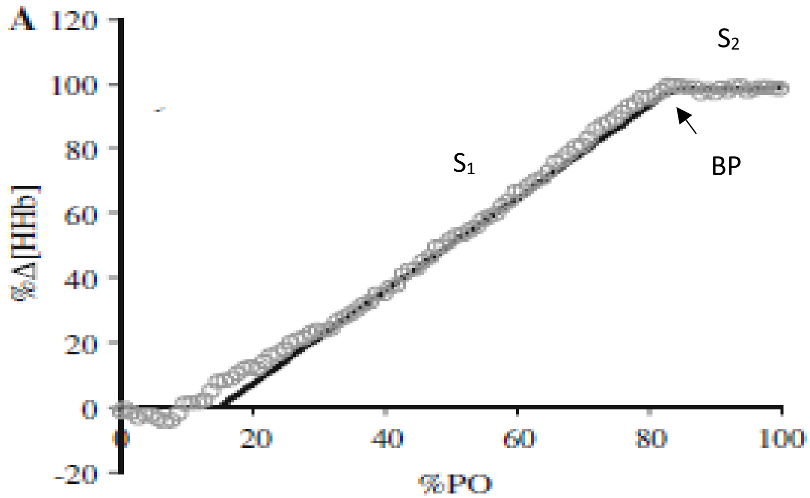

Figure 2.4. Representative plot of the bilinear regression model used to analyse the NIRS derived [HHb+Mb] data. (Taken from Spencer *et al.* 2012).

2.2.6. Data Analysis.

2.2.6.1 $\dot{V}O_2$ analysis.

In the present study all participants demonstrated a plateau in $\dot{V}O_2$ during the confirmatory tests. A plateau was deemed to be achieved when $\dot{V}O_2$ did not increase by more than 2.1 mL.min.kg^{-1} in response to an increase in exercise intensity. In addition, the $\dot{V}O_2$ values recorded during this confirmatory test were not different to those obtained during the ramp incremental cycle test. The concordance in the data increased the likelihood that the participants reached $\dot{V}O_{2max}$. Thus, $\dot{V}O_{2max}$ was taken as the mean $\dot{V}O_2$ value achieved during the last 30s of the ramp incremental test. The ventilatory threshold was determined using the V-slope method by a single investigator (Beaver *et al.* 1986), by identifying the point where $\dot{V}CO_2$ increases disproportionally to $\dot{V}O_2$. The respiratory compensation point (RCP) was determined as the second disproportionate increase in ventilation ($\dot{V}_e$) relative to work rate. All participants had two verified ventilator breakpoints. Peak power output was taken as the work rate performed at exhaustion.

2.2.7. Statistical Analysis.

Unless stated otherwise data are presented as mean (SD). Statistical Analysis were performed using SigmaPlot 12.0 (Systat Software, San Jose, CA, USA). The normality of the data was assessed using the Shapiro-Wilk test (Shapiro & Wilk, 1965). Non-normally distributed the data and data that did exhibit equality of variance were transformed to resemble normally distributed data. At baseline, age, anthropometric and metabolic data were compared using a one-way ANOVA. Time point analysis of anthropometric data, peak responses, [HHb + Mb] responses and VO_2 responses were performed using a 2-way (group x time) repeated-measures ANOVA. In case of significant differences observed from the ANOVA and to reduce the risk of type I and II errors, post-hoc Tukey tests were performed. The significance level was set at $P < 0.05$.

The primary outcome variable in this study is maximal oxygen uptake ($\dot{V}O_{2max}$) at each time point throughout the intervention period. Recently published studies investigating the effect of 12 weeks of MICT or LVHIIT in T2DM have reported average $\dot{V}O_{2max}$ values of 19.1 ± 2.0 mL^{-1}.kg^{-1}.min^{-1} (Mean ± SD) with the difference in $\dot{V}O_{2max}$ between pre- and post-training being 4.6 mL^{-1}.kg^{-1}.min^{-1}

(i.e. ~24%) (Brandeburg *et al.* 1999; McAnaney *et al.* 2012). Given that the estimated standard deviation (SD) of each population is 2.0 $mL^{-1}.kg^{-1}.min^{-1}$, and that the minimum difference we wish to detect as significant would be 4.6 $mL^{-1}.kg^{-1}.min^{-1}$, the minimum sample size needed to detect a significant effect at β=0.05 and α=0.05 (90% power) for an ANOVA calculation design based on 3 groups, is 7 participants per group.

2.3. Results.

2.3.1. Participants.

2.3.1.1. Recruitment of participants.

The flow of participants into the study is displayed in Fig. 2.3. Fifty-nine individuals who met the inclusion criteria and expressed an interest in participating in the study attended St. Colmcille's Hospital, in order to complete the screening protocol. Twelve participants did not pass the screening protocol (i.e. failed the exercise stress test) and were referred on to the relevant healthcare team, while 4 other participants who passed the screening protocol did not complete the baseline assessments in the laboratory.

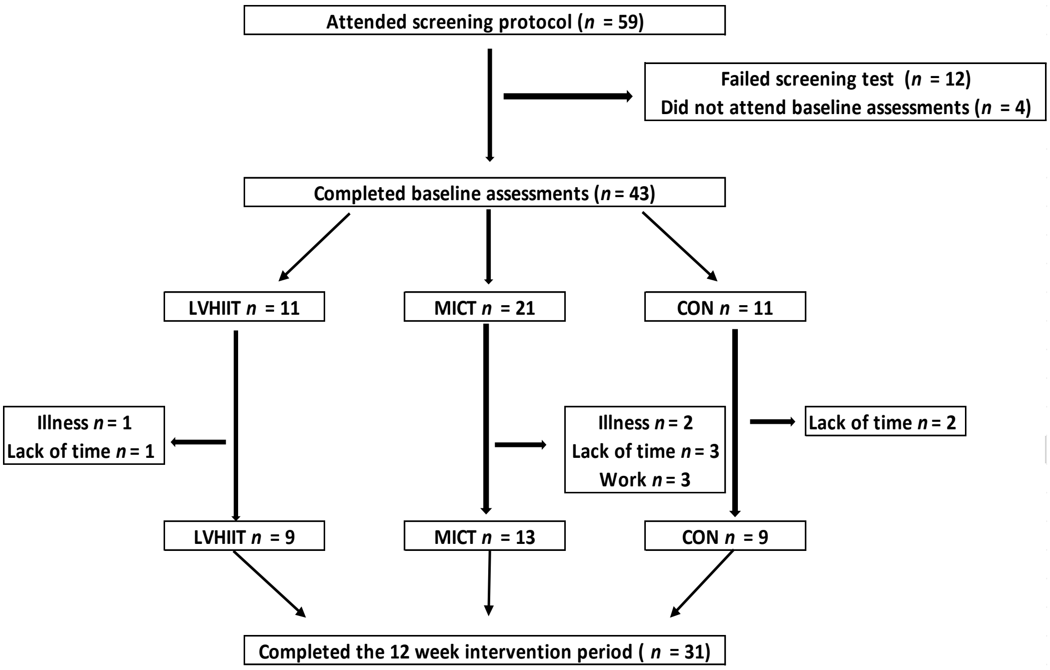

Figure 2.5. Schematic of participant recruitment**.**

Therefore, 43 participants who passed the screening protocol entered the study and completed all aspects of the baseline assessments. However, 12 participants dropped out of the study and did not complete the study. Reasons for dropping out of the study included lack of time (*n* = 6), illness (*n* = 3) and work commitments (*n* = 3). Thirty-one participants completed all aspects of the study intervention and assessment protocols. One participant from the MICT group did not complete the $\dot{V}O_2$ measurements as they did not tolerate the mouth piece.

2.3.1.2. Participants' baseline physical characteristics and prescriptive medications.

Participants' characteristics are reported in Table 2.3 All participants included in the analysis completed the full 12 week intervention. Study randomisation successfully matched each group for BMI, age and time since diagnosis. In addition, no differences were observed between groups in terms of ABI, baseline $HbA1_c$ levels or the subcutaneous fat layer of VL. The medication record of each group is displayed in Table 2.4.

2.3.1.3. Physical Activity Levels.

Group mean averages for physical activity levels as measured by RT3 accelerometers are shown in Tables 2.5. There were no differences in baseline physical activity levels between groups.

Table 2.3. ***Participants' baseline characteristics.***

	MICT (*n* = 13)	LVHIIT (*n* = 9)	Control (*n* =9)	*Between Group P value*
Age (years)	52.7 (9.6)	52.0 (10.1)	53.9 (9.4)	0.91
Male/female	8/5	6/3	5/4	
BMI (m.kg^{-2})	30.9 (5.9)	28.7 (3.0)	30.5 (3.6)	0.53
Time since diagnosis (years)	6.9 (3.7)	6.6 (3.5)	6.6 (3.3)	0.97
Pre-exercise ABI (a.u.)	1.10 (0.10)	1.07 (0.04)	1.13 (0.07)	0.13
Post-exercise ABI (a.u.)	1.10 (0.10)	1.05 (0.10)	1.14 (0.08)	0.06
HbA_{1c} (%)	6.8 (0.5)	7.3 (0.5)	6.8 (1.0)	0.33
Fat layer of VL (mm)	7.7 (3.9)	6.4 (2.6)	8.6 (3.2)	0.39

Data are mean (SD). BMI, body mass index; ABI, Ankle: Brachial Index; a.u., arbitrary units; VL, vastus lateralis.

Table 2.4. ***Prescriptive medications for individuals in each group.***

	MICT (*n* = 13)	LVHIIT (*n* = 9)	CON (*n* = 9)
Anti-hypertensives			
Angiotensin converting enzyme inhibitor		1	
Angiotensin II receptor blocker	1		1
Aspirin	3	1	2
Statins	5	3	3
Hypoglycaemic medications			
Oral hypo-glycaemic			
Metformin	7	5	5
Glucophage	2	2	1
Diamicron	1	2	2
Sitagliptin			2
Glicalzide	1	1	
Subcutaneous hypo-glycaemic			
Victoza	1		1

Table 2.5. ***Baseline physical activity data expressed in hours per day.***

	MICT (n = 9)	LVHIIIT (n = 7)	CON (n = 8)	*Between group P Value*
Inactive ($h.day^{-1}$)	17.4 (1.5)	17.5 (2.2)	18.2 (1.2)	0.54
Light ($h.day^{-1}$)	5.3 (0.7)	5.3 (1.6)	4.8 (0.9)	0.50
Moderate ($h.day^{-1}$)	1.1 (1.0)	1.0 (0.5)	0.8 (0.6)	0.69
Vigorous ($h.day^{-1}$)	0.3 (0.3)	0.2 (0.2)	0.2 (0.3)	0.45

Data are mean (SD)

2.3.2. Exercise training responses.

2.3.2.1. Participants' physical characteristics, exercise adherence and glycaemic control.

2.3.2.1.1 Exercise adherence.

The mean exercise adherence was 94 ± 6% (range 31-36 sessions) and 96 ± 6% (range 31-36 sessions) in the LVHIIT and MICT groups respectively. The average training intensity (PO) increased significantly after each testing session (i.e., every 3 weeks) in both the MICT (weeks 1–3, 82 ± 32 W; weeks 4–6, 100 ± 39 W; weeks 7–9, 110 ± 42 W; weeks 10-12, 119 ± 44 W) and LVHIIT groups (weeks 1–3, 166 ± 45 W; weeks 4–6, 181 ± 46 W; weeks 7–9, 195 ± 46 W; weeks 10-12, 197 ± 45 W). No adverse effects to training were observed throughout the intervention period in either exercising group.

2.3.2.1.2. Anthropometric characteristics.

Anthropometric data are summarised in Table 2.6.). There was no significant reduction in body mass or BMI at any time point throughout the intervention period in all groups.

2.3.2.1.3. Glycaemic control.

Changes in glycaemic control from baseline to post-training are shown in Table 2.7. There was a significant reduction in $HbA1_c$ levels after 12 weeks of LVHIIT while there was a tendency towards a change in the MICT group (P = 0.09). There were no changes in $HbA1_c$ values in the control group after the intervention period. In addition, no changes between baseline and post-intervention periods were observed in fasting blood glucose levels in any group.

Table 2.6. ***Anthropometric characteristics during the intervention period in the MICT, LVHIIT and CON groups.***

	Week 0	Week 3	Week 6	Week 9	Week 12	*P value*		
Body mass (kg)						Time effect	Group effect	Time x Group
MICT	92.1 (20.6)	91.6 (20.4)	91.1 (20.5)	90.7 (20.2)	89.7 (20.1)			
LVHIIT	87.5 (12.4)	87.1 (12.4)	86.8 (12.1)	86.7 (12.2)	86.5 (12.2)	0.02	0.77	0.08
CON	86.0 (14.0)	86.5 (15.1)	86.6 (15.6)	86.0 (16.0)	86.4 (15.6)			
BMI ($kg.m^{-2}$)								
MICT	30.7 (5.6)	30.6 (5.6)	30.4 (5.6)	30.3 (5.5)	29.9 (5.4)			
LVHIIT	28.8 (3.2)	28.8 (3.6)	28.6 (3.5)	28.6 (3.5)	28.4 (3.4)	0.02	0.65	0.29
CON	30.5 (3.6)	30.8 (4.3)	30.7 (4.5)	30.6 (4.4)	30.6 (4.1)			

Data are mean (SD). BMI, body mass index;

Table 2.7. ***Glycaemic control pre- and post-training.***

	Week 0	**Week 12**	*P value*		
Fasting $HbA1_c$ (%)			Time effect	Group effect	Time x Group
MICT (*n = 12)*	6.8 (0.5)	6.6 (0.5)			
LVHIIT (*n = 7)*	7.3 (0.5)	6.6 (0.8)*	0.02	0.74	0.02
CON (*n = 7)*	6.8 (1.0)	7.0 (1.0)			
Fasting blood glucose ($mmol.L^{-1}$)					
MICT (*n = 11)*	7.6 (1.2)	7.2 (1.3)			
LVHIIT (*n = 7)*	9.3 (3.3)	8.2 (1.0)	0.07	0.36	0.76
CON (*n = 7)*	7.9 (3.6)	7.0 (2.0)			

Data are mean (SD). * Significantly different from week 0 (*P* < 0.05).

2.3.2.2. Peak physiological responses during ramp incremental exercise.

2.3.2.2.1. Peak physiological responses.

Peak physiological responses throughout the training period are summarised in Table 2.8; while percentage changes in PO_{peak} and $\dot{V}O_{2max}$ are illustrated in Fig 2.4. PO_{peak} significantly increased by a similar magnitude after 3 weeks in both the LVHIIT and MICT groups. In addition, in both groups PO_{peak} continued to progressively increase until the end of the intervention period (Table 2.8). The total percentage change from pre-training to post-training was 25.6% and 15.8% in MICT and LVHIIT, respectively (Fig. 2.4). No increases in PO_{peak} were observed in the CON group at any stage during the intervention period.

In absolute terms ($L.min^{-1}$), $\dot{V}O_{2max}$ increased significantly after 3 weeks of MICT and after 6 weeks of LVHIIT, even if a strong tendency was observed for an increase in absolute $\dot{V}O_{2max}$ after 3 weeks in the LVHIIT group ($P < 0.07$) (Table 2.8). When $\dot{V}O_{2max}$ measurements were normalised to body mass, a significant increase in $\dot{V}O_{2max}$ of a similar magnitude was observed in both the LVHIIT and MICT groups after 3 weeks of training. Further non-significant progressions in $\dot{V}O_{2max}$ (expressed in both absolute and relative terms) continued to be observed until the end of the intervention period. The total percentage change in relative $\dot{V}O_{2max}$ from pre-training to post-training was 24.4% and 12.8% in MICT and LVHIIT, respectively (Fig 2.4). No increases in $\dot{V}O_{2max}$ were observed in the CON group at any stage during the intervention period.

Group mean RER values were > 1.1 and similar across groups at each time point in each group. Although time to failure numerically increased in the MICT and LVHIIT it was not different.

Table 2.8. ***Peak physiological responses during the intervention period in MICT, LVHIIT and CON.***

	Week 0	Week 3	Week 6	Week 9	Week 12	*P Value*		
$\dot{V}O_{2max}$ (L.min^{-1})						Time effect	Group effect	Time x Group
MICT	2.0 (0.7)	2.3 (0.7)$^{*\#}$	2.5 (0.8) $^{*\#}$	2.4 (0.8)$^{\#}$	2.4 (0.8)$^{*\#}$			
LVHIIT	2.3 (0.5)	2.5 (0.6)	2.5 (0.5)$^{*\#}$	2.6 (0.6)$^{*\#}$	2.6 (0.5)$^{*\#}$	<0.001	0.13	0.003
CON	1.9 (0.5)	1.9 (0.6)	1.9 (0.6)	1.9 (0.6)	1.9 (0.5)			
$\dot{V}O_{2max}$ (mL.kg^{-1}.min^{-1})								
MICT	22.1 (4.4)	25.9 (5.5)*	27.6 (5.0)$^{*\#}$	26.81 (5.7)$^{*\#}$	27.5 (5.2)$^{*\#}$			
LVHIIT	26.4 (4.0)	28.5 (4.2)$^{*\#}$	29.2 (3.5)$^{*\#}$	30.2 (4.4)$^{*\#}$	29.8 (3.9)$^{*\#}$	<0.001	0.08	0.002
CON	21.5 (3.6)	22.1 (4.4)	21.6 (4.0)	22.2 (4.2)	22.0 (3.4)			
Peak PO (W)								
MICT	162 (57)	186 (66)*	193 (63)*	201 (68)*‡	202 (69)*‡†			
LVHIIT	187 (51)	204 (52)*	216 (52)*	220 (50)*‡	217 (55)*‡	<0.001	0.07	<0.001
CON	148 (49)	149 (52)	146 (55)	151 (51)	153 (50)			
TTF (s)								
MICT	664 (166)	749 (195)	776 (201)	805 (202)	764 (314)			
LVHIIT	712 (88)	771 (90)	817 (94)	831 (100)	816 (94)	0.03	0.11	021
CON	656 (123)	633 (127)	617 (125)	664 (124)	648 (116)			
Peak RER (a.u.)								
MICT	1.14 (0.09)	1.14 (0.06)	1.12 (0.08)	1.14 (0.06)	1.16 (0.09)			
LVHIIT	1.16 (0.05)	1.22 (0.06)	1.18 (0.07)	1.24 (0.09)	1.19 (0.06)	0.58	0.01	0.25
CON	1.13 (0.07)	1.10 (0.12)	1.11 (0.13)	1.10 (0.10)	1.11 (0.06)			

Data are mean (SD). $\dot{V}O_{2max}$, maximal oxygen uptake PO, power output; TTF, time to failure; RER, respiratory exchange ratio. * 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 CON ($P < 0.05$).

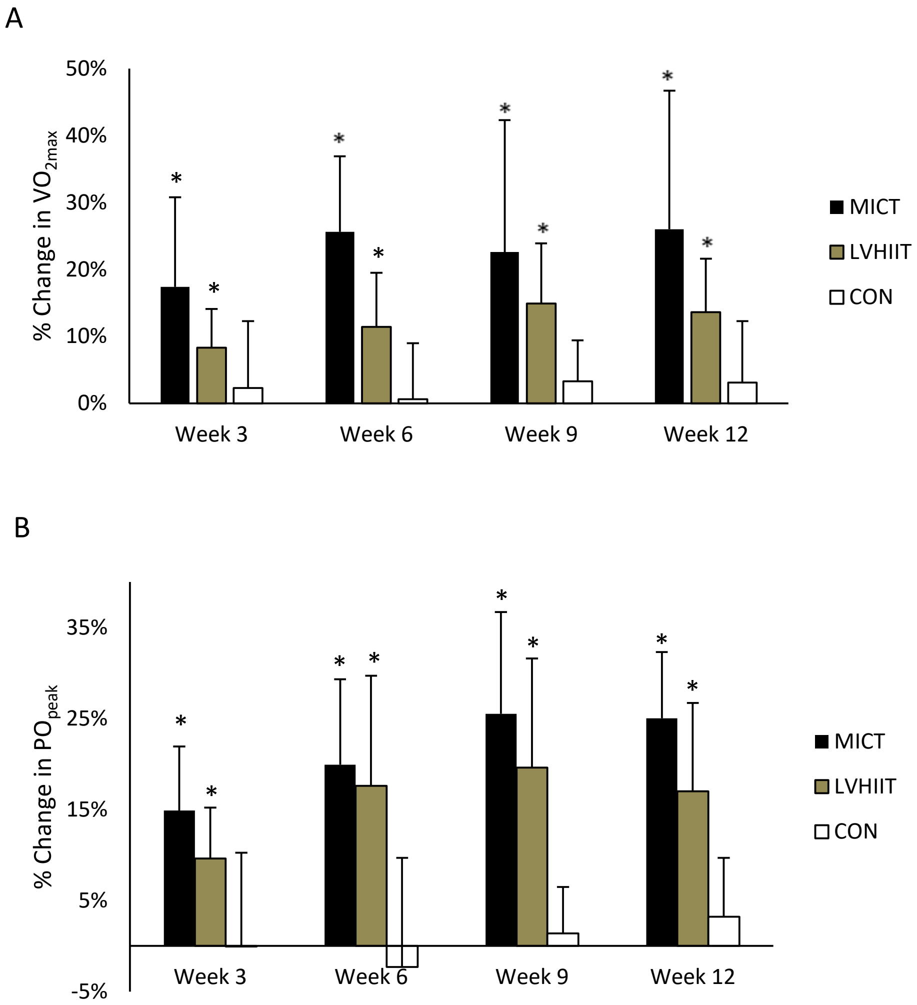

Figure 2.6. Illustration of the % changes from week 0 in $\dot{V}O_{2max}$ (Panel A) and PO_{peak} (Panel B). * Significantly different from week 0 (*P* < 0.05); Error bars denote SD.

2.3.2.2.2. Physiological Responses at VT.

Time course physiological responses at VT are shown in Table 2.9. $\dot{V}O_2$ ($mL.min^{-1}.kg^{-1}$) at VT was significantly increased after 3 weeks of MICT, and it further significantly increased after 9 weeks, which was maintained until the end of the intervention period. In the LVHIIT group there was a trend towards an increase in $\dot{V}O_2$ at VT (P < 0.10) by week 3 of training, with a significant increase observed after 6 weeks of training which was maintained until the end of the intervention period. In absolute terms, $\dot{V}O_2$ ($L.min^{-1}$) at VT was increased significantly after 6 weeks in both training groups. In addition, in both groups PO (W) at VT was significantly improved after 3 weeks, with further significant improvements observed after 6 weeks and until week 12. The PO at VT was significantly higher in the LVHIIT group than the CON group beyond 3 weeks and significantly higher in the MICT group than the CON group beyond 9 weeks of training (Table 2.9).

Table 2.9. ***Physiological responses at VT during the intervention in the MICT, LVHIIT and CON groups.***

	Week 0	Week 3	Week 6	Week 9	Week 12	*P value*		
PO @ VT (W)						Time effect	Group effect	Time x Group
MICT	91 (32)	111 (42)*	123 (45) *‡	132 (47) $^{*‡\#}$	131 (44) $^{*‡\#}$			
LVHIIT	115 (32)	129 (34)$^{*\#}$	142 (37) $^{*‡\#}$	145 (34) $^{*‡\#}$	148 (43) $^{*‡\#}$	<0.001	0.02	<0.001
CON	83 (25)	83 (20)	87 (27)	82 (26)	90 (27)			
$\dot{V}O_2$ @ VT ($L.min^{-1}$)								
MICT	1.5 (0.5)	1.6 (0.4)	1.9 (0.5) *‡	1.9 (0.6) *‡	1.9 (0.6) *‡			
LVHIIT	1.7 (0.4)	1.9 (0.4)	1.9 (0.4)*	2.0 (0.4) *‡	2.0 (0.4)*	<0.001	0.02	<0.001
CON	1.3 (0.3)	1.4 (0.3)	1.4 (0.3)	1.3 (0.4)	1.4 (0.30			
$\dot{V}O_2$ @ VT ($ml.kg^{-1}.min^{-1}$)								
MICT	16.8 (3.1)	18.5 (3.5)*	21.3 (3.8) *‡	21.5 (4.6) *‡	21.9 (4.1) *‡			
LVHIIT	19.7 (3.7)	21.3 (3.1)	22.2 (2.9) *‡	23.3 (3.7) *‡	23.0 (3.0) *‡	<0.001	<0.001	<0.001
CON	15.3 (2.4)	15.6 (2.2)	15.7 (2.5)	15.6 (2.8)	16.1 (2.2)			

Data are mean (SD). PO, power output; $\dot{V}O_2$, oxygen consumption; VT, ventilatory threshold; * significantly different from week 0 (P < 0.05); ‡ significantly different from week 3 (P < 0.05); $^{\#}$ significantly different from CON (P < 0.05).

2.3.2.2.3. Physiological Responses at RCP.

Time course physiological responses at RCP are shown in Table 2.10. $\dot{V}O_2$ ($mL.min^{-1}.kg^{-1}$) at RCP was significantly increased after 3 weeks of MICT with no further improvements after that time point. There was a trend towards a difference in RCP after 6 weeks of LVHIIT, and a significant increase at week 9, however, by the end of the training period (week 12) there was only a trend ($P < 0.10$) towards a change in $\dot{V}O_2$ at RCP from week 0. In absolute terms, $\dot{V}O_2$ ($L.min^{-1}$) at RCP was significantly increased after 3 weeks of MICT with no further improvements after that time point. No improvements in absolute $\dot{V}O_2$ at RCP were observed in the LVHIIT or CON groups. In terms of PO (W) at RCP, there was a significant increase after 3 weeks of training in the MICT group and after 6 weeks in the LVHIIT with further significant improvements observed in both groups at week 9. However, these further improvements were not maintained by week 12 in both groups. No changes in PO (W) at RCP were observed in the CON group at any time point.

Table 2.10. ***Physiological responses at RCP during the intervention in the MICT, LVHIIT and CON groups.***

	Week 0	Week 3	Week 6	Week 9	Week 12	*P value*		
PO @ RCP (W)						Time effect	Group effect	Time x Group
MICT	130 (48)	153 (53)*	161 (58)*	166 (53)*‡	162 (52)*			
LVHIIT	166 (44)	174 (47)	185 (41)*	192 (46)*‡	187 (46)*	<0.001	0.07	<0.001
CON	129 (52)	125 (43)	126 (47)	126 (44)	130 (43)			
$\dot{V}O_2$ @ RCP ($ml.kg^{-1}.min^{-1}$)								
MICT	20.5 (4.0)	23.7 (4.8)*	25.4 (4.4)*	24.9 (5.5)*	24.5 (4.5)*			
LVHIIT	24.9 (3.7)	26.6 (4.8)	27.2 (3.5)	28.5 (3.9)*	27.1 (3.5)ᵃ	<0.001	0.09	0.04
CON	19.6 (3.9)	20.0 (3.8)	20.2 (3.8)	20.4 (3.7)	20.6 (3.2)			
$\dot{V}O_2$ @ RCP ($L.min^{-1}$)								
MICT	1.9 (0.6)	2.1 (0.6)*	2.3 (0.7)*	2.2 (0.7)*	2.1 (0.6)*			
LVHIIT	2.2 (0.5)	2.3 (0.5)	2.4 (0.5)	2.5 (0.6)	2.3 (0.5)	<0.001	0.004	0.01
CON	1.7 (0.5)	1.8 (0.5)	1.7 (0.6)	1.8 (0.6)	1.8 (0.5)			

Data are mean (SD). PO, power output; $\dot{V}O_2$ RCP, respiratory compensation point; * significantly different from week 0 ($P < 0.05$); ‡ significantly different from week 3 ($P < 0.05$).

2.3.2.3. Muscle deoxygenation responses during ramp exercise.

The parameter estimates from the bilinear model of the Δ [HHb+Mb] % vs Δ%PO_{peak} profiles are summarised in Table 2.11 with representative plots of the response from each group displayed in Figs 2.5, 2.6 and 2.7. After 3 weeks of training there was a significant decrease in the slope of the first linear component of the Δ[HHb+Mb]% vs Δ%PO_{peak} profile (S_1) in both the LVHIIT and MICT groups with no further changes observed thereafter. No changes in S_1 were observed in the CON group at any stage of the intervention period. In addition, no changes were observed for the second linear component (S_2) or break point (BP) of the Δ [HHb+Mb] % vs Δ%PO_{peak} profile at any time point throughout the intervention period in any group.

Table 2.11. ***Parameter estimates for the normalised % [HHb+Mb] profile for all groups plotted as a function of %PO during ramp incremental exercise throughout the intervention period.***

	Week 0	Week 3	Week 6	Week 9	Week 12	*P Value*		
S_1						Time effect	Group effect	Time x Group
MICT	1.67 (0.41)	1.38 (0.18)*	1.41 (0.32)*	1.28 (0.19)*	1.35 (0.26)*			
LVHIIT	1.62 (0.30)	1.24 (0.16)*	1.22 (0.20)*	1.23 (0.18)*	1.23 (0.18)*	0.03	0.004	<0.001
CON	1.38 (0.27)	1.47 (0.27)	1.47 (0.36)	1.42 (0.44)	1.57 (0.42)			
S_2								
MICT	0.24 (0.24)	0.27 (0.25)	0.31 (0.28)	0.19 (0.21)	0.18 (0.38)			
LVHIIT	0.05 (0.63)	-0.09 (0.26)	0.18 (0.33)	0.32 (0.22)	-0.07 (0.45)	0.12	0.03	0.18
CON	0.03 (0.34)	-0.27 (0.75)	-0.27 (0.57)	-0.8 (1.42)	-0.45 (0.88)			
BP (%PO)								
MICT	63.5 (15.9)	71.3 (13.7)	69.3 (14.6)	73.0 (12.9)	75.0 (12.5)			
LVHIIT	75.9 (20.8)	71.1 (15.5)	74.2 (17.1)	67.6 (18.8)	79.4 (10.2)	0.44	0.57	0.05
CON	80.6 (14.5)	76.4 (17.0)	60.8 (25.6)	77.4 (11.8)	64.4 (21.4)			

Data are mean (SD). S_1, Slope 1 of linear regression before BP; S_2, Slope 2 of linear regression after BP; BP, breakpoint; PO, power output * significantly different from week 0 (*P* < 0.05).

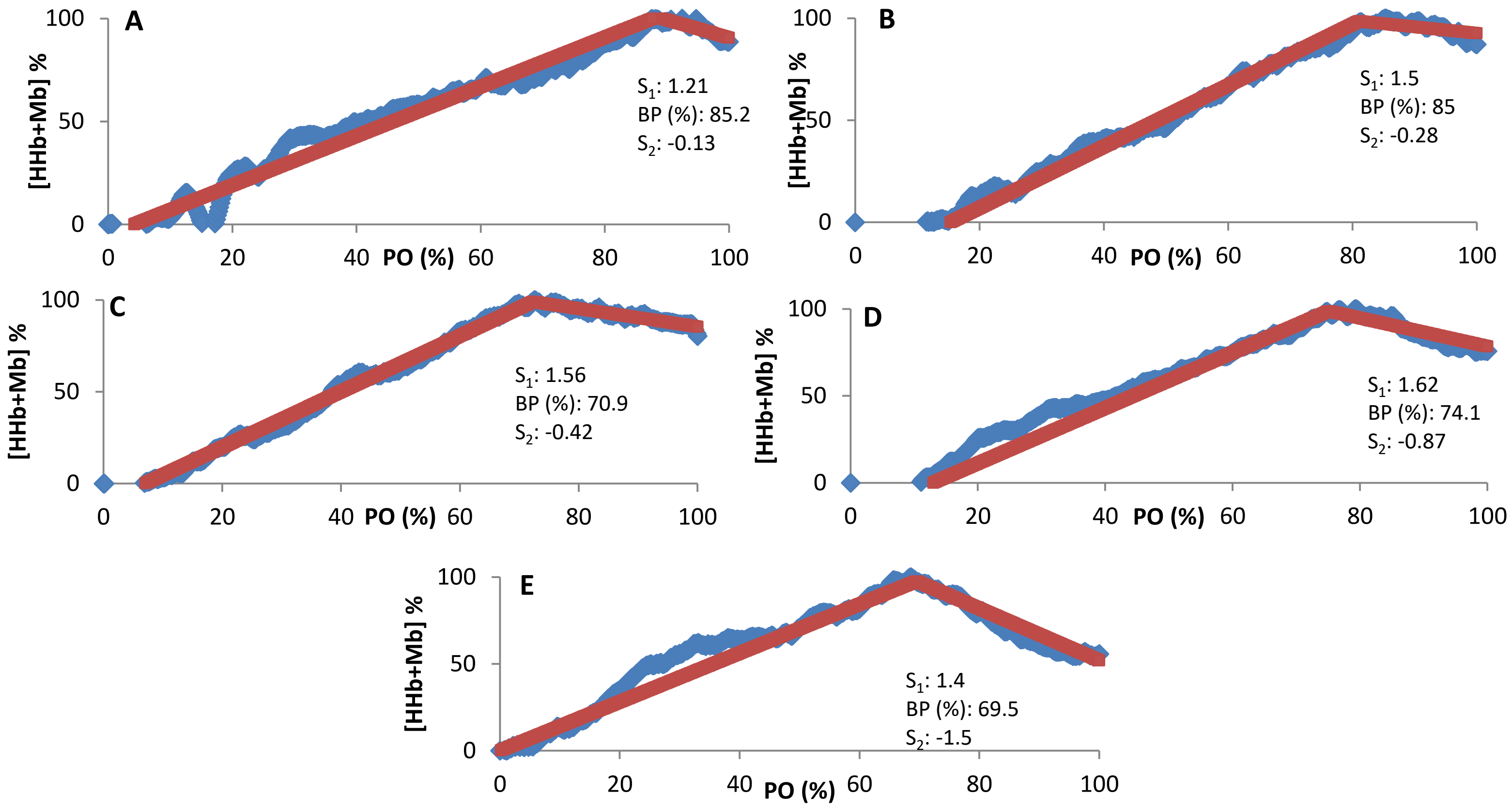

Figure 2.7. Representative profiles of the Δ [HHb+Mb] % vs Δ%PO_{peak} responses during ramp exercise from an individual from the CON group. Bi-linear regression models are superimposed on the data (red line); associated parameters are included on each panel (S_1, S_2 and BP). Panels A,B,C,D & E represent the response at week 0, week 3, week 6, week 9 and week 12 respectively.

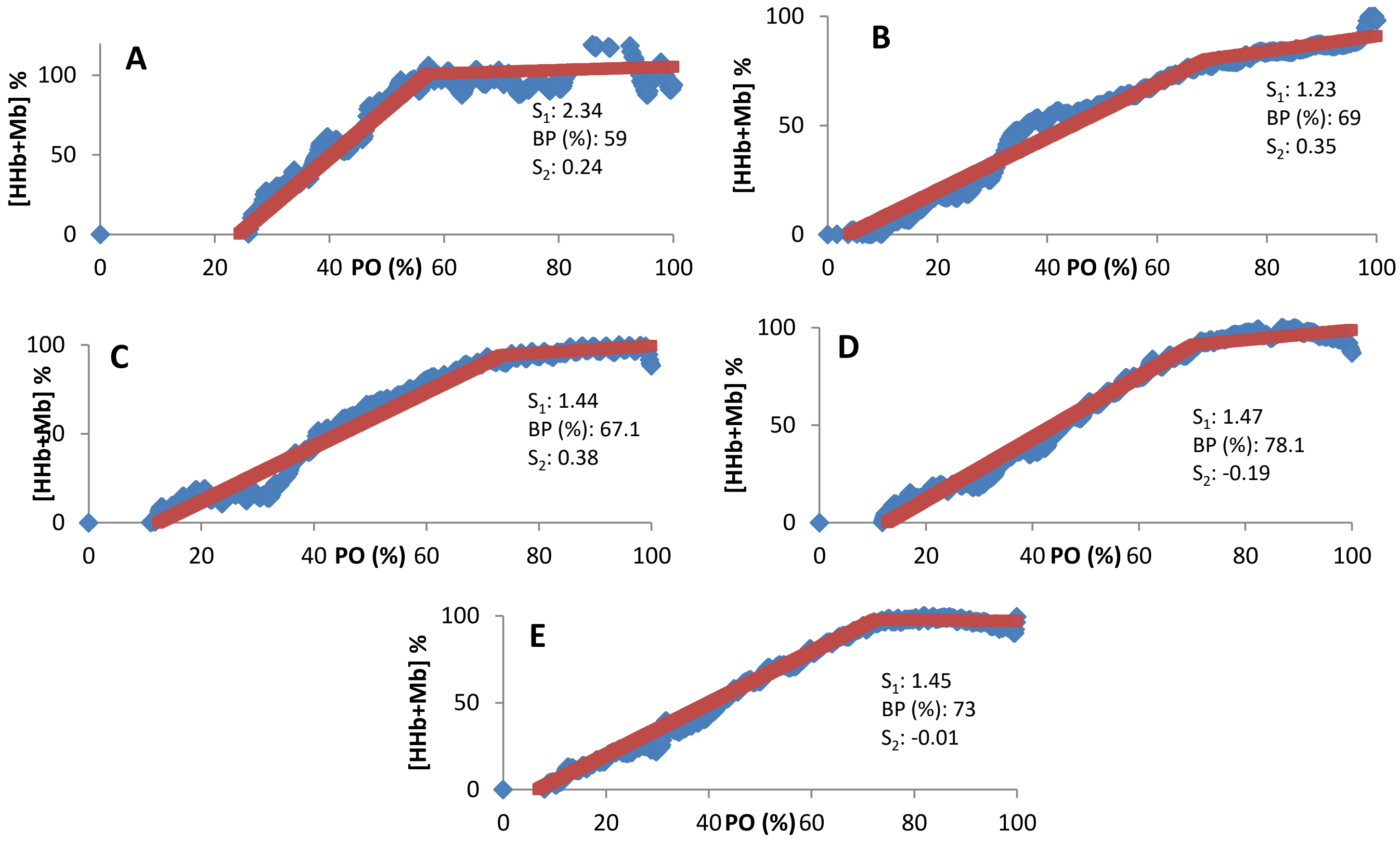

Figure 2.8. Representative profiles of the Δ [HHb+Mb] % vs Δ%PO_{peak} responses during ramp exercise from an individual from the MICT group. Bi-linear regression models are superimposed on the data (red line); associated parameters are included on each panel (S_1, S_2 and BP). Panels A,B,C,D & E represent the response at week 0, week 3, week 6, week 9 and week 12 respectively.

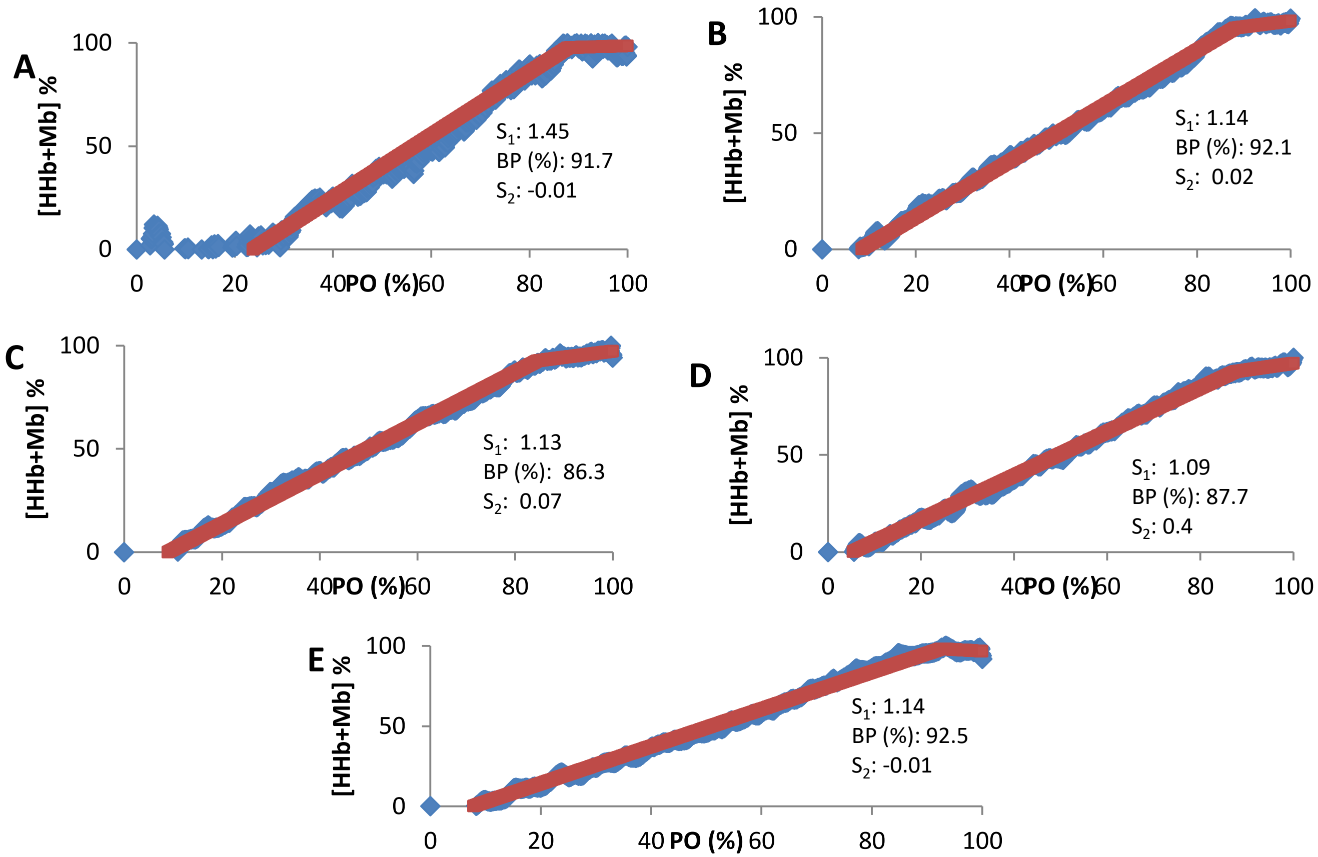

Figure 2.9. Representative profiles of the Δ [HHb+Mb] % vs Δ%PO_{peak} responses during ramp exercise from an individual from the LVHIIT group. Bi-linear regression models are superimposed on the data (red line); associated parameters are included on each panel (S_1, S_2 and BP). Panels A,B,C,D & E represent the response at week 0, week 3, week 6, week 9 and week 12 respectively.

2.3.2.4. Maximal cardiac responses.

Maximal cardiac responses are displayed in Table 2.12 whereas the percentage change in Q, a-vO_2 diff and SV are shown in Fig. 2.9. After 3 weeks of training in the MICT group Q_{max} increased significantly (+1.4 L.min^{-1}, $P < 0.05$) with no further changes thereafter. After 9 weeks of exercise in the LVHIIT group there was a significant increase in Q_{max} from week 0 that remained larger at week 12 (+1.4 L.min^{-1}, $P < 0.05$), while there was a tendency towards a change in Q_{max} after 6 weeks of training (+1.1 L.min^{-1}, $P < 0.10$). There were no changes in Q_{max} in the control group. By the end of the training period Q_{max} increased by 17% in the MICT group and 9% in the LVHIIT respectively (see Fig. 2.9A). There was a significant increase in SV_{max} in the MICT group after 3 weeks with no further changes and SV_{max} increased after 12 weeks in the LVHIIT group (Table 2.12, Fig 2.9C). There were no significant or numerical increases in a-vO_2 diff in the L.VHIIT and CON groups throughout the study period. However, in the MICT group there was a 10% numerical increase in a-vO_2 after 6 weeks which dropped to 5% by the end of the intervention period. There were no changes in peak HR in the LVHIIT and MICT groups. In the CON group there was a significant reduction in HR_{max} after 3 weeks, however, this was not maintained at week 12.

Table 2.12. ***Maximal cardiac responses throughout the intervention period in the MICT, LVHIIT and CON groups.***

	Week 0	Week 3	Week 6	Week 9	Week 12	*P value*		
Q_{max} ($L.min^{-1}$)						Time effect	Group effect	Time x Group
MICT	14.4 (4.2)	15.8 (4.9)*	16.4 (4.7)*	16.8 (5.3)*	16.9 (5.2)*			
LVHIIT	15.7 (4.6)	16.7 (4.6)	16.4 (3.9)	16.2 (3.6)*	17.1 (4.3)*	<0.001	0.21	0.04
CON	14.0 (4.5)	14.0 (4.3)	13.9 (3.9)	13.8 (3.7)	14.1 (4.6)			
HR_{max} (BPM)								
MICT	157 (14)	155 (15)	156 (14)	160 (17)	158 (16)			
LVHIIT	162 (13)	165 (13)	162 (13)	165 (13)	162 (15)	0.14	0.53	0.04
CON	164 (13)	155 (20)*	153 (15)*	158 (16)	157 (18)			
SV_{max}								
MICT	92 (26)	102 (30)*	103 (27)*	103 (32)*	106 (37)*			
LVHIIT	97 (28)	102 (29)	105 (26)	105 (30)	107 (30)*	<0.001	0.25	0.03
CON	85 (28)	90 (25)	90 (21)	87 (20)	90 (27)			
a-vO_2 $diff_{max}$ (mL of $O_2.100ml^{-1}$)								
MICT	13.9 (2.1)	14.6 (1.9)	15.6 (1.5)	14.7 (1.3)	14.6 (2.0)			
LVHIIT	15.1 (1.4)	15.2 (1.4)	15.3 (1.0)	15.6 (2.0)	15.3 (1.6)	0.17	0.37	0.50
CON	13.6 (1.6)	13.8 (1.6)	13.6 (1.4)	14.0 (1.8)	13.9 (2.1)			

Data are mean (SD). *Significantly different from week 0 (*P* < 0.05). Q, cardiac output; HR, heart rate; SV, stroke volume; a-vO_2diff, arteriovenous difference.

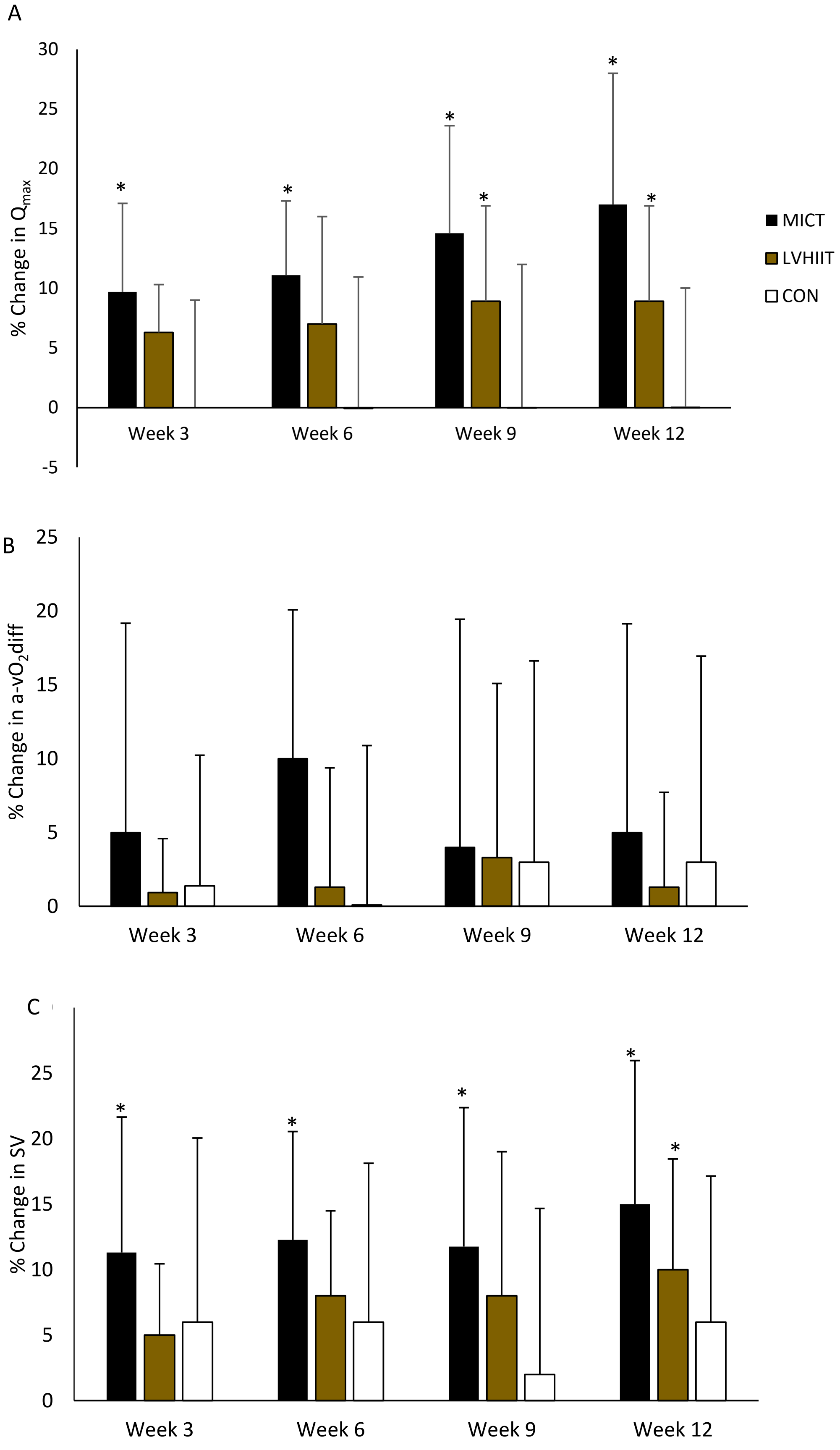

Figure 2.10. Illustration of the % changes in Q, a-vO_2 diff and SV with training in the MICT, LVHIIT and CON groups. Panels A-C represent the percentage change from week 0 in Q, a-vO_2 diff and SV with training. *denotes significant change from week 0 ($P < 0.05$). Error bars denote SD.

2.3.2.5. Maximal and resting blood pressure responses.

There were no changes in any blood pressure parameter at rest or at the end of the ramp tests throughout the intervention period (see Table 2.13).

Table 2.13. ***Blood pressure responses during ramp incremental exercise throughout the intervention period in the MICT, LVHIIT and CON groups.***

	Week 0	Week 3	Week 6	Week 9	Week 12	*P Value*		
Resting SBP (mmHg)						Time effect	Group effect	Time x Group
MICT	121 (16)	124 (19)	125 (16)	123 (13)	121 (12)			
LVHIIT	124 (13)	124 (12)	129 (9)	122 (8)	123 (11)	0.59	0.65	0.87
CON	130 (12)	128 (12)	126 (12)	124 (11)	127 (13)			
Resting DBP (mmHg)								
MICT	75 (9)	72 (11)	74 (10)	71 (9)	70 (8)			
LVHIIT	72 (6)	72 (11)	76 (11)	73 (6)	73 (5)	0.26	0.81	0.82
CON	73 (7)	69 (9)	72 (6)	71 (10)	71 (9)			
Resting MAP (mmHg)								
MICT	90 (11)	89 (12)	91 (11)	88 (10)	87 (9)			
LVHIIT	89 (11)	89 (11)	94 (10)	89 (6)	89 (9)	0.32	0.94	0.90
CON	92 (6)	89 (9)	90 (7)	88 (10)	90 (8)			
Peak SBP (mmHg)								
MICT	167 (27)	181 (22)	159 (17)	174 (25)	181 (23)			
LVHIIT	167 (17)	192 (21)	191 (18)	185 (18)	180 (17)	0.02	0.34	0.13
CON	175 (27)	180 (24)	180 (25)	174 (17)	181 (21)			
Peak DBP (mmHg)								
MICT	91 (19)	99 (12)	92 (18)	98 (14)	98 (12)			
LVHIIT	85 (8)	104 (11)	105 (10)	102 (7)	100 (8)	0.01	0.71	0.1
CON	96 (12)	95 (13)	97 (12)	101 (9)	97 (13)			
Peak MAP (mmHg)								
MICT	115 (19)	126 (14)	114 (16)	123 (17)	126 (15)			
LVHIIT	112 (10)	133 (13)	134 (11)	129 (10)	126 (10)	0.01	0.49	0.07
CON	122 (15)	123 (15)	125 (16)	125 (11)	125 (14)			

Data are mean (SD). For peak responses; MICT n = 8 LVHIIT, n = 8, CON n = 9. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

2.4. Discussion.

The primary aim of the current study was to compare the effects of 12 weeks of MICT with LVHIIT on the mechanisms and time course of adaptations in systemic cardiorespiratory fitness and peripheral microvascular responses in individuals with uncomplicated T2DM. The primary findings of the current study were that:

1) Both LVHIIT and MICT groups significantly improved $\dot{V}O_{2max}$ within a similar timeframe.
2) The underlying mechanisms for the significant improvements in $\dot{V}O_{2max}$ in both groups appear to be due to significant improvements in Q_{max} and this effect is accompanied by improvements in microvascular blood flow delivery (reflected by a reduction in the reliance on fractional O_2 extraction) during ramp incremental exercise.

2.4.1. Time Course changes in $\dot{V}O_{2max}$ with training.

In the present study, in the MICT group there was a 24% increase in $\dot{V}O_{2max}$ after 12 weeks of training which is similar to the increases in $\dot{V}O_{2max}$ observed in previous investigations into exercise training in this population. For instance, Brandenburg *et al.* (1999) reported a 27% increase in $\dot{V}O_{2max}$ following 12 weeks of moderate-intensity aerobic training (3 days per week, 50 mins at 70-85% HR_{max}) in a group of women with uncomplicated T2DM. More recently, MacAnaney *et al.* (2012) reported a 24% increase in $\dot{V}O_{2max}$ after 12 weeks of combined aerobic and resistance training in 13 individuals with uncomplicated T2DM.

One of the novelties of the current study is that the time course of adaptation in $\dot{V}O_{2max}$ in response to MICT in T2DM was examined for the first time. The majority of the overall increase in $\dot{V}O_{2max}$ (+17.2%) occurred after the first 3 weeks of MICT. Interestingly, the time course of adaptation observed in the present study in individuals with T2DM is similar to that reported in healthy populations reported by previous studies. For instance, significant increases in $\dot{V}O_{2max}$ have been previously reported after 3 weeks of MICT (3 days per week, 45mins at 70% $\dot{V}O_{2max}$) in both young and older healthy males (Murias *et al.* 2010).

In the present study LVHIIT significantly improved $\dot{V}O_{2max}$ after 12 weeks by 13%. This is in line with the previous investigations into LVHIIIT and T2DM. For instance, Madsen *et al.* (2015) reported a 7.4% increase in $\dot{V}O_{2max}$ following 8 weeks of LVHIIT (3 days per week, 10 x 60 s at 90% HR_{max}) in 13 individuals with uncomplicated T2DM. Similarly, an 11.2% increase in $\dot{V}O_{2max}$ was reported after 12 weeks of LVHIIT (3 days per week, 2 days aerobic LVHIIT; 10 x 60 s at 85-90% HR_{max}, 1 day resistance LVHIIT; 10 x 60 s maximum reps at a 'hard' RPE) in 53 individuals with uncomplicated T2DM (Francois *et al.* 2017) while more recent work by Winding *et al.* (2018) reported a higher 20.7% increase in $\dot{V}O_{2max}$ after 11 weeks of LVHIIT in individuals with uncomplicated T2DM (Winding *et al.* 2018).

To the author's knowledge this is the first study to investigate the time course of adaptations in $\dot{V}O_{2max}$ in response to LVHIIT in T2DM. Similar to MICT, the majority of the increase in $\dot{V}O_{2max}$ occurred after just 3 weeks of LVHIIT (+8%). This is a similar magnitude to previously observed increases in $\dot{V}O_{2max}$ after just 2 and 3 week of LVHIIT interventions in young healthy males (McKay *et al.* 2009; Jacobs *et al.* 2013). McKay *et al.* (2009) reported a significant 4% increase in VO_{2max} after just 8 sessions of LVHIIT completed over 19 days (8-12 x 60s at 120% PO_{peak}). Similarly, Jacobs *et al.* (2013) reported a significant 8% increase in VO_{2max} in untrained young healthy males following 6 sessions of LVHIIT completed over 2 weeks (8-12 x 60s at 100 PO_{peak}).

In the current study, the percentage increase in $\dot{V}O_{2max}$ was higher after MICT than LVHIIT (24% vs 13%), and the absolute magnitude of the increase in $\dot{V}O_{2max}$ was also higher after 3 weeks of MICT than LVHIIT (+5.4mL.min^{-1}.kg^{-1} vs +3.4 mL.min^{-1}.kg^{-1}). However, it is important to note that there were no significant differences observed between the 2 groups in terms of absolute or relative increases in $\dot{V}O_{2max}$. Our findings are in contrast to the limited available data of studies comparing the effect of LVHIIT and MICT on $\dot{V}O_{2max}$ in T2DM. Mitranun *et al.* (2014) reported a superior effect of 8 week of LVHIIT on $\dot{V}O_{2max}$ (+25%, 4-6 x 1 minute intervals at 80-85% $\dot{V}O_{2max}$ with 4 min active recovery at 50% $\dot{V}O_{2max}$), compared to MICT (+14%, 20-30 min at 60-65% $\dot{V}O_{2max}$) in a group of men and women with uncomplicated T2DM. However, it is important to note that the 2 interventions in the study by Mitranun *et al.* (2014) were matched for exercise energy expenditure resulting in a similar time commitment between the 2 exercise modes (LVHIIT 26 mins vs MICT 30 mins) (Mitranun *et al*. 2014). In addition, the LVHIIT protocol included by the authors had significantly longer rest periods than those proposed for LVHIIT by Gibala *et al.* (2006). More recently, Winding *et al.* (2018) reported a significant 20% increase in $\dot{V}O_{2peak}$ after 11 weeks of LVHIIT (10 x 60 s cycling at 95% PO_{peak}) compared to a significant 8% increase in $\dot{V}O_{2peak}$ after 11 weeks of MICT (3 days per week, 40 mins cycling at 50% PO_{peak}). $\dot{V}O_{2peak}$ was reassessed at week 4 and week 8 in order to adjust the exercise intensities so that participants maintained the desired prescribed intensity. However, the weekly exercise time for MICT (120 mins) in the study by Winding *et al.* (2018) was considerably less than the weekly recommended ADA exercise guidelines and of the MICT intervention utilised in the current study (150 mins). In addition, the baseline $\dot{V}O_{2peak}$ of the participants in the MICT group reported by Winding *et al.* (2018) was markedly higher than that of the MICT group in the current study (27.8 ± 5.5 $mL.min^{-1}.kg^{-1}$ vs 22.1 ± 4.4 $mL.min^{-1}.kg^{-1}$) which may, at least in part, explain the greater increase in $\dot{V}O_{2peak}$ observed in the current study with MICT (+26%) compared to that by Winding *et al.* (2018) (+ 8%).

2.4.2. Time course changes in Q_{max} and a-vO_2diff_{max} with training.

$\dot{V}O_2$ is constrained by the ability of the body to delivery (Q) and extract O_2 (a-vO_2diff) in order to meet the oxidative demand of the working muscles. Therefore, increases in $\dot{V}O_{2max}$ with aerobic training should be as a result of an increase in Q_{max}, a-vO_2diff_{max} or a combination of both factors. In the present study there was a significant increase in Q_{max} after 3 weeks of MICT and after 9 weeks of LVHIIT although a tendency for an increase in Q_{max} was observed after 6 weeks of LVHIIT (P = 0.07).

In terms of MICT, our findings are in agreement with those previously reported in healthy populations. For instance, Murias *et al.* (2010) reported a significant increase in $\dot{V}O_{2max}$ in young and older healthy males after just 3 weeks of MICT which was accompanied by a significant improvement in Q_{max} (acetylene (C_2H_2) open-circuit inert gas-wash in method) in both the young and older male participants (Murias *et al.* 2010). The authors reported that in the older participants the changes in Q_{max} accounted for 66% (calculated as % change in Q_{max} / % change in $\dot{V}O_{2max}$) of the observed changes in $\dot{V}O_{2max}$ while in the younger participants 54% of the change in $\dot{V}O_{2max}$ was accounted for by changes in Q_{max}. A similar pattern was observed in the present study with changes in Q_{max} accounting for the majority of the change (~70%) in $\dot{V}O_{2max}$ following MICT. The significant improvement in Q_{max} with MICT in the current study was accompanied by a significant increase in SV_{max}. Increases in SV with aerobic training are most likely due to an improvement in left ventricular filling and contractility which ultimately leads to a more compliant left ventricle (Levine, 2008). Increased left ventricular compliance will in turn result in an increase in end-diastolic volume which will yield an increase in stroke volume due to the influence of the intrinsic Frank-Starling mechanism (Seals *et al.* 1994).

To the author's knowledge this is the first study to show that LVHIIT increases Q_{max} in individuals with T2DM. A significant increase in Q_{max} was observed after 9 week of LVHIIT. Our findings are in line with current evidence from healthy populations that has shown that LVHIIT is effective at increasing Q_{max} (Daussin *et al.* 2007; Astorino *et al.* 2017). Recent work by Astorino *et al.* (2017) has shown that 3 weeks of LVHIIT (8-12 x 60 s at 90-100% PO_{peak}) yielded a significant 6% increase in $\dot{V}O_{2max}$ in both recreationally active healthy males and females which was accompanied by a 5% increase (P < 0.05) in Q_{max} as measured using thoracic impedance (Astorino *et al.* 2017). Furthermore, Astorino *et al.* (2017) reported no changes in a-vO_2 $diff_{max}$ with training but did observe a significant increase in SV_{max}. Similar to Astorino *et al.* (2017), no changes in a-vO_2diff_{max} were observed with training in the current study after LVHIIT while a significant increases in SV_{max} was observed after 12 weeks of training. Also in similar lines, Daussin *et al.* (2007) reported a significant increase in $\dot{V}O_{2max}$, Q_{max} (measured using bioimpedence) and SV_{max} after 8 weeks of HIIT (4-7 X 60s at 90% PO_{peak} interspersed with 4 min recovery at VT) in healthy males and females. One possible mechanism underlying this increase in SV may be an increase in plasma volume (PV) with interval training which has been previously reported in untrained individuals (Warburton *et al*. 2004; Esfandiairi *et al*. 2014). For instance, Warburton *et al*. (2004) reported significant increases in PV and $\dot{V}O_{2max}$ after 6 weeks of HIIT (2 min at 90 % $\dot{V}O_{2max}$ interspersed by 2 min rest for 30-48mins) in a group of young recreationally active males (age, 30 ± 5 yr; $\dot{V}O_{2max}$, 38.7 ± 7.9 $mL.min^{-1}.kg^{-1}$) (Warburton *et al*. 2004). More recently, six sessions of HIIT at (8-12 x 60 s at

95%–100% $\dot{V}O_{2max}$) induced a significant increase in PV which was accompanied by significant increase in $\dot{V}O_{2max}$ in untrained young men (age, 24.5 ± 3.1; $\dot{V}O_{2max}$, 39.5 ± 7.1 mL.min^{-1}.kg^{-1}) (Esfandiairi *et al*. 2014).

In contrast to the current study and to Astorino *et al.* (2017), Daussin *et al.* (2007) reported a significant increase in a-vO_2 diff$_{max}$ (+10%) following LVHIIT. The a-vO_{2diff} reflects the ability of the skeletal muscle to extract O_2 from the arterial blood, and it has been documented that both continuous and interval training can be effective at increasing muscle capillary density which increases the surface area for O_2 exchange at the level of the skeletal muscle (Hepple *et al.* 2000; Jensen *et al*. 2004). Consequently this would result in an increased surface area for diffusion into the myocyte, a decrease in diffusion path length within the muscle and an increased length of time for diffusive exchange between the blood and the myocyte (Kalliokoski *et al*. 2001; Prior *et al.* 2004). As mentioned before, this effect is not always evident and we did not observe significant changes in a-vO_2diff$_{max}$ with LVHIIT when systematic a-vO_2 diff values were estimates using the Fick equation. However, we observed a non-significant 5% increase in a-vO_2 diff in the MICT group after 12 weeks of training which is of a similar magnitude to that reported in older healthy males after 12 weeks of MICT (Murias *et al.* 2010).

2.4.3. Time course changes in ∆ [HHb + Mb] % vs ∆PO% profiles.

At a peripheral level, active muscle O_2 extraction can be investigated through the use of the deoxy-haemoglobin signal from NIRS (DeLorey *et al.* 2003; Grassi *et al.* 2003; Ferreira *et al*. 2005). This technique was utilised to measure changes in tissue deoxygenation (∆ [HHb + Mb]) within the microvasculature of the vastus lateralis muscle during ramp incremental exercise. Recent work has suggested that the initial slope of the bilinear model used to assess the rate of muscle deoxygenation is significantly steeper in people with T2DM compared with healthy controls (Gildea *et al.* 2016). This is suggestive of a reduced capacity to increase peripheral O_2 delivery to match increasing O_2 demands (Rissanen *et al.* 2015) thus, reflecting an over reliance on O_2 extraction for a given increase in $\dot{V}O_2$.

After 3 weeks of training there was a significant decrease in the slope of the first linear component of the ∆ [HHb + Mb] % vs ∆PO% profile (S_1) in both the

LVHIIT and MICT groups with no further changes observed thereafter. These findings are suggestive of a significant reduction in the over reliance on O_2 extraction during ramp exercise brought about possibly by an improvement in local microvascular blood flow in the area of interrogation. Previous work has shown that there is an impaired microvascular blood flow response and subsequent over reliance on O_2 extraction during moderate-intensity exercise in T2DM (Bauer *et al.* 2007). Moreover, recent work from our laboratory has indicated that the peak hyperaemic response during maximal plantar flexion exercise is also significantly impaired in individuals with T2DM (Kiely *et al.* 2014). Therefore, it is tempting to suggest that exercise-induced improvements in vascular function and thus microvascular O_2 delivery may have reduced the dependence on fractional O_2 extraction during ramp exercise as reflected by a rightward shift of S_1.

The profiles of systematic Q_{max} and a-vO_2diff$_{max}$ as estimated from the Fick equation do not reflect the dynamic peripheral responses of blood flow to and O_2 extraction by the active muscle tissue during exercise (Murias *et al.* 2013). While a small widening in a-vO_2diff$_{max}$ was observed in the MICT group alone, the reduction in the magnitude of S_1 in both training groups is reflective of a reduced peripheral dependency on O_2 extraction for a given workload due to a likely improvement in peripheral microvascular blood flow distribution and delivery. LVHIIT and MICT have both been shown to be effective at inducing improvements in endothelial function and structure as measured by FMD (Maoirana *et al.* 2001; Schreuder *et al* 2015; Madsen *et al.* 2015; Francois *et al.* 2017). It is likely that the underlying mechanisms of this improved vascular function with training may be an increased bioavailability of nitric oxide due to the chronic shear stress experienced by the endothelium during chronic exercise (Mitranun *et al.* 2014) and a reduction in localised oxidative stress within the vasculature (Taddei *et al.* 2004).

2.4.4. Skeletal Muscle Adaptations.

It is well established that skeletal muscle mitochondrial content and oxidative capacity are reduced in T2DM (Kelley *et al.* 2002; Ritov *et al.* 2005). Moreover, muscle fibre type distribution is altered in individuals with T2DM reflected by a lower proportion of oxidative Type I muscle fibres and a higher proportion of glycolytic Type IIb fibres (Marin *et al*. 1994). Although we did not specifically measure skeletal muscle fibre distribution and mitochondrial capacity it is likely that adaptations to both occurred as a result of LVHIIIT and MICT. For instance, investigations have shown that both interval and continuous training stimulate changes in muscle fibres to a more oxidative phenotype while also increasing oxidative enzyme activity, increasing type I muscle fibre capillarisation and stimulating mitochondrial biogenesis (Ingjer, 1979; Jensen *et al*. 2004; Liang & Ward 2006; Gjovaag & Dahl, 2008)

With regard to the effect of MICT on mitochondrial function, Toledo *et al*. (2007) reported a 67% increase in mitochondrial density, a 20% increase in mitochondrial DNA content and a significant increase in CS activity and NADH oxidase activity (both of which are indicators of mitochondrial oxidative capacity), following a 16 weeks of MICT in middle-aged men with T2DM. Similar findings were reported by Meex *et al.* (2010) who reported a significant 48% increase in mitochondrial oxidative capacity post-training while Pheilix *et al.* (2010) reported a significant increase in mitochondrial density and a 30% increase in mitochondrial content post-training. In terms of LVHIIT, Little *et al.* (2011) reported a 10% increase in peak power output as well as a significant increase in citrate synthase activity (a marker of mitochondrial oxidative activity) after only 2 weeks of LVHITT (3 sessions per week, 10x60s at 90% HRmax) in participants with uncomplicated T2DM. LVHIIT has been postulated to induce an increase in the activity of peroxisome-proliferator activated ϒ coactivator (PGC-1α). PGC-1α is thought to be the key regulator of mitochondrial biogenesis (Gibala *et al.* 2012) and exercise intensity is suggested to be the key determinant of PGC-1α activity (Egan *et al.* 2010). Indeed, studies of LVHIIT and PGC-1α levels in healthy populations have indicated towards a 50% increase in PGC-1α activity with LVHITT which is associated with significant increases in mitochondrial content and oxidative activity (Little *et al.* 2011b; Hood *et al.* 2011; Gibala *et al.* 2012).

Although we observed no LVHIIT-induced changes in systemic a-vO_2diff_{max}, MICT caused a non-significant widening of a-vO_2diff_{max} by 10% at week 6 which was reduced to 5% by week 12, and this is similar to the magnitude of increase in a-vO_2diff_{max} observed by Murias *et al.* (2010) in both younger (+9%) and older healthy males (+7%) following 12 weeks of MICT. In addition, in the present study in both training groups reliance on peripheral O_2 extraction during the RI test was observed to decrease after 3 weeks of training (reflected by the significant reduction in S_1). Therefore, it is likely that the reductions in S_1 and the widening of a-vO_2diff$_{max}$ with MICT indicate towards both cardiovascular and skeletal adaptations with exercise while the change in S_1 alone with LVHIIT is suggestive of predominately cardiovascular adaptations.

2.4.5. Glycaemic Control.

Frontline management of T2DM aims to prevent the development of diabetes associated complications and to maintain optimal glycaemic control. In the present study, 12 weeks of LVHIIT significantly reduced HbA_{1c} levels while there was a strong trend for a reduction in HbA_{1c} levels after 12 weeks of MICT ($P = 0.09$). Our findings are in line with recent work that has shown that LVHIIT interventions of 8-12 weeks are effective at reducing HbA_{1c} (Madsen *et al.* 2015; Francois *et al*. 2017). Furthermore, LVHIIIT has been shown to be effective at improving 24 hr glucose levels as measured with continuous glucose monitoring, after only 2 weeks of training in T2DM (Little *et al.* 2011a).

The mechanisms underlying the positive influence of LVHIIT on HbA_{1c} levels remain to be elucidated. Reduced mitochondrial capacity in skeletal muscle has been reported in T2DM (Kelley *et al.* 2002; Ritov *et al.* 2005) while muscle oxidative capacity has been shown to be a significant predictor of insulin sensitivity (Bruce *et al*. 2003). Therefore, it is possible that the rapid increase in skeletal muscle mitochondrial content with LVHIIT may be a contributing factor related to reduced insulin resistance and improved glycaemic control (Little *et al.* 2011). However, it is important to note that the theory that mitochondrial dysfunction induces insulin resistance was called into question by Holloszy (2009) who suggested that other adaptations in skeletal muscle may be more important (Holloszy, 2009). For instance, LVHIIT-induced increases in GLUT4 content may at least in part play a role in improving glucose regulation (Gibala *et al.* 2012).

A reduction in HbA_{1c} has a major clinical significance for an individual's morbidity and mortality. A higher HbA_{1c} level is a key predictor of cardiovascular events and microvascular complications in T2DM (Boule *et al.* 2003). Research suggests that a 1% absolute decrease in HbA_{1c} can result in a

15-20% decrease in the risk of a person experiencing a major cardiovascular event (Selvin *et al.* 2004). Moreover, an absolute decrease in HbA_{1c} of 1% is also associated with a 37% decrease in the risk of developing microvascular complications such as peripheral neuropathies and peripheral vascular disease (Stratton *et al.* 2000). Therefore, the findings of the current study further strengthen the evidence that an appropriately prescribed exercise intervention can potentially help to reduce the risk of developing microvascular complications and cardiovascular events in T2DM through reductions in HbA_{1c}.

2.4.6. Limitations.

The author acknowledges the limitations that lie within the use of NIRS and that adipose tissue layer thickness at the site of measurement has the potential to influence NIRS measurements through its effect on the scattering properties of the tissue (Elwell, 1995). However, the 3 groups in the present study were well matched in terms of adipose layer thickness as we determined the thickness of the skin and adipose tissue layer at the site of the interrogation via 2D ultrasound operating in B-mode, and no significant differences were observed between groups. In addition, the fact that all 3 groups included males and females may have influenced the underlying mechanisms that were responsible for the changes in $\dot{V}O_{2max}$. For instance, it appears that changes in $\dot{V}O_{2max}$ with MICT in women are predominantly due to a widening of a-vO_2diff whereas in males VO_{2max} increases with training due to adaptation in Q_{max} and a-vO_2diff (Spina *et al.* 1993).

2.4.7. Conclusion.

This study has shown that LVHIIT and MICT both increase $\dot{V}O_{2max}$ to a similar extent and within a similar time frame in individuals with uncomplicated T2DM. Furthermore, both interventions inferred significant improvements in Q_{max} and in microvascular blood flow during maximal exercise (as reflected by a decreased reliance on fractional O_2 extraction) of a similar magnitude. Importantly LVHIIT can induce these benefits with a time commitment that is 50% less than MICT. Therefore, both of these exercise interventions are safe and effective at improving the characteristic exercise intolerance that is present in those living with T2DM.

Chapter 3. ***Effects of MICT vs LVHIIT on oxygen uptake and muscle deoxygenation kinetics during moderate-intensity exercise in type 2 diabetes.***

3.1. Introduction.

Young and middle-aged individuals with T2DM exhibit a marked slowing of the $\dot{V}O_2$ kinetics response during moderate-intensity exercise compared to healthy age-matched controls (Regensteiner *et al*. 1998; Brandenburg *et al.* 1999; Bauer *et al.* 2007; MacAnaney *et al.* 2011; O'Connor *et al.* 2012; O'Connor *et al.* 2015). Specifically, the attenuation of the $\dot{V}O_2$ kinetics response is mostly due to a significant lengthening of the time constant of the primary component of $\dot{V}O_2$ kinetics; $\tau\dot{V}O_{2P}$. For instance, those with T2DM present with a $\tau\dot{V}O_{2P}$ that is typically 34-36% slower than that observed in healthy individuals (Green *et al.* 2015). The functional significance of a prolonged $\tau\dot{V}O_{2P}$ is an over reliance on anaerobic metabolism at the onset of exercise which will incur an excessive O_2 deficit resulting in premature fatigue and exercise intolerance.

The underlying mechanism of this impairment remains unclear, but based on the Fick equation impairments in O_2 delivery and/or utilisation must be responsible. There is substantial evidence to suggest that O_2 delivery to active muscles during exercise is impaired in T2DM. For instance, Bauer *et al.* (2007) reported a significantly longer $\tau\dot{V}O_{2P}$ in individuals with T2DM compared to age-matched healthy controls which was accompanied by a significant lengthening of the estimated microvascular blood flow response at the onset of exercise as measured by NIRS (Bauer *et al.* 2007). Moreover, reduced steady state blood flow responses during moderate-intensity exercise (Kingwell *et al.* 2003; Lalande *et al.* 2008*)* and significantly longer leg vascular conductance kinetics during moderate-intensity plantar flexion exercise (MacAnaney *et al.* 2012) have been reported in individuals with T2DM compared to healthy controls. However, it is important to note that other studies have reported no T2DM related impaired limb blood flow responses during low and moderate-intensity exercise. (Pak *et al*. 2010; Poitras *et al.* 2015; Kiely *et al.* 2015).

The skeletal muscle mitochondria is also likely to be implicated in the slowed $\dot{V}O_2$ kinetics response in T2DM (Grassi *et al.* 2001; Hughson *et al*. 2001; Poole *et al.* 2008; Murias *et al.* 2011). Ritov *et al.* (2005), reported a seven-fold reduction in electron transport chain activity in addition to a reduction in the

DNA and protein content of mitochondria present in skeletal muscle biopsies taken from the vastus lateralis of individuals with uncomplicated T2DM (Ritov *et al.* 2005). Furthermore, Kelley *et al.* (2002) reported decreased oxidative enzyme activity and mitochondrial size and surface area in individuals with T2DM compared with healthy individuals (Kelley *et al.* 2002). This attenuation of mitochondria oxidative capacity may result in a prolonged metabolic inertia and delayed activation of oxidative cellular energetics at the onset of exercise in individuals with T2DM, thus, contributing to a prolonged $\tau\dot{V}O_{2P}$.

Acute and chronic exercise interventions have both been suggested to be effective at speeding $\tau\dot{V}O_{2P}$ in individuals with and without T2DM. For instance, acute heavy-intensity priming exercise (PE) has been shown to be effective at significantly reducing $\tau\dot{V}O_{2P}$ in young healthy untrained populations who present with initially slow $\dot{V}O_2$ kinetics ($\tau\dot{V}O_{2P}$ > 20-30 s) (Gurd *et al.* 2005; Gurd *et al.* 2006; Murias *et al.* 2011; Spencer *et al.* 2012). In addition, PE has been observed to significantly decrease $\tau\dot{V}O_{2P}$ in populations that typically present with abnormal $\dot{V}O_2$ kinetics such as healthy elderly individuals (Scheuermann *et al.* 2002; DeLorey *et al.* 2004b; DeRoia *et al.* 2012). Possible mechanisms for the beneficial effect of PE on $\tau\dot{V}O_{2P}$ during moderate-intensity exercise include; increased O_2 availability at the onset of exercise (Gurd *et al.* 2005; Nederveen *et al*. 2017), improved matching of O_2 delivery and utilisation due to improved microvascular blood flow (Murias *et al*. 2011; Spencer *et al*. 2013) and increased activity of mitochondrial enzymes at the onset of exercise (Behnke *et al.* 2002; Gurd *et al*. 2005; Gurd *et al.* 2006; Faisal *et al.* 2009). Recently, Rocha *et al*. (2016) showed that a prior bout of heavy-intensity PE significantly reduces $\tau\dot{V}O_{2P}$ during a subsequent bout of moderate-intensity exercise in individuals with uncomplicated T2DM. The speeding of $\dot{V}O_2$ kinetics post PE was accompanied by a tendency ($P < 0.1$) for a reduction in $\Delta HHb/\Delta\dot{V}O_2$ ratio towards 1.0 thus suggesting that heavy-intensity PE may improve the matching of microvascular O_2 delivery and utilisation during subsequent bouts of moderate-intensity exercise in T2DM (Rocha *et al.* 2016)

In terms of chronic exercise, MICT has been shown to be effective at speeding the $\dot{V}O_2$ kinetics response during moderate-intensity exercise in T2DM. For instance, Brandenburg *et al.* (1999) reported a significant reduction in $\tau\dot{V}O_{2P}$ at the onset of moderate-intensity cycling exercise at an absolute intensity of 50W following 12 weeks of MICT in female participants with uncomplicated T2DM (Brandenburg *et al.* 1999). Similarly, MacAnaney *et al.* (2012) reported a significant 45% reduction in $\tau\dot{V}O_{2P}$ at the onset of a moderate-intensity cycling exercise at relative intensities equivalent to 80% VT after 12 weeks of combined aerobic and resistance training in participants with uncomplicated T2DM. However, the mechanism and time course of adaptation in $\tau\dot{V}O_{2P}$ in response to MICT in T2DM remains to be elucidated. Among healthy younger and older males without T2DM, Murias *et al*. (2010) explored the effect of 12 weeks of MICT on $\tau\dot{V}O_{2P}$ while measuring time course adaptations (every 3 weeks) in Δ [HHb + Mb]/$\Delta\dot{V}O_2$ ratios. The authors reported a significant speeding of the $\dot{V}O_2$ kinetics response after only 3 weeks of training which was accompanied by a significant reduction in the Δ [HHb + Mb]/$\Delta\dot{V}O_2$ ratio. Therefore, a contributing mechanism to the improvement in $\dot{V}O_2$ kinetics in the study by Murias *et al.* (2010) is likely to be an improved microvascular blood flow and distribution resulting in an improved matching of O_2 delivery and utilisation (Murias *et al.* 2010).

The effect of LVHIIT on $\dot{V}O_2$ kinetics in T2DM remains to be investigated. In healthy populations, LVHIIT has been shown to induce a significant reduction in $\tau\dot{V}O_{2P}$. McKay *et al.* (2009) showed that both LVHIIT and MICT reduce $\tau\dot{V}O_{2P}$ during moderate-intensity exercise by ~40% in young healthy males after 3 weeks of training (McKay *et al.* 2009). In addition, Williams *et al*. (2013) reported a 37.5% reduction of $\tau\dot{V}O_{2P}$ during moderate-intensity exercise in young healthy males after just 4 weeks of LVHIIT. Furthermore, Williams *et al.* (2013) reported that LVHIIT significantly reduced the Δ[HHb + Mb]/$\Delta\dot{V}O_2$ ratio so that it was no longer significantly different from 1.0; thus indicating a LVHIIT-induced improvement in the matching of O_2 utilisation and delivery (Williams *et al.* 2013).

Accordingly, the primary aim of the present study was to compare the effects of MICT and LVHIIT in terms of the time course and mechanism of adaptation of $\dot{V}O_2$ and muscle deoxygenation kinetics during moderate-intensity exercise in individuals with uncomplicated T2DM. In addition, a secondary aim of this study was to investigate the effect of LVHIIT and MICT on the effects of priming exercise on pulmonary oxygen uptake kinetics during moderate-intensity exercise at the same time points. Given that both exercise training modalities improve $\dot{V}O_{2P}$ by 3 weeks of training, albeit in healthy participants, and that these benefits are induced, at least in part, by a better matching of O_2 delivery and utilisation it was hypothesised that:

1) LVHIIT and MICT would both accelerate $\dot{V}O_2$ kinetics by a similar magnitude and within a similar time scale and that the benefits induced by both types of exercise training would be as a result of an improvement in the matching of microvascular O_2 delivery and O_2 utilisation as reflected by a reduction in the Δ[HHb + Mb]/$\Delta\dot{V}O_2$.

2) At week 0, priming exercise would speed the $\dot{V}O_2$ kinetics response in all 3 groups as a result of an improvement in the matching of microvascular O_2 delivery and O_2 utilisation, but the influence of PE on $\dot{V}O_2$ kinetics would diminish in both the LVHIIT and MICT groups as exercise training progressed due to training-induced improvements in the matching of microvascular O_2 delivery and O_2 utilisation. However, in the control group PE would still speed $\dot{V}O_2$ kinetics at all time points.

3.2. Methodology.

3.2.1. Participants.

3.2.1.1. Recruitment of participants.

Thirty-one participants entered the study however, 3 participants from the MICT group were excluded from the end analysis due to poor quality data (n =1), not completing the primed exercise bout (n = 1) or not completing the moderate-intensity bouts as they did not tolerate the silicon mouth piece during data collection (n = 1). Therefore, Twenty-eight participants (17 men/11 women) with uncomplicated T2DM volunteered to partake in the study. Participant characteristics and medications are displayed in Table 3.1 and Table 3.2. Upon entering the study, the participants were randomised into one of three training groups; low-volume high-intensity interval training (LVHIIT; n = 9), moderate-intensity interval training (MICT; n = 10) or control (CON; n = 9). Five of the female participants were pre-menopausal (LVHIIT n = 2; MICT n = 1; CON n = 2) and 6 were post-menopausal (LVHIIT n = 2; MICT n = 2; CON n = 2 not undergoing HRT. All the participants were non-smokers or had ceased smoking at least 12 months prior to commencing the study. The participants who partook in the present study also carried out the measurements shown in Chapter 2.

3.2.1.2. Exclusion criteria

As per section 2.2.1.1.

3.2.2. Study overview.

Each participant was required to visit the exercise testing facility in St. Colmcille's Hospital on an additional separate occasion (in addition to the visit described in Chapter 2) with testing visits separated by at least 48 hours (see Fig 3.1). All premenopausal participants were tested during the mid-follicular phase (days 5-12) of the menstrual cycle which was determined by self-evaluation. All participants were requested to abstain from alcohol, caffeine and strenuous physical activity for at least 24 hours prior to any testing procedures. Each participant repeated both study visits at 3 week intervals during the exercise intervention, thus allowing for assessment of the time course of adaptation to exercise at 5 time points; weeks 0, 3, 6, 9 and 12.

3.2.2.1. Visit 1 overview

Visit 1 has been described in detail in Chapter 2. Briefly, initially anthropometric data was collected. Participants then performed a ramp incremental cycling test to exhaustion in order to assess $\dot{V}O_{2max}$ (see *section 2.2.4.2.2.*) and to allow for the calculation of ventilatory threshold (VT) by the V-Slope method (Beaver *et al.* 1986) (as per *section 2.2.6.1.*). Within 5 mins of completion of the ramp test, participants completed a 'confirmatory' high-intensity cycling bout to determine whether $\dot{V}O_{2max}$ had been obtained (as per *section 2.2.4.2.2.).*

3.2.2.2. Visit 2 overview

During this visit each participant completed 4, 6 min moderate-intensity exercise bouts in order to assess the VO_2 kinetics response during moderate-intensity exercise. Two of the bouts were unprimed and two of the bouts were completed after a bout of priming exercise. The power outputs required for this protocol were equivalent to 80% of the PO at VT achieved during the ramp incremental cycling test.

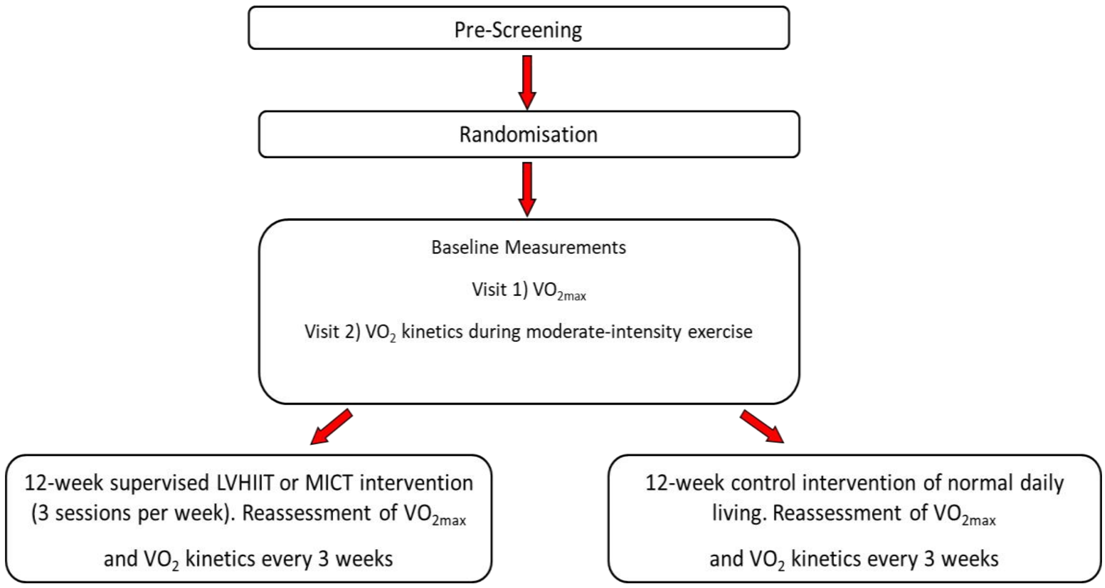

Figure 3.1. Study overview

3.2.3. Exercise Training Interventions

As per section 2.2.3

3.2.3.1 Moderate-intensity continuous training

As per section 2.2.3.1.

3.2.3.2. Low-volume high-intensity interval training

As per section 2.2.3.2.

3.2.4. Laboratory measurements.

3.2.4.1. Pre-screening

3.2.4.1.1. Exercise stress test.

As per section 2.2.4.1.1.

3.2.4.1.2. Evaluation of physical activity levels

As per section 2.2.4.1.2.

3.2.4.1.3. Ankle: brachial index

As per section 2.2.4.1.3.

3.2.4.1.4. Metabolic Profile

As per section 2.2.4.1.4.

3.2.4.2. Visits to the exercise physiology laboratory.

3.2.4.2.1 Visit 1

3.2.4.2.1.1. Anthropometric measurements.

As per section 2.2.4.2.1.

3.2.4.2.1.2 Maximal ramp incremental exercise test.

As per section 2.2.4.2.2

3.2.4.2.2. Visit 2.

3.2.4.2.1 Measurement of $\dot{V}O_2$ kinetics responses during moderate-intensity cycling exercise with and without priming exercise.

Each participant completed four bouts of constant-load, moderate-intensity cycling at a PO equivalent to 80% of that achieved at VT during the ramp test (80% VT) (Fig. 3.1). Each bout consisted of a 3 minute warm up cycling at 10W which was followed by an immediate step-wise increase to the 80% VT moderate intensity for 6 minutes. Two of the exercise bouts were performed without priming exercise (MOD A) while two bouts were preceded by a bout of priming exercise (MOD B). The priming exercise consisted of a 3 minute warm up cycling at 10 W followed by a 6 min high intensity exercise bout equivalent to 50% of the difference between peak PO and the PO at VT achieved during the ramp protocol (50% Δ). All of the cycling protocols were performed on an electrically braked cycle ergometer (Excalibur Sport, LODE B.V., Groningen, The Netherlands). There was a 12 minute passive rest period between each of the cycling bouts, except following the first primed bout (MOD B) whereby participants remained passively seated in a chair for the duration of 45 minute. This is the minimum time required for the physiological restoration of $\dot{V}O_2$, HR and blood lactate to resting levels following a bout of exercise. This prolonged rest period ensured that the preceding cycling bouts had no effect on physiological parameters (i.e. HR and $\dot{V}O_2$) during subsequent exercise bouts (Burnley *et al.* 2006a).

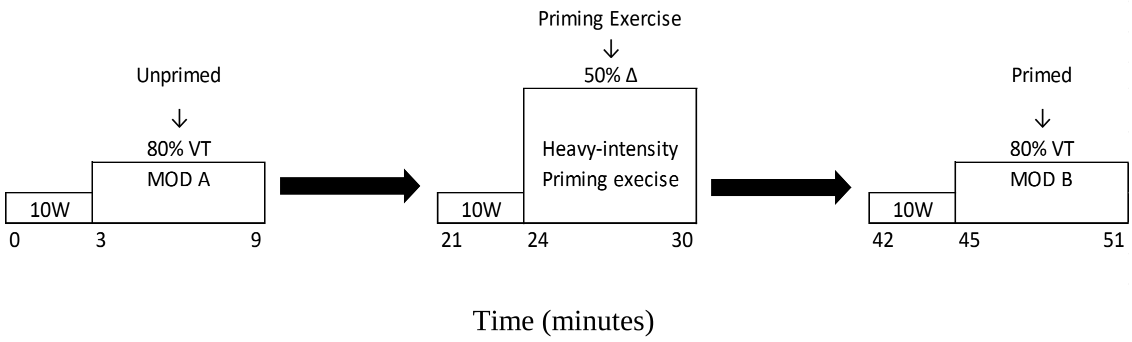

Figure 3.2. Representative figure of the study protocol. The above protocol was repeated after a 45 min rest

3.2.5. Laboratory equipment and measurement techniques

3.2.5.1. Cardio-metabolic unit.

As per section 2.2.5.1.

3.2.5.2. Heart rate.

As per section 2.2.5.2.

3.2.5.3 Muscle deoxygenation.

As per section 2.2.5.3.

3.2.6. Data Analysis.

3.2.6.1. Peak physiological responses during ramp exercise and determination of VT.

As per section 2.2.6.1.

3.2.6.2. Analysis of 80% VT data.

3.2.6.2.1. $\dot{V}O_2$ kinetics.

Breath-by-breath $\dot{V}O_2$ data for each moderate-intensity transition were linearly interpolated to provide second-by-second values. $\dot{V}O_2$ at time 0 was calculated as the average $\dot{V}O_2$ during the last 60 s of the warm-up period. Data from each exercise bout were combined to yield a single, average response for each study participant and were further time-averaged into 5 s bins. The initial 20 s of data after the onset of the transition from warm up to the moderate-intensity exercise were excluded from the analysis in order to remove data points containing the cardio-dynamic phase of the $\dot{V}O_2$ kinetics response (Murias *et al.* 2011c). This ensured that to the greatest possible extent, only data from Phase II of the $\dot{V}O_2$ kinetics response were represented in the analysis. Therefore, the model parameters of the $\dot{V}O_2$ kinetics response were analysed from 20-360 s of the step transition by way of a weighted least-squares non-linear regression procedure (TableCurve 2D, Systat) in which the best fit was defined by minimization of the residual sum of squares. Data points lying outside the 95% prediction interval during the initial fit of a model were excluded.

The $\dot{V}O_2$ kinetics response to moderate-intensity exercise can be described using a mono-exponential function (Whipp & Wasserman, 1972) referred to as primary phase or phase II, whereby $\dot{V}O_2$ rises to attain a steady-state (Phase III) within ~2 mins on exercise onset. However, for exercise above the VT, attainment of a steady-state in $\dot{V}O_2$ is delayed due to the emergence of the $\dot{V}O_2$ slow component and is better described by a bi-exponential function (Whipp *et al.*1982). Each exponential function has an amplitude and a time constant (τ), which reflects the time required for the attainment of 63% of the total amplitude. The exponential nature of the Phase II $\dot{V}O_2$ response during moderate-intensity exercise can thus be described with the following equation:

$$\dot{V}O_2\ (t) = \dot{V}O_2\ \text{baseline} + A\ [1\text{-}e^{-\ (t\text{-}TD)/\tau)}]$$

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 $\dot{V}O_2$ during the last 30s of the warm-up; A is the steady-state amplitude of the increase in $\dot{V}O_2$, and $[1\text{-}e^{-\ (t\text{-}TD)/\tau)}]$ is the exponential function describing the rate at which $\dot{V}O_2$ is rising towards the steady-state amplitude. In this exponential function, TD represents the time delay before the start of the exponential term and τ is the time constant.

At baseline, 4 participants revealed an apparent $\dot{V}O_2$ slow component, suggesting that the ventilatory threshold was overestimated in these participants. So, for these participants' data were fitted using a bi-exponential function (Whipp *et al.*1982) of the form:

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

where A_p and A_s are the amplitudes of the $\dot{V}O_2$ primary and slow components respectively, TD_p and TD_s are the independent time delays before the commencement of the respective primary and slow components, and τp and τs are the time constants for the primary and slow components, respectively. The presence of a third phase in these 4 participants has minimal impact on the interpretation of our data, since parameters related to the primary phase are unaffected by the presence of the third phase (Wilkerson *et al*. 2007). Beyond, week 3 no participant revealed an apparent $\dot{V}O_2$ slow component during moderate-intensity exercise.

The steady-state $\dot{V}O_2$ response or the absolute primary component amplitude, referred to as $\dot{V}O_2$ End A was calculated as the average $\dot{V}O_2$ during last 30 s of the exercise bout.

Additionally, the functional "gain" of the primary $\dot{V}O_2$ response, reflective of the increase in $\dot{V}O_2$ per unit increase in power output was computed by the following formula:

$$\dot{V}O_2 \text{ gain} = (\text{End A} - \text{Baseline } \dot{V}O_2 \,/\, (\text{PO @80\% VT} - 10\text{W})$$

3.2.6.2.2. Muscle deoxygenation kinetics.

The NIRS-derived [HHb + Mb] data were linearly interpolated to provide second-by-second values. Data from each transition were ensemble-averaged to produce a single response for each individual which were further time-averaged into 5 s bins.

At the onset of exercise, a time delay (TD) is present in the [HHb + Mb] profile before it increases exponentially to a steady-state (DeLorey *et al.* 2003). This has been suggested to reflect the matching of muscular O_2 uptake and local O_2 delivery at the onset of exercise (DeLorey *et al*. 2003; Grassi *et al.* 2003). The TD in the present study was determined via visual inspection by the study investigator as the exponential increase in [HHb + Mb] above the resting level. The data were then fitted from the TD to 150 s of the response with a mono-exponential model similar to that utilised to model the $\dot{V}O_2$ data in order to analyse the time course of the [HHb + Mb] response;

$$[\text{HHb + Mb}]\ (t) = [\text{HHb + Mb}] \text{ baseline} + A\ [1- e^{-(t-TD)/\tau)}]$$

Whereby [HHb + Mb] (t) represents [HHb + Mb] at a given time; [HHb + Mb] baseline represents [HHb + Mb] at Time 0 at the commencement of the transition to the moderate exercise intensity; A is the steady state amplitude of the increase in [HHb + Mb]. TD is the time delay marking the beginning of the exponential rise and τ is the time constant of the response.

A shorter fitting window of 150 s was utilised in order to counteract the possible variations in the [HHb + Mb] (which have been indicated to appear between 180-240 s after the onset of exercise), from impacting the fitting of the on-transient response whilst allowing for the attainment of a steady-state (Ferreira *et al*. 2005a, 2005b; Murias *et al.* 2011a, 2011b). Visual inspection of the NIRS-derived [HHb + Mb] signal and analysis of least squares residuals indicated that a mono-exponential model would reliably estimate the time course of [HHb + Mb] during the time period corresponding to the primary phase of the $\dot{V}O_2$ response (DeLorey *et al.* 2003).

The time course for the increase in Δ [HHb + Mb] can be described by the τ [HHb + Mb], however, the time course for the overall change of the Δ [HHb + Mb] for the primary response phase, referred to as the effective τ' [HHb+Mb], was determined from the sum of TD [HHb + Mb] and τ [HHb + Mb] from the onset of exercise.

The end amplitude of the [HHb + Mb] response, referred to as [HHb + Mb] End was calculated as per $\dot{V}O_2$ End (*see section 3.2.6.2.1*).

3.2.6.2.3. Δ *[HHb + Mb]/*Δ$\dot{V}O_2$ *ratios.*

[HHb + Mb] parameters were utilised in order to determine the Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio during the primary phase of the response. As the [HHb + Mb] signal does not measure microvascular blood flow or O_2 delivery, the Δ[HHb + Mb]/Δ$\dot{V}O_2$ ratio is instead a ratio of the degree of O_2 extraction required for a given increase in $\dot{V}O_2$, therefore providing insight into the dynamic balance between O_2 delivery and utilisation (Murias & Paterson, 2015).

For the calculation of the Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio (Murias *et al.* 2010a, 2011b) the individual second-by-second Δ [HHb + Mb] and $\dot{V}O_2$ data were normalised (from 0%, corresponding to the warm-up 10W baseline value to 100% representing the steady-state response). Then, Δ [HHb + Mb] and $\dot{V}O_2$ were time aligned by left-shifting the normalised $\dot{V}O_2$ data by 20 s to account for the cardio-dynamic phase of the $\dot{V}O_2$ kinetic response. The normalised and time aligned data was then averaged into 5 s bins.

The overall Δ [HHb + Mb]/$\Delta\dot{V}O_2$ ratio for the adjustment during the exercise transition was defined for each participant as the mean value from 20-150 s into the transition. The starting point of 20 s was selected as it is representative of the region where the Δ[HHb + Mb] and $\dot{V}O_2$ signals meet, with the 150 s end point indicative of the time point at which a steady-state value of 1.0 had been achieved by the Δ[HHb + Mb]/$\Delta\dot{V}O_2$ ratio. Values > 1.0 are indicative of a greater reliance on O_2 extraction compared with the exercise steady-state (values at steady state = 1.0). Therefore, this is reflective of a mismatching of local O_2 delivery relative to muscle O_2 utilisation in the area of NIRS interrogation (Murias *et al.* 2011b) (see Fig. 3.3).

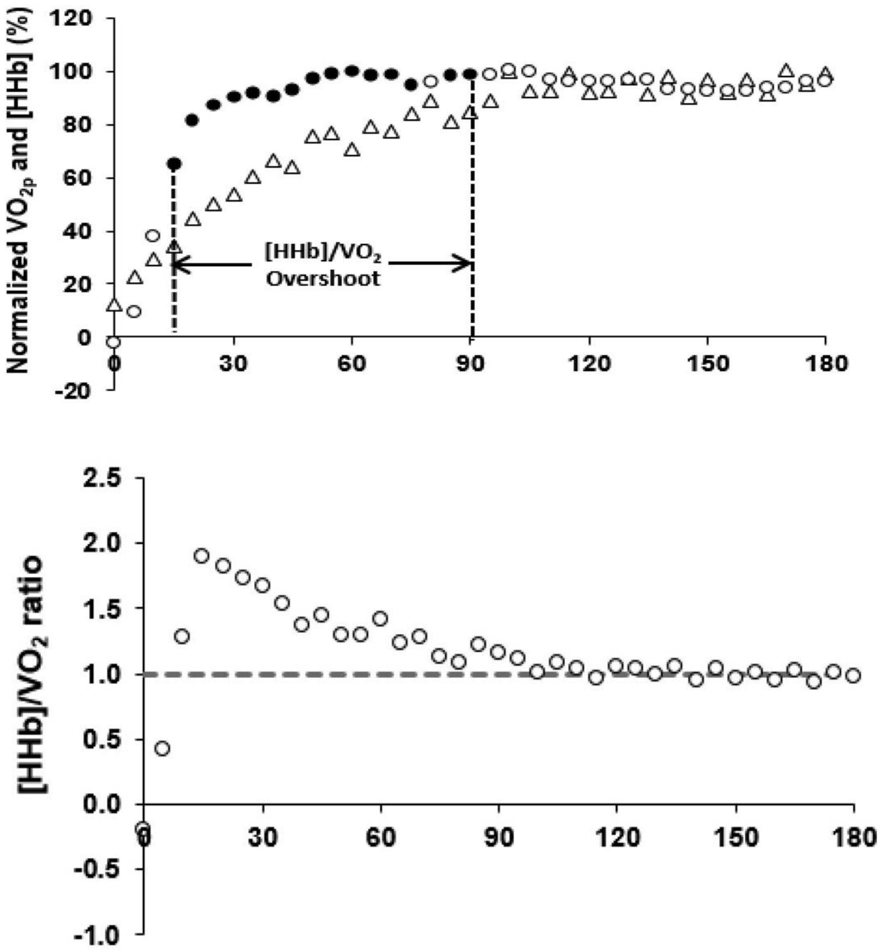

Figure 3.3 Top Panel: Representative plot of the adjustment of [HHb] (circles) and VO_{2P} (triangles) during the initial 150s of a transition from rest to moderate-intensity cycling exercise in individuals with 'slow' VO_2 kinetics. Filled circles indicate timepoints at which the relative increase in of [HHb] is greater than VO_{2P}. Bottom panel: Representative plot of the adjustment of [HHb]/ VO_{2P} ratio during a transition from rest to moderate-intensity cycling exercise in individuals with 'slow' VO_2 kinetics. A [HHb]/ VO_{2P} ratio >1.0 is indicative of an imbalance between O_2 delivery and utilisation in the area of interrogation (Taken from Murias & Paterson, 2015).

3.2.6.2.4. Heart rate kinetics.

Beat-by-beat heart rate data was linearly interpolated to provide second-by-second values and time-aligned. Data for each transition were ensemble-averaged to produce a single average response for each participant.

Baseline HR (time 0) was determined to be the average of the last 60 s of the 3 minute warm up period. The model parameters of the HR kinetic response were calculated from 0 – 360 s of the step transition via a weighted least-squares nonlinear regression procedure (TableCurve 2D, Systat), in which the best fit was defined by minimization of the residual sum of squares. Data points lying outside the 95% prediction interval during the initial fit of a model were excluded. A mono-exponential model was used to describe the HR kinetic response:

$$HR\ (t) = HR\ baseline + A\ [1- e^{-(t-TD)/\tau)}]$$

Whereby HR (t) represents HR at a given time; HR baseline represents the heart rate at time 0 at the commencement of the transition to the moderate exercise intensity; A is the amplitude of the increase in HR; TD is the time delay marking the beginning of the exponential rise and τ is the time constant of the response. The end amplitude of the [HR] response, referred to as [HR] End was calculated as the average HR during the last 30 s of exercise.

3.2.7. Statistical Analysis.

Statistical analysis of the data was performed using SigmaPlot Version 12.0 software (Systat Software, Point Richmond, CA, USA) and DataDesk Version 8.0 software (Data Description). Normality of the data was assessed using the Shapiro-Wilk test. Non normal data and data that did not have equality of variance were transformed to resemble normalised data. Baseline analysis of participant characteristics was completed with a one-way analysis of variance (ANOVA). The effect of priming exercise during the different time points of the intervention on $\dot{V}O_2$, HR and [HHb + Mb] kinetics parameters were completed using a 3-way repeated measures ANOVA (priming exercise vs time vs group). The effects of the different time points of the intervention on peak physiological responses, anthropometric data and unprimed $\dot{V}O_2$, HR and [HHb + Mb] kinetics parameters were analysed using a 2-way repeated measures ANOVA (group vs time). Post-hoc Tukey tests were performed in incidences of statistical significance. Statistical significance was set at $P < 0.05$. Data are displayed as mean ± standard (SD) unless otherwise stated.

The key variable in this study is the time constant of the primary component of $\dot{V}O_2$ kinetics; $\tau\dot{V}O_{2P}$, during moderate-intensity exercise. Recently published studies investigating the effect of exercise training on $\tau\dot{V}O_{2P}$ during moderate-intensity exercise in T2DM (Brandenberg *et al.* 1999; MacAnaney *et al.* 2011) and in sedentary healthy individuals with 'slow' $\dot{V}O_2$ kinetics (Murias *et al.* 2010a; Murias *et al.* 2010b) have reported an average $\tau\dot{V}O_{2P}$ of 39.8 ± 6.8 s (Mean ± SD) and the difference in $\tau\dot{V}O_{2P}$ pre- and post-training was 12.8 s. Given that the estimated standard deviation (SD) of each population is 6.8 s, and that the minimum difference we wish to detect as significant would be ~13 s, the minimum sample size needed to detect a significant effect at $\beta = 0.05$ and $\alpha = 0.05$ (90% power) for an ANOVA calculation design based on 3 groups, is 9 individuals.

3.3. Results.

3.3.1. Participants.

3.3.1.1. Recruitment of participants.

See section 2.3.1.1

3.3.1.2. Participant's physical characteristics, prescription medications and exercise adherence.

Participant characteristics and prescription medications are shown in Table 3.1 and Table 3.2. The mean exercise adherence was 98 ± 4% (range, 32-36 sessions) in the MICT group and 94 ± 6% (range 31-36 sessions) in the LVHIIT group. The average training intensity (PO) increased significantly after each retesting session (i.e., every 3 weeks) in both the MICT (weeks 1–3, 79 ± 29 W; weeks 4–6, 106 ± 39 W; weeks 7–9, 117 ± 42 W; weeks 10-12, 128 ± 42 W) and LVHIIT groups (weeks 1–3, 166 ± 45 W; weeks 4–6, 181 ± 46 W; weeks 7–9, 195 ± 46 W; weeks 10-12, 197 ± 45 W). No adverse effects to training were reported in either group.

Table 3.1. ***Participant baseline characteristics.***

	MICT (n = 10)	LVHIIT (n = 9)	Control (n = 9)	*Between Groups P value*
Age (years)	53.0 (10.0)	52.0 (10.1)	53.9 (9.4)	0.95
Male/female	7/3	6/3	4/5	
BMI (m.kg $^{-2}$)	30.7 (5.9)	28.7 (3.0)	30.5 (3.6)	0.57
Time since diagnosis (years)	6.4 (3.8)	6.6 (3.5)	6.6 (3.3)	0.42
Pre-exercise ABI (a.u.)	1.13 (0.13)	1.07 (0.04)	1.13 (0.07)	0.24
Post-exercise ABI (a.u.)	1.12 (0.12)	1.05 (0.10)	1.14 (0.08)	0.06
HbA_{1c} (%)	6.8 (2.3)	7.3 (0.5)	6.8 (0.9)	0.42
Fat layer of VL (mm)	6.8 (2.8)	6.4 (2.6)	8.6 (3.2)	0.22

Data are mean (SD). BMI, body mass index; ABI, ankle: brachial index; a.u., arbitrary units; VL, vastus lateralis

Table 3.2. ***Prescriptive medications for individuals in each group.***

	MICT (n = 10)	LVHIIT (n = 9)	CON (n = 9)
Anti-hypertensives			
Angiotensin converting enzyme inhibitor		1	
Angiotensin II receptor blocker	1		1
Aspirin	3	1	2
Statins	5	3	3
Hypoglycaemic medications			
Oral hypo-glycaemic			
Metformin	5	5	5
Glucophage	2	2	1
Diamicron		2	2
Sitagliptin			2
Glicalzide	1	1	
Subcutaneous hypo-glycaemic			
Victoza	1		1

3.3.1.3 Physical activity levels

Group mean averages for physical activity levels as measured by RT3 accelerometers are shown in Table 3.3. There were no differences in physical activity levels between groups.

Table 3.3. ***Mean group physical activity data expressed in hours per day as determined by RT3 accelerometers.***

	MICT (n = 8)	LVHIIIT (n = 7)	CON (n = 8)	*Between Group P value*
Inactive ($h.day^{-1}$)	17.4 (1.6)	17.5(2.2)	18.2 (1.2)	0.44
Light ($h.day^{-1}$)	5.2 (0.7)	5.3 (1.6)	4.8 (0.9)	0.65
Moderate ($h.day^{-1}$)	1.2 (1.0)	1.0 (0.5)	0.8 (0.6)	0.42
Vigorous ($h.day^{-1}$)	0.3 (0.3)	0.2 (0.2)	0.2 (0.3)	0.13

Data are mean (SD)

3.3.2. Time course changes in peak physiological responses during ramp exercise.

PO_{peak} responses throughout the training period are summarised in Table 3.4. PO_{peak} significantly increased by a similar magnitude after 3 weeks in both the LVHIIT and MICT groups. In addition, in both groups PO_{peak} continued to progressively increase until the end of the intervention period. The total percentage change from pre-training to post-training was 25% and 16% in the MICT and LVHIIT groups respectively. No increases in PO_{peak} were observed in the CON group at any stage during the intervention period. $\dot{V}O_{2max}$ in absolute terms ($L.min^{-1}$), increased significantly after 3 weeks of MICT and after 6 weeks of LVHIIT although a strong tendency was observed for an increase in absolute $\dot{V}O_{2max}$ after three weeks in the LVHIIT group ($P < 0.07$). When $\dot{V}O_{2max}$ measurements were normalised to body mass, a significant increase in $\dot{V}O_{2max}$ of a similar magnitude was observed in both the LVHIIT and MICT groups after 3 weeks of training. Further non-significant progressions in $\dot{V}O_{2max}$ (expressed in both absolute and relative terms) continued to be observed until the end of the intervention period. The total percentage change in relative $\dot{V}O_{2max}$ from pre-training to post-training was 25% and 13% in the MICT and LVHIIT groups respectively. No increases in $\dot{V}O_{2max}$ were observed in the CON group at any stage during the intervention period. Group mean RER values were similar across groups at each time point in each group. Time to failure increased significantly after 3 and 6 weeks in the MICT and LVHIIT groups respectively with further significant improvements observed in the MICT group at week 9 and 12 only.

Table 3.4. ***Peak physiological responses during the intervention period in the MICT, LVHIIT and CON groups.***

	Week 0	Week 3	Week 6	Week 9	Week 12	*P value*		
$\dot{V}O_{2max}$ (L.min^{-1})						Time effect	Group effect	Time x Group
MICT	2.1 (0.7)	2.5 (0.6)*	2.6 (0.7)$^{*\#}$	2.5 (0.7)$^{*\#}$	2.6 (0.8)$*\#$			
LVHIIT	2.3 (0.5)	2.5 (0.6)	2.5 (0.5)$^{*\#}$	2.6 (0.6)$^{*\#}$	2.6 (0.5)$^{*\#}$	<0.001	0.08	0.002
CON	1.9 (0.5)	1.9 (0.6)	1.9 (0.6)	1.9 (0.6)	1.9 (0.5)			
$\dot{V}O_{2max}$ (mL.kg^{-1}.min^{-1})								
MICT	22.8 (4.4)	27.0 (5.0)$^{*\#}$	28.6 (4.6)$^{*\#}$	27.9 (5.4)$^{*\#}$	28.5 (5.0)$^{*\#}$			
LVHIIT	26.4 (4.0)	28.5 (4.2)$^{*\#}$	29.2 (3.5)$^{*\#}$	30.2 (4.4)$^{*\#}$	29.8 (3.9)$^{*\#}$	<0.001	0.004	<0.001
CON	21.5 (3.6)	22.1 (4.4)	21.6 (4.0)	22.2 (4.2)	22.0 (3.4)			
Peak PO (W)								
MICT	168 (50)	192 (60)*	198 (62)*	208 (62)*‡	210 (64)*‡†			
LVHIIT	187 (51)	204 (52)*	217 (52)*‡	220 (50)*‡	217 (55)*‡	<0.001	0.07	<0.001
CON	148 (49)	149 (52)	146 (55)	151 (51)	153 (50)			
TTF (s)								
MICT	689 (153)	777 (187)*	802 (197)*	838 (195)*‡	873 (241)*‡†			
LVHIIT	712 (88)	771 (90)	816 (94)*	831 (100)*	816 (94)*	<0.001	0.047	<0.001
CON	656 (123)	633 (127)	617 (125)	664 (124)	648 (116)			
Peak RER (a.u.)								
MICT	1.15 (0.10)	1.13 (0.07)	11.12 (0.07)	1.14 (0.07)	1.15 (0.10)			
LVHIIT	1.16 (0.05)	1.22 (0.06)	1.18 (0.07)	1.24 (0.09)	1.19 (0.06)	0.58	0.01	0.25
CON	1.13 (0.07)	1.10 (0.12)	1.11 (0.13)	1.10 (0.10)	1.11 (0.06)			

Data are mean (SD) *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 CON ($P < 0.05$). $\dot{V}O_{2max}$, maximal oxygen uptake; PO, power output; TTF, time to failure; RER, respiratory exchange ratio; a.u., arbitrary units.

Table 3.5. ***Power outputs for determination of $\dot{V}O_2$ kinetics and priming exercise.***

	MICT (n = 10)	LVHIIT (n = 9)	CON (n = 9)
PO @ VT (W)	91 (32)	115 (32)	83 (25)
%PO_{peak} @ VT	59 (9)	62 (6)	57 (7)
PO @ 50% Δ	123 (43)	151 (41)	115 (36)
%PO_{peak} @ 50% Δ	78 (3)	81 (3)	78 (3)

Data are mean (SD). PO, power output; VT, ventilatory threshold

3.3.3. Effect of training on physiological responses during moderate-intensity exercise.

3.3.3.1. $\dot{V}O_2$ kinetics.

Group mean estimates and percentage changes in $\tau\dot{V}O_{2P}$ at each time point are displayed in Fig. 3.2 and Fig. 3.3. Individual parameter estimates are shown in Appendix 7.5. At week 0, $\tau\dot{V}O_{2P}$ values across all three groups were similar. After 3 weeks of MICT and LVHIIT there was a significant decrease in the $\tau\dot{V}O_{2P}$ which was maintained throughout the training period. Moreover, the $\tau\dot{V}O_{2P}$ was significantly faster in the LVHIIT and MICT groups than in the CON from week 3 until the end of the intervention. The rest of the $\dot{V}O_2$ kinetics parameters were not affected by the intervention in any of the groups. Power outputs utilised during the moderate-intensity bouts are shown in Table 3.5.

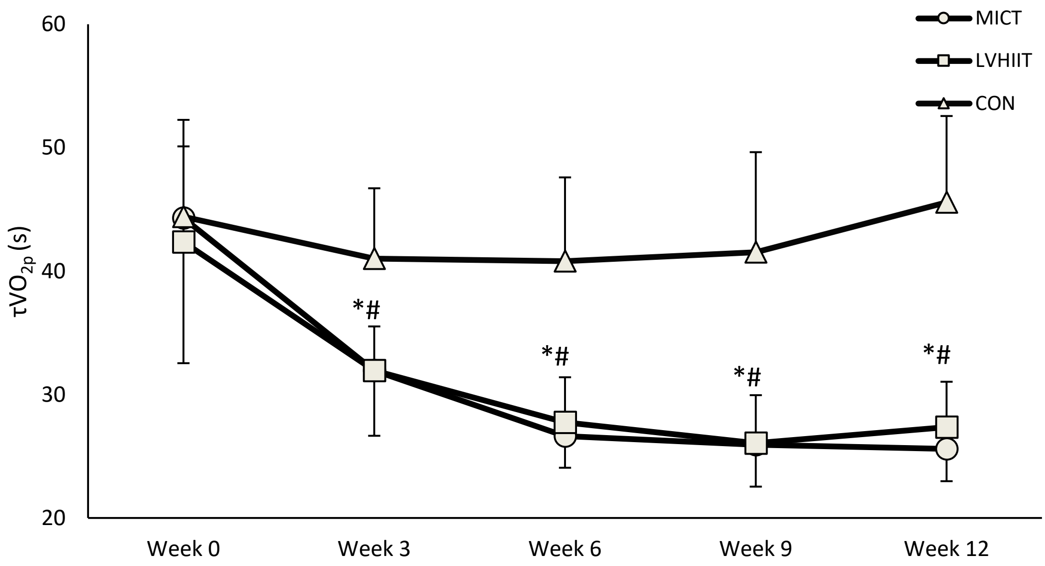

Figure 3.4. Changes in $\tau\dot{V}O_{2P}$ during MOD A (i.e. unprimed transitions to moderate-intensity exercise) with training. * infers LVHIIT and MICT significantly different from week 0 ($P < 0.05$). # LVHIIT and MICT significantly different from CON. Error bars denote SD.

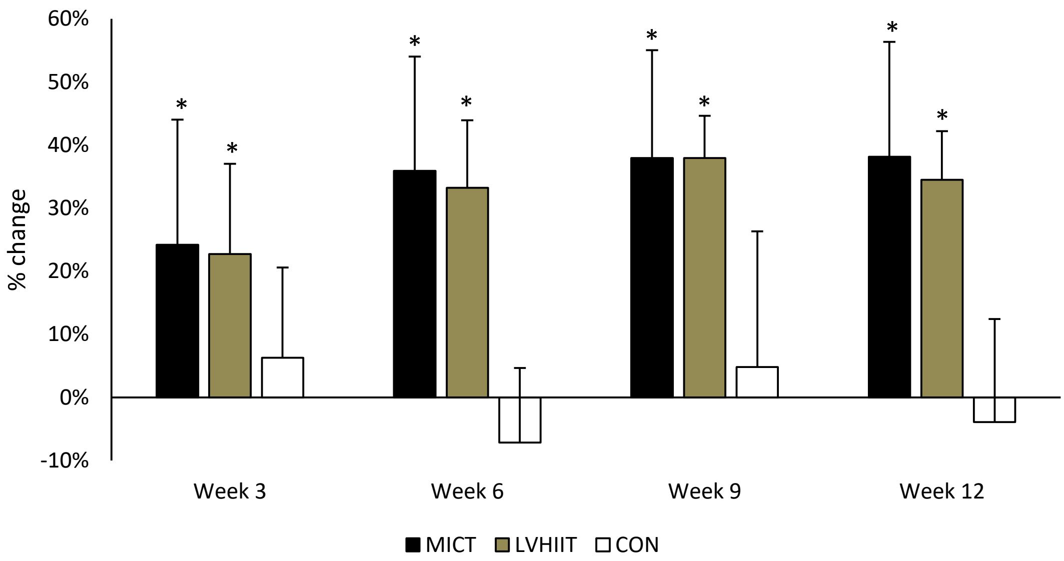

Figure 3.5. Illustration of the percentage change from week 0 in $\tau\dot{V}O_{2P}$ during MOD A with training. *significantly different from week 0 ($P < 0.05$). Error bars denote SD.

3.3.3.2. Muscle deoxygenation kinetics.

Kinetic parameters for [HHb + Mb] response profiles are displayed in Table 3.7 and individual responses can be found in Appendix 8.5. There were no changes in any parameter of the [HHb + Mb] response profile in any group during the intervention period. Comparisons of $\tau\dot{V}O_{2p}$ with the effective response time of [HHb + Mb] (i.e. [HHb + Mb] TD + [HHb + Mb] τ; τ'[HHb +Mb]) are shown in Fig 3.4. At baseline $\tau\dot{V}O_{2p}$ was significantly longer than τ'[HHb +Mb]) in all groups. However, after 3 weeks of both MICT and LVHIIT there was no difference in $\tau\dot{V}O_{2p}$ and τ '[HHb + Mb] and this remained until the completion of the intervention. In the CON condition, $\tau\dot{V}O_{2p}$ remained significantly longer than τ'[HHb +Mb] during the whole intervention period.

Table 3.6. Mean parameter estimates for [HHb + Mb] kinetics during the intervention period for the MICT, LVHIIT and CON groups.

	Week 0	**Week 3**	**Week 6**	**Week 9**	**Week 12**		*P Value*	
[HHb + Mb] A (a.u)						Time effect	Group effect	Time x Group
MICT	79 (38)	103 (57)	95 (57)	93 (52)	79 (34)			
LVHIIT	141 (104)	157 (103)	151 (101)	160 (103)	169 (120)	0.44	0.03	0.45
CON	73 (65)	71 (54)	40 (79)	68 (55)	78 (52)			
[HHb + Mb] End A								
MICT	40 (73)	33 (79)	192 (109)#	13 (80)	82 (84)			
LVHIIT	99 (109)	117 (91)	93 (102)	107 (105)	88 (115)	<0.001	0.51	<0.001
CON	33 (80)	21 (66)	95 (88)	46 (102)	139 (64)			
TD [HHb + Mb] (s)								
MICT	14 (4)	18 (6)	17 (7)	18 (10)	18 (6)			
LVHIIT	14 (2)	15 (4)	14 (3)	13 (5)	15 (3)	0.06	0.43	0.43
CON	16 (2)	15 (2)	14 (4)	15 (2)	17 (7)			
τ [HHb + Mb] (s)								
MICT	19 (11)	21 (17)	16 (10)	17 (14)	15 (6)			
LVHIIT	11 (4)	13 (6)	11 (7)	11 (6)	10 (6)	0.89	0.27	0.60
CON	13 (5)	12 (6)	18 (12)	17 (9)	15 (7)			
τ ‘ [HHb + Mb] (s)								
MICT	32 (8)	39 (21)	32 (15)	35 (22)	33 (10)			
LVHIIT	25 (4)	28 (6)	25 (8)	24 (9)	25 (8)	0.24	<0.001	0.69
CON	28 (5)	27 (6)	31 (10)	32 (9)	32 (9)			

Data are mean (SD). [HHb + Mb], deoxygenated haemoglobin and myoglobin concentration; A, amplitude; TD, time delay; τ, time constant of the primary response; τ’ [HHb + Mb], effective time constant. # significantly different to CON (*P* < 0.05).

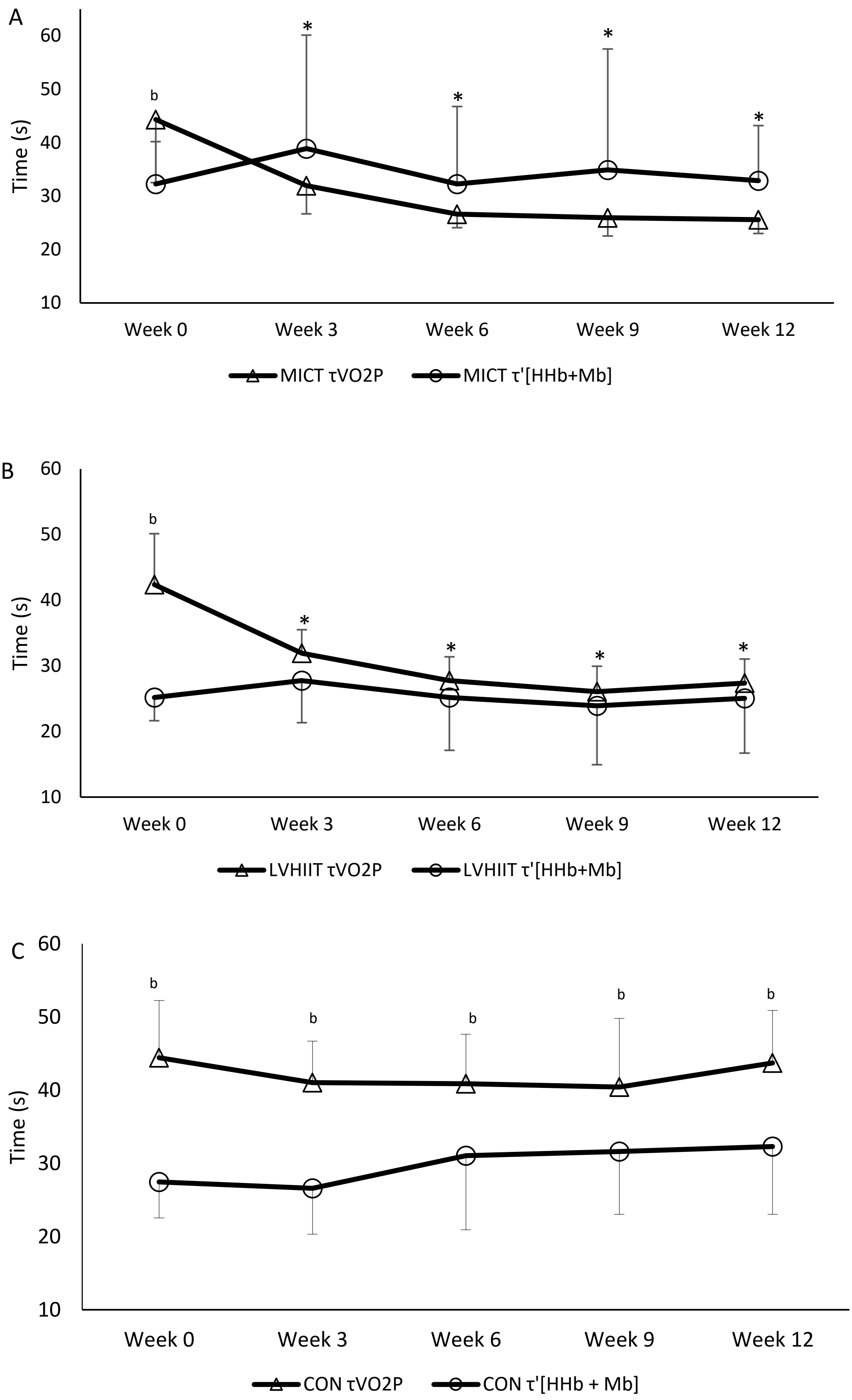

Figure 3.6. Representative plots of the group mean time course changes in $\tau\dot{V}O_{2P}$ and τ' [HHb + Mb] during MOD A. Panels A-C represent the MICT, LVHIIT and CON groups respectively. *infers MOD A $\tau\dot{V}O_{2P}$ significantly different from week 0 (P < 0.05). [b] signifies $\tau\dot{V}O_{2P}$ significantly different from τ' [HHb + Mb} (*P* < 0.05).

3.3.3.3. Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratios

The overall Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio responses for the MICT, CON and LVHIIT groups are shown in Table 3.8. and representative plots can be seen in Fig. 3.5., Fig. 3.6. and Fig. 3.7. Respectively. After 3 weeks of LVHIIT and MICT the Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio of MOD A was significantly lower than week 0 and remained so for the rest of the intervention period. However, the Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio was not affected in the CON group.

Table 3.7. Δ ***[HHb + Mb]/Δ$\dot{V}O_2$ ratios during the intervention period in the MICT, LVHIIT and CON groups.***

	Week 0	**Week 3**	**Week 6**	**Week 9**	**Week 12**	*P Value*		
Δ[HHb + Mb]/Δ$\dot{V}O_2$						Time effect	Group effect	Time x Group
MICT	1.15 (0.08)	1.04 (0.10)$^{*\#}$	1.05 (0.09)$^{*\#}$	1.04 (0.06)$^{*\#}$	1.02 (0.06)$^{*\#}$			
LVHIIT	1.20 (0.08)	1.06 (0.06)$^{*\#}$	1.06 (0.05)$^{*\#}$	1.03 (0.06)$^{*\#}$	1.02 (0.06)$^{*\#}$	0.001	0.007	0.007
CON	1.12 (0.05)	1.17 (0.14)	1.14 (0.10)	1.16 (0.05)	1.15 (0.11)			

Data are mean (SD). * Significantly different to week 0 ($P < 0.05$); # significantly different to CON ($P < 0.05$).

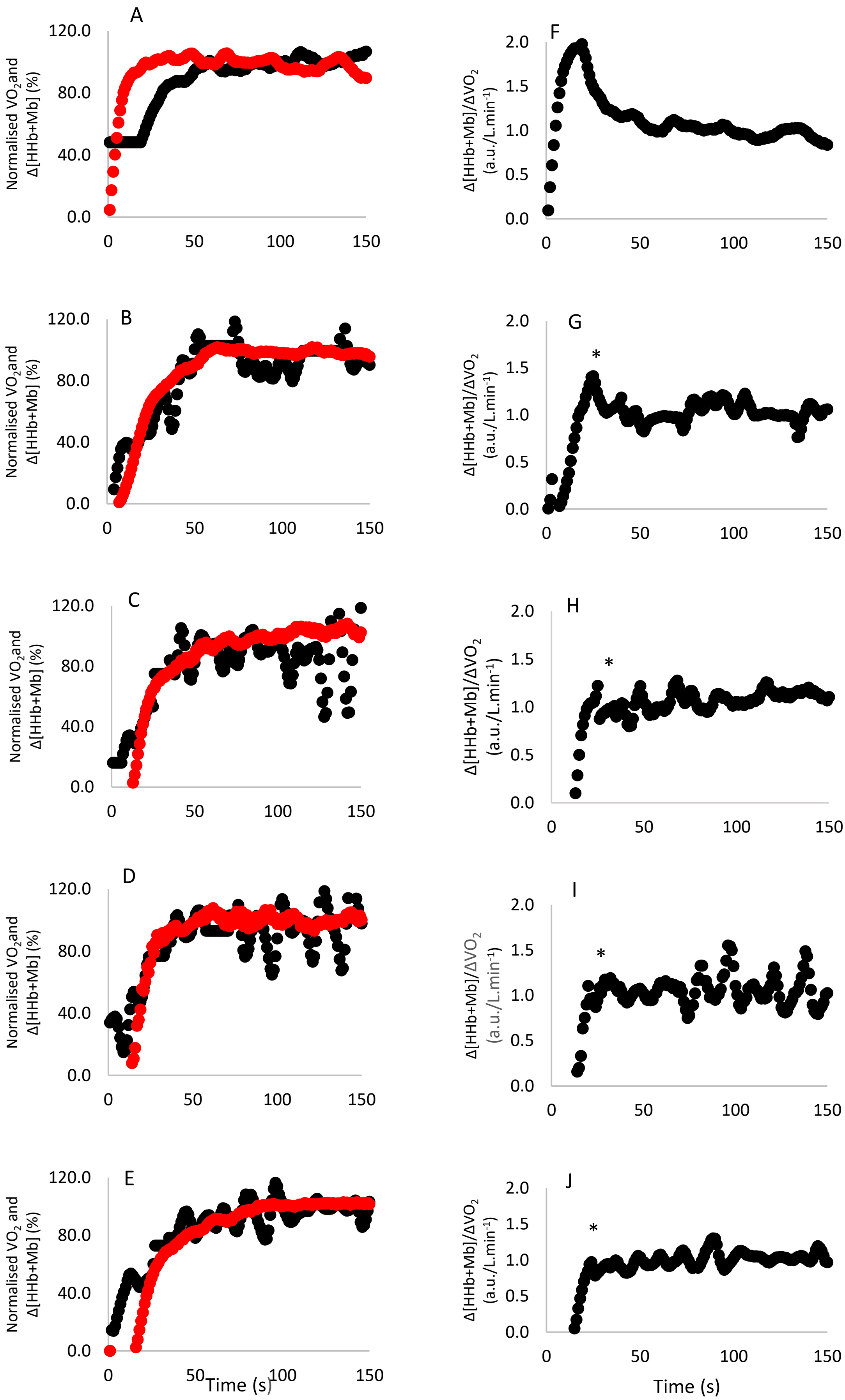

Fig 3.7. Right panels; Representative profile from the MICT group for the adjustment of deoxygenated haemoglobin concentration ([HHb+Mb]; red) and oxygen uptake ($\dot{V}O_{2P}$) (black) during the initial 150s of MOD A at week 0 (A), week 3 (B), week 6 (C), week 9 (D) and week 12 (E). Left panels; Representative profile from the MICT group for the adjustment of Δ[HHb]/$\Delta\dot{V}O_{2P}$ (black) during the initial 150 s of MOD A at week 0 (F), week 3 (G), week 6 (H),and week 9 (I) week 12 (J). a.u., Arbitrary units. *Δ[HHb+Mb]/$\Delta\dot{V}O_{2P}$ significantly lower than week 0 (*P* < 0.05).

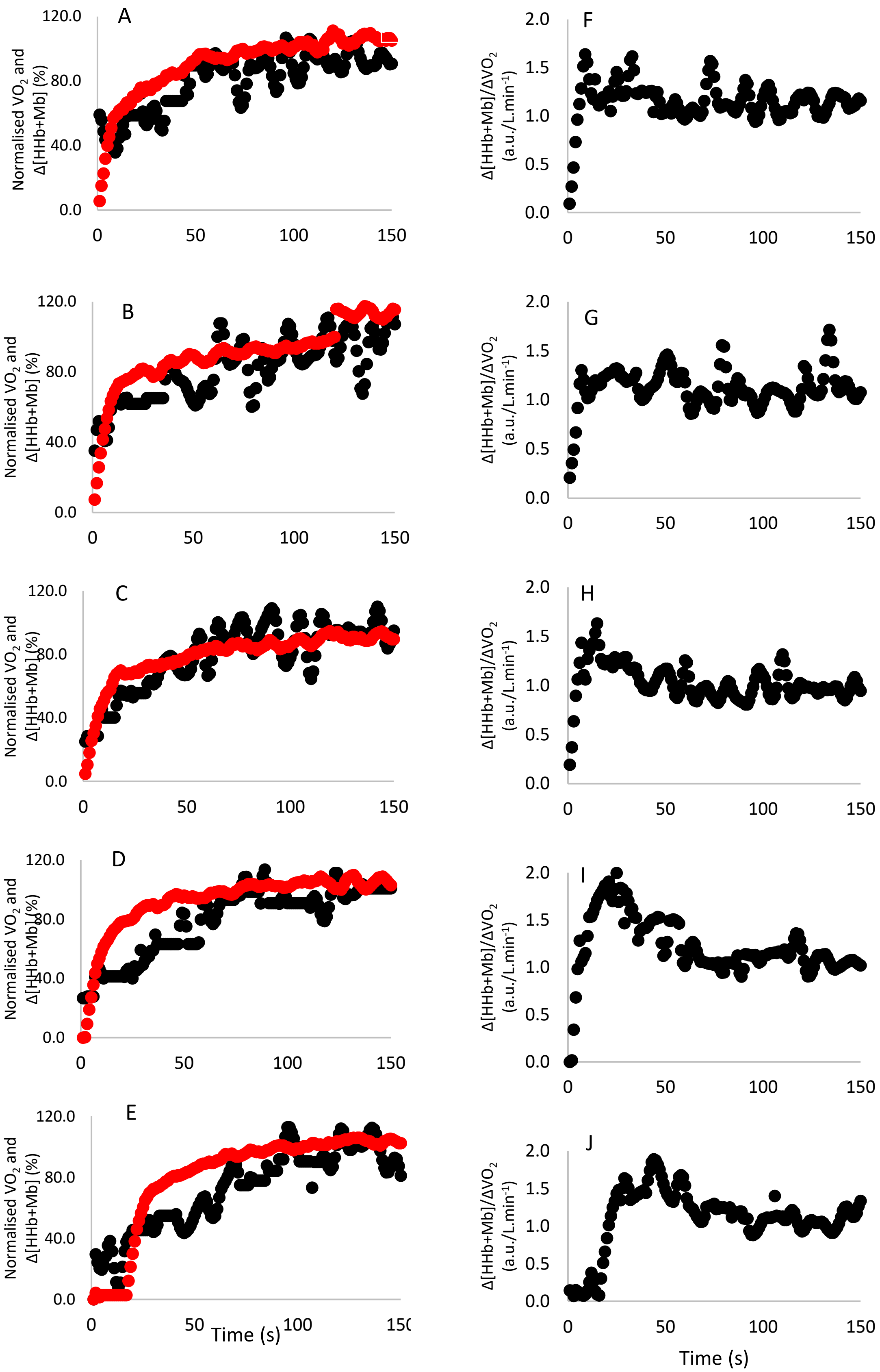

Fig 3.8. Right panels; Representative profile from the CON group for the adjustment of deoxygenated haemoglobin concentration ([HHb+Mb]; red) and oxygen uptake ($\dot{V}O_{2P}$) (black) during the initial 150s of MOD A at week 0 (A), week 3 (B), week 6 (C), week 9 (D) and week 12 (E). Left panels; Representative profile from the MICT group for the adjustment of Δ[HHb]/Δ$\dot{V}O_{2P}$ (black) during the initial 150 s of MOD A at week 0 (F), week 3 (G), week 6 (H),and week 9 (I) week 12 (J). a.u., Arbitrary units.

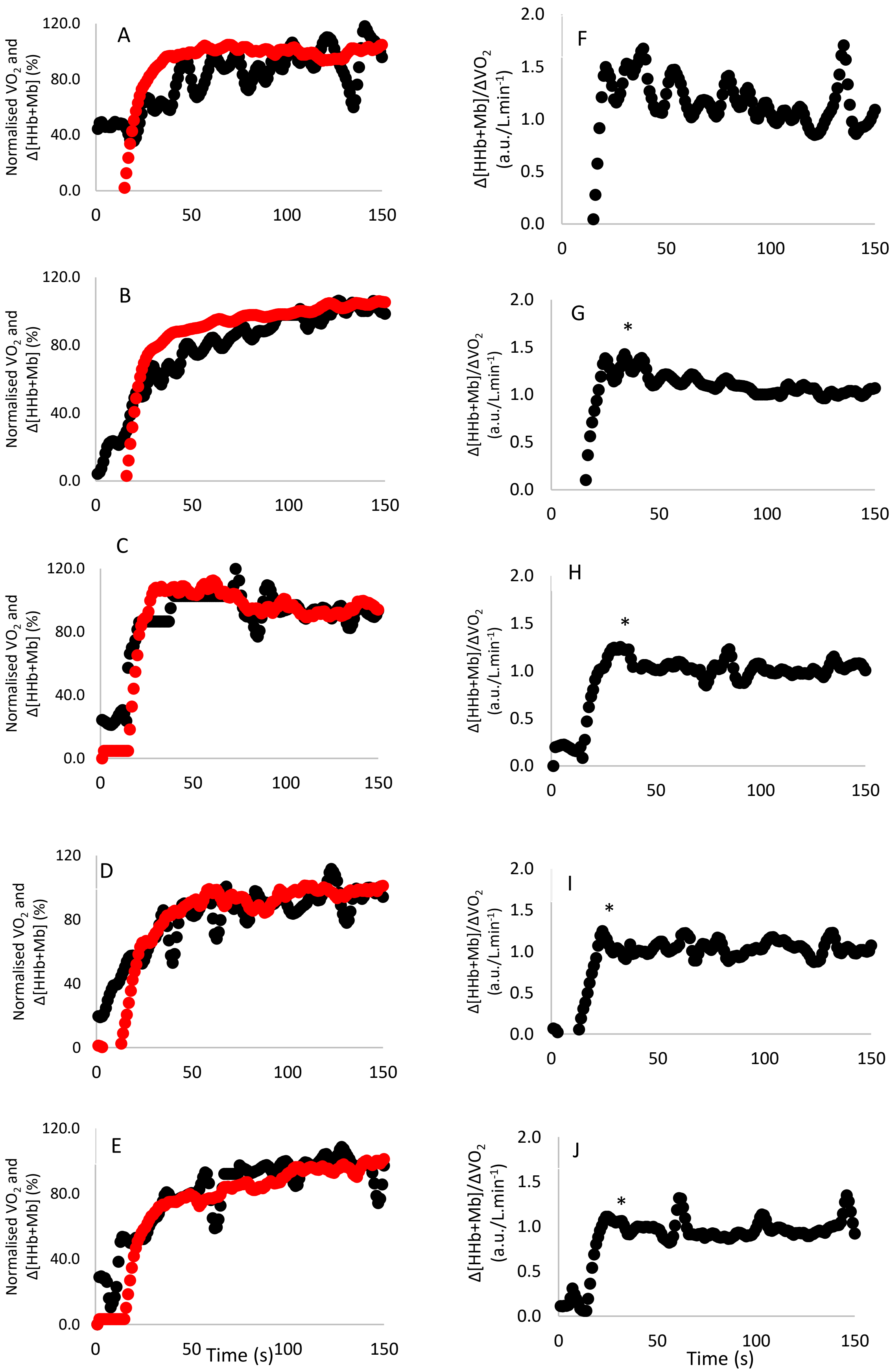

Fig 3.9. Right panels; Representative profile from the LVHIIT group for the adjustment of deoxygenated haemoglobin concentration ([HHb+Mb]; red) and oxygen uptake ($\dot{V}O_{2P}$) (black) during the initial 150s of MOD A at week 0 (A), week 3 (B), week 6 (C), week 9 (D) and week 12 (E). Left panels; Representative profile from the MICT group for the adjustment of Δ[HHb]/Δ$\dot{V}O_{2P}$ (black) during the initial 150 s of MOD A at week 0 (F), week 3 (G), week 6 (H),and week 9 (I) week 12 (J). a.u., Arbitrary units. *Δ[HHb+Mb]/Δ$\dot{V}O_{2P}$ significantly lower than week 0 (*P* < 0.05).

3.3.3.4. Heart rate Kinetics.

Parameter responses for HR kinetics are shown in Table 3.9. The amplitude of the HR response significantly decreased after 6 weeks of MICT and after 9 weeks of LVHIIT with no further reductions thereafter. The end exercise HR amplitude was also significantly decreased after three weeks of LVHIIT and 6 weeks of MICT. In terms of τHR, there was a significant reduction in τHR after three weeks of MICT and after 6 weeks of LVHIIT with no further changes until week 12. No changes in amplitude or the time constant in HR were observed in the CON group throughout the study period

Table 3.8. ***Mean parameter estimates for heart rate kinetics during the intervention period in the MICT, LVHIIT and CON groups.***

	Week 0	**Week 3**	**Week 6**	**Week 9**	**Week 12**	*P value*		
HR baseline (beats.min^{-1})						Time effect	Group effect	Time x Group
MICT	103 (15)	98 (11)	97 (14)	96 (14)	95 (13)			
LVHIIT	100 (10)	97 (10)	93 (8)	94 (9)	94 (7)	<0.001	0.86	0.53
CON	98 (10)	98 (10)	97 (11)	98 (12)	94 (11)			
HR A (beats.min^{-1})								
MICT	23 (6)	22 (6)	20 (6)*#	19 (5)*	17 (6)*‡			
LVHIIT	30 (7)[a]	27 (5)	26 (6)[a]	25 (6)*	25 (5)*	0.003	0.05	0.001
CON	24 (7)	24 (5)	25 (4)	26 (3)	24 (5)			
HR End A (beats.min^{-1})								
MICT	126 (17)	120 (11)[a]	116 (14)*	115 (14)*	113 (13)*‡			
LVHIIT	131 (12)	124 (11)*	119 (8)*	118 (8)*	119 (8)*	<0.001	0.81	0.06
CON	122 (9)	121 (13)	122 (13)	124 (14)	118 (14)			
τHR (s)								
MICT	70 (17)	47 (12)*	44 (11)*	47 (18)*	38 (10)*			
LVHIIT	78 (31)	69 (29)	52 (21)*‡	47 (13)*‡	50 (12)*‡	0.003	0.90	0.06
CON	55 (27)	54 (17)	67 (40)	59 (30)	63 (19)			

Data are mean (SD). HR, heart rate A, amplitude; τ, time constant of the primary response * significantly different from week 0 (*P* < 0.05); ‡ significantly different from week 3 (*P*<0.05).

3.3.4. Effect of priming exercise on physiological responses during moderate-intensity exercise.

3.3.4.1. $\dot{V}O_2$ kinetics.

At week 0 a prior bout of PE significantly reduced $\tau\dot{V}O_{2P}$ in all 3 groups (Table 3.10, Fig. 3.8). However, after 3 weeks of both LVHIIT and MICT training, PE no longer had an effect on any $\dot{V}O_2$ kinetic parameter during moderate-intensity exercise in the LVHIIT and MICT groups and this was maintained until the end of the intervention (Fig. 3.8). PE continued to significantly reduce $\tau\dot{V}O_{2P}$ in the CON group at all time points. No changes in any $\dot{V}O_2$ kinetics parameter of the MOD B bout were observed with training in any of the groups (Table 3.10). Power outputs utilised during the priming exercise and moderate-intensity bouts are shown in Table 3.5.

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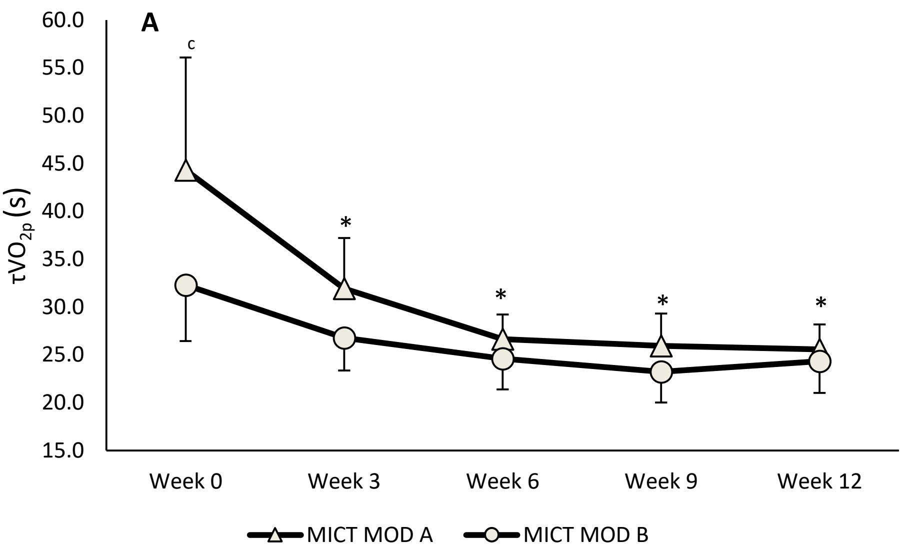
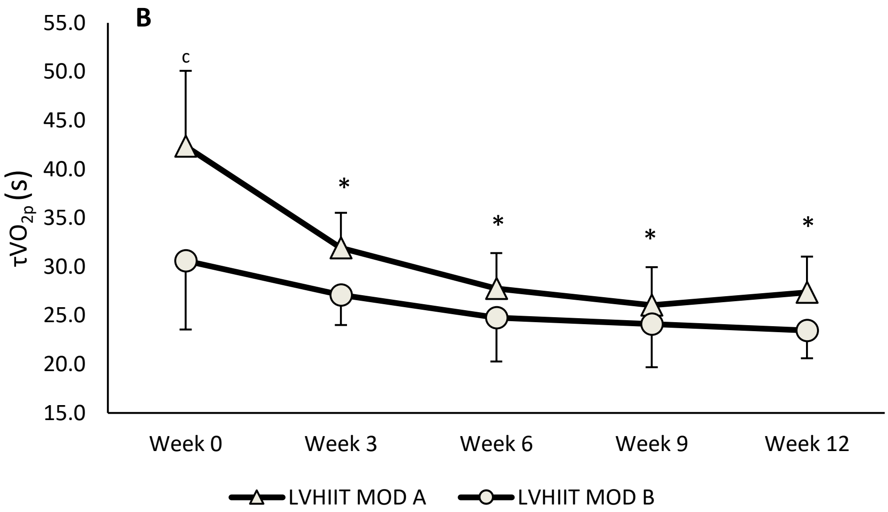
Table 3.9. ***Mean parameter estimates for $\dot{V}O_2$ kinetics for all groups throughout the intervention period.***

	Week 0		Week 3		Week 6		Week 9		Week 12		*P value*			
$\dot{V}O_2$ A (L.min^{-1})	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	Time effect	Group effect	Priming effect	Time x group x priming
MICT	0.7 (0.3)	0.7 (0.3)	0.6 (0.3)	0.6 (0.2)	0.7 (0.2)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	0.6 (0.3)				
LVHIIT	0.9 (0.4)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.8 (0.2)	0.8 (0.3)	0.8 (0.3)	0.87	<0.001	0.77	0.98
CON	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.5 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)				
$\dot{V}O_2$ End A (L.min^{-1})														
MICT	1.7 (0.4)	1.7 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	1.5 (0.4)	1.6 (0.4)				
LVHIIT	1.7 (0.4)	1.7 (0.4)	1.6 (0.3)	1.7 (0.3)	1.6 (0.3)	1.7 (0.3)	1.6 (0.3)	1.6 (0.3)	1.6 (0.3)	1.7 (0.3)	0.83	<0.001	0.49	1
CON	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)	1.3 (0.3)	1.4 (0.3)	1.1 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)				
$\tau\dot{V}O_{2P}$ (s)														
MICT	45 (12)	31 (5)[c]	33 (5)*[#]	27 (3)	29 (11)*[#]	25 (2)	26 (4) *[#]	23 (2)	26 (4) *[#]	24 (3)				
LVHIIT	42 (8)	31 (7)[c]	32 (4)*[#]	27 (3)	28 (4)*[#]	24 (5)	26 (4) *[#]	24 (4)	27 (4) *[#]	24 (3)	<0.0001	<0.0001	<0.0001	<0.001
CON	43 (7)	31 (5)[c]	41 (6)	29 (4)[c]	41 (7)	31 (6)[c]	40 (8)	32 (6)[c]	45 (7)	32 (6)[c]				
$\dot{V}O_2$ gain (mL.min^{-1}.W^{-1})														
MICT	10.7 (2.0)	10.6 (1.8)	9.0 (2.0)	9.4 (1.5)	9.9 (1.8)	10.0 (1.3)	9.5 (1.2)	9.5 (1.6)	9.7 (1.2)	9.6 (1.6)				
LVHIIT	10.8 (2.4)	9.7 (1.9)	9.2 (1.5)	9.6 (1.6)	9.9 (1.0)	10 (1.4)	9.4 (1.5)	9.0 (0.9)	10.6 (1.5)	9.9 (0.9)	0.51	0.15	0.33	0.12
CON	10.2 (1.8)	9.8 (0.9)	10.5 (0.9)	9.8 (1.1)	10.5 (1.1)	9.5 (1.7)	9.8 (0.4)	10.0 (1.1)	10.3 (0.8)	9.8 (0.7)				

Data are mean (SD). $\dot{V}O_2$, oxygen uptake; A, amplitude; τ, time constant of the primary response* significantly different to week 0 (P <0.05); [c] significantly different to MOD A (P < 0.05). [#]significantly different from CON (P<0.05).





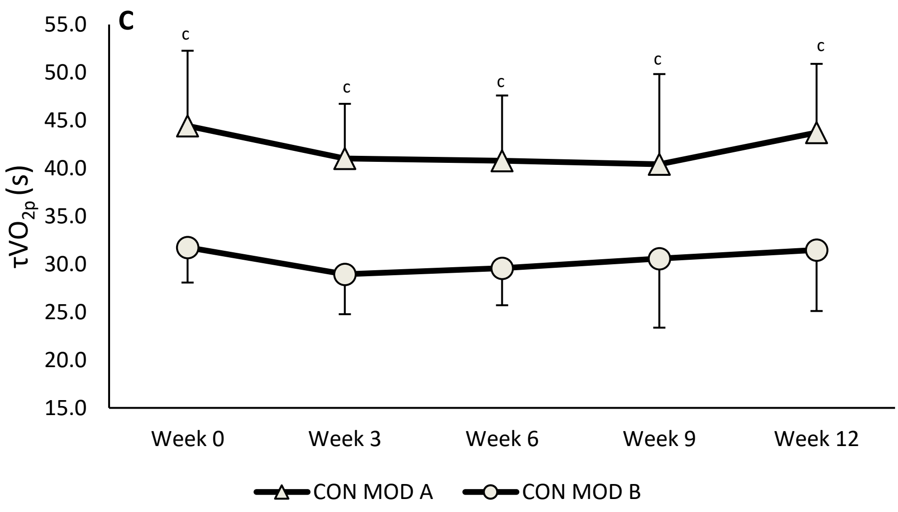


Figure 3.10. Illustration of the time course changes in $\tau\dot{V}O_{2P}$ during MOD A and MOD B with training. Panels A-C represent the MICT, LVHIIT and CON groups respectively. [c] MOD A significantly different from MOD B (P < 0.05). *MOD A significantly different from week 0 (*P* < 0.05).

3.3.4.2. Muscle deoxygenation kinetics and Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratios.

Kinetic parameters for [HHb + Mb] kinetics response profiles are displayed in Table 3.11. There was no effect of PE on any [HHb + Mb] kinetics parameters in any group throughout the training period. The responses in Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratios for the MICT, CON and LVHIIT groups are shown in Table 3.12. The Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio was significantly reduced with priming exercise at week 0 in all three groups. In the CON group this PE induced reduction in the Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio was maintained at all time points while in the LVHIIT and MICT groups the Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio of MOD A and MOD B were not significantly different at week 3, 6, 9, and 12. At baseline, PE reduced τ$\dot{V}O_{2p}$ to the extent that it was no longer different to τ'[HHb + Mb] in all groups, however, this effect was no longer evidenced in the LVHIIT and MICT groups beyond 3 weeks of training (results not shown).

Table 3.10. ***Mean parameter estimates for [HHb + Mb] kinetics for all groups throughout the intervention period.***

	Week 0		Week 3		Week 6		Week 9		Week 12		*P Value*			
[HHb+Mb] A (a.u)	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	Time effect	Group effect	Priming effect	Time x group x priming
MICT	79 (38)	92 (60)	103 (57)	106 (54)	95 (57)	98 (42)	93 (52)	86 (51)	79 (34)	95 (36)				
LVHIIT	141 (104)	153 (150)	157 (103)	172 (123)	151 (101)	152 (118)	160 (103)	175 (141)	169 (120)	154 (124)	0.91	<0.0001	0.35	0.99
CON	73 (65)	77 (60)	71 (54)	89 (68)	40 (79)	77 (54)	68 (55)	76 (63)	78 (52)	75 (56)				
[HHb+Mb] End A (a.u)														
MICT	40 (73)	73 (118)	33 (79)	32 (77)	192 (109)	149 (81)	13 (80)	20 (61)	82 (84)	167 (75)				
LVHIIT	99 (109)	162(196)	117 (91)	159 (135)	93 (102)	97 (103)	107 (105)	155 (144)	88 (115)	128 (97)	0.38	<0.0001	0.02	0.99
CON	33 (80)	52 (84)	21 (66)	76 (84)	95 (88)	45 (65)	46 (102)	69 (76)	139 (64)	103 (51)				
TD[HHb+Mb] (s)														
MICT	14 (4)	12 (4)	18 (6)	14 (4)	17 (7)	14 (4)	18 (10)	15 (6)	18 (6)	15 (5)				
LVHIIT	14 (2)	13 (6)	15 (4)	12 (3)	14 (3)	13 (4)	13 (5)	12 (4)	15 (3)	13 (4)	0.24	0.08	0.05	0.87
CON	16 (2)	17 (8)	15 (2)	12 (3)	14 (4)	13 (3)	15 (2)	14 (4)	17 (7)	16 (8)				
τ[HHb+Mb] (s)														
MICT	19 (11)	20 (10)	21 (17)	19 (10)	16 (10)	17 (10)	17 (14)	15 (6)	15 (6)	18 (10)				
LVHIIT	11 (4)	19 (9)	13 (6)	15 (6)	11 (7)	14 (7)	11 (6)	12 (4)	10 (6)	14 (9)	0.97	0.01	0.43	0.98
CON	13 (5)	13 (3)	12 (6)	14 (3)	18 (12)	19 (10)	17 (9)	16 (6)	15 (7)	17 (5)				
τ ' [HHb+Mb] (s)														
MICT	32 (8)	32 (11)	39 (21)	33 (9)	32 (15)	30 (11)	35 (22)	31 (6)	33 (10)	33 (10)				
LVHIIT	25 (4)	32 (12)	28 (6)	26 (5)	25 (8)	27 (8)	24 (9)	24 (5)	25 (8)	27 (12)	0.69	0.002	0.81	0.98
CON	28 (5)	30 (6)	27 (6)	26 (5)	32 (9)	32 (9)	32 (9)	29 (8)	32 (9)	33 (9)				

Data are mean (SD). [HHb+Mb], deoxygenated haemoglobin concentration; A, amplitude; TD, time delay; τ, time constant of the primary response; τ' [HHb + Mb], effective time constant.

Table 3.11. Δ *[HHb + Mb]/Δ$\dot{V}O_2$ ratios throughout the intervention period in the MICT, LVHIIT and CON groups.*

	Week 0		**Week 3**		**Week 6**		**Week 9**		**Week 12**		*P value*			
Δ[HHb+Mb]/Δ$\dot{V}O_2$	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	Time effect	Group effect	Priming effect	Time x Group x Priming
MICT	1.15 (0.08)	1.06 (0.10)^{c}	1.04 (0.1)*$^{\#}$	1.01 (0.06)	1.05 (0.09)*$^{\#}$	0.97 (0.10)	1.04 (0.06)*$^{\#}$	1.03 (0.05)	1.02 (0.06)*$^{\#}$	0.98 (0.07)				
LVHIIT	1.20 (0.08)	1.04 (0.06)^{c}	1.06 (0.06)*$^{\#}$	1.02 (0.06)	1.06 (0.05)*$^{\#}$	1.04 (0.07)	1.03 (0.06)*$^{\#}$	1.05 (0.03)	1.02 (0.06)*$^{\#}$	1.05 (0.07)	0.003	<0.001	<0.001	0.02
CON	1.12 (0.05)	1.01 (0.06)^{c}	1.17 (0.14)	1.08 (0.04)^{c}	1.14 (0.10)	1.03 (0.08)^{c}	1.16 (0.05)	1.03 (0.05)^{c}	1.15 (0.11)	0.99 (0.15)^{c}				

Data are mean (SD). [HHb+Mb], deoxygenated haemoglobin concentration * significantly different to week 0 (*P*<0.05); $^{\#}$ significantly different to CON (*P*<0.05); ^{c} significantly different from MOD A (*P* < 0.05).

3.3.4.3. Heart rate Kinetics.

Parameter responses for HR kinetics during MOD A and MOD B are shown in Table 3.13. There was no effect of PE on any HR parameter at baseline or during the intervention period in any group during MOD A or MOD B.

Table 3.12. ***Mean parameter estimates for heart rate kinetics for all groups throughout the intervention period.***

	Week 0		Week 3		Week 6		Week 9		Week 12		P Value			
HR baseline (beats.min^{-1})	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	Time effect	Group Effect	Priming Effect	Time x Group x Priming
MICT	103 (15)	116 (14)	98 (11)	106 (13)*	97 (14)	105 (15)*	96 (14)	105 (15)*	95 (13)	106 (13)*				
LVHIIT	100 (10)	113 (9)	97 (10)	108 (9)	93 (8)	101 (9)*	94 (9)	104 (10)*	94 (7)	101 (7)*	0.62	0.21	0.90	0.28
Control	98 (10)	110 (9)	98 (10)	107 (9)	97 (11)	109 (8)	98 (12)	110 (14)	94 (11)	106 (15)				
HR A (beats.min^{-1})														
MICT	23 (6)	20 (5)	22 (6)	19 (6)	20 (6)*	18 (6)	19 (5)*	17 (6)	17 (6)*‡	15 (5)				
LVHIIT	30 (7)	27 (7)	27 (5)	25 (4)	26 (6)	26 (5)	25 (6)*	25 (5)	25 (5)*	24 (5)	0.48	<0.001	<0.001	0.53
Control	24 (7)	23 (4)	24 (5)	24 (5)	25 (4)	24 (5)	26 (3)	24 (5)	24 (5)	24 (7)				
HR End A (beats.min^{-1})														
MICT	126 (17)	135 (15)	120 (11)	125 (13)*	116 (14)*	123 (15)*	115 (14)*	122 (14)*	113 (13)*‡	121 (14)*				
LVHIIT	131 (12)	139 (10)	124 (11)*	133 (10)	119 (8)*	127 (7)*	118 (8)*	129 (6)*	119 (8)*	125 (7)*	0.65	0.09	0.57	0.31
Control	122 (9)	134 (9)	121 (13)	131 (10)	122 (13)	133 (11)	124 (14)	135 (16)	118 (4)	129 (17)				
τHR (s)														
MICT	70 (17)	76 (19)	47 (12)*	55 (22)*	44 (11)*	53 (15)*	47 (18)*	50 (18)*	38 (10)*	45 (22)*				
LVHIIT	78 (31)	66 (22)	69 (29)	56 (15)	52 (21)*‡	49 (15)*	47 (13)*‡	46 (13)*	50 (12)*‡	45 (14)*	0.05	0.62	0.008	0.99
Control	55 (27)	54 (13)	54 (17)	59 (21)	67 (40)	63 (21)	59 (30)	59 (23)	63 (19)	62 (21)				

Data are mean (SD). HR, heart rate; A, amplitude; τ, time constant of the primary response * significantly different from week 0 ($P < 0.05$); ‡ significantly different from week 3 ($P < 0.05$).

3.4. Discussion.

The aim of the current study was to compare the effects of MICT and LVHIIT on the time course and mechanism of adaptation of $\dot{V}O_2$ and muscle deoxygenation kinetics during moderate-intensity exercise in individuals with uncomplicated T2DM. In addition, a secondary aim of this study was to investigate the effect of LVHIIT and MICT on the effects of priming exercise on $\dot{V}O_2$ and [HHb + Mb] kinetics during moderate-intensity exercise. The primary findings were that:

1. Both LVHIIT and MICT significantly reduced the length of the $\dot{V}O_2$ kinetics response during a bout of moderate-intensity cycling exercise by a similar magnitude after only three weeks of training with no further changes thereafter.
2. The primary mechanism underlying the speeding of $\dot{V}O_2$ kinetics with training appears to be an improved matching in local O_2 delivery to utilisation as reflected by a significant reduction in the Δ [HHb + Mb]/$\Delta\dot{V}O_2$ ratio after 3 weeks of training.
3. PE significantly reduced the $\tau\dot{V}O_{2P}$ of a subsequent bout of moderate-intensity cycling exercise in the CON group throughout the study period; but PE did not reduce $\tau\dot{V}O_{2P}$ in the 2 exercising groups beyond 3 weeks of training.

3.4.1. Time course adaptation of $\dot{V}O_2$ kinetics in response to LVHIIT and MICT.

To our knowledge this is the first study that looked at the time course changes in $\dot{V}O_2$ kinetics with training in individuals with uncomplicated T2DM following both LVHIIT and MICT. LVHIIT and MICT reduced $\tau\dot{V}O_{2P}$ by 26% and 24% respectively after just 3 weeks of training, which was accompanied by a significant reduction in the Δ [HHb+Mb]/$\Delta\dot{V}O_2$ ratio. This was due to a significant reduction in $\tau\dot{V}O_{2P}$ and no change in τ' [HHb+Mb] with training which is indicative of an improvement in local O_2 delivery/perfusion and therefore an improved matching of O_2 delivery and utilisation. The total % reduction in $\tau\dot{V}O_{2P}$ after 12 weeks of training was 42% and 36% in the MICT and LVHIIT groups respectively. Regarding the MICT intervention, our findings are consistent with previous studies that reported a positive influence of MICT on $\dot{V}O_2$ kinetics in uncomplicated T2DM. For instance Brandenburg *et al.* (1999) reported a 28% reduction in $\tau\dot{V}O_{2P}$ when cycling at an absolute intensity of 50W after 12 weeks of MICT (3 days per week, 50 mins at 70-85% HRmax) in a group of women with uncomplicated T2DM (Brandenburg *et al.* 1999). More recent work from our laboratory has shown that 12 weeks of combined moderate-intensity aerobic and resistance exercise resulted in a 45% decrease in $\tau\dot{V}O_{2P}$ in men and women with uncomplicated T2DM during cycling exercise at a similar relative intensity to the current study (80% VT) (MacAnaney *et al.* 2012). The results of the present study extend the current body of knowledge by firstly providing evidence for a potential mechanism for the improvement in $\tau\dot{V}O_{2P}$ with training and secondly, providing an insight into the time course of the adaptation of $\tau\dot{V}O_{2P}$ in response to MICT.

Recent advances with NIRS have allowed for the continuous assessment of muscle deoxygenation during cycling exercise which can be used as an indicator for the matching of local microvascular O_2 delivery to muscle O_2 utilization (DeLorey *et al*. 2004). Indeed, recent work from our laboratory and others has used this technique to show that in T2DM there is an over reliance on O_2 extraction and an impairment in microvascular blood flow at the onset of exercise which results in a mismatch in O_2 delivery and utilisation as reflected by an exaggerated Δ [HHb+Mb]/$\Delta\dot{V}O_2$ ratio (>1.0) (Bauer *et al.* 2007; Rocha *et al.* 2016). In the present study, we showed that after 3 weeks of MICT the overshoot in Δ [HHb+Mb]/$\Delta\dot{V}O_2$ ratio was significantly reduced to the extent that it was almost abolished. In addition, the $\tau\dot{V}O_{2P}$ and τ'[HHb+Mb] during moderate-intensity exercise were almost identical after three weeks of training which is indicative of faster rate of O_2 delivery than O_2 extraction. Our findings are similar to that of Murias *et al.* (2011), who reported a significant reduction in $\tau\dot{V}O_{2P}$ as well as Δ[HHb+Mb]/$\Delta\dot{V}O_2$ ratios in older healthy males who presented with a slowed initial $\tau\dot{V}O_{2P}$ (43 ± 10 s) after 3 weeks of their 12 week MICT intervention (Murias *et al.* 2011).

In regard to LVHIIT, this is the first study to show that LVHIIT speeds $\dot{V}O_2$ kinetics during moderate-intensity exercise in individuals with T2DM. Although there is a dearth of evidence looking at LVHIIT and $\dot{V}O_2$ kinetics in T2DM, our results are consistent with findings observed in young healthy males (McKay *et al.* 2009; Williams *et al.* 2013). For instance, McKay *et al*. (2009) reported a significant 38% decrease in $\tau\dot{V}O_{2P}$ after only 8 sessions of LVHIIT in a group of young healthy males (McKay *et al*. 2009) while Williams *et al*. (2013) reported a significant 40% decrease in $\tau\dot{V}O_{2P}$ after 4 weeks of training (Williams *et al*. 2013). Interestingly both McKay *et al*. (2009) and Williams *et al*. (2013) reported that with training $\tau\dot{V}O_{2P}$ decreased to such an extent that it was similar to τ'[HHb+Mb] by the end of the study period which suggests that LVHIIT improved the local matching of O_2 delivery and utilisation. Similarly, in the present study we observed no difference between τ'[HHb+Mb] and $\tau\dot{V}O_{2P}$ by week 3 of LVHIIT which resulted in an overall reduction of the Δ[HHb+Mb]/$\Delta\dot{V}O_2$ ratios which is indicative that LVHIIT improved the localised matching of O_2 delivery to utilisation.

In the present study we observed a significant reduction in $\tau\dot{V}O_{2P}$ after 3 weeks which was maintained until the completion of 12 weeks of LVHIIT and MICT; and that the reductions were of a similar magnitude. This has great significance as LVHIIT only requires 50% of the weekly time commitment as MICT (90 mins vs 180 mins). Furthermore, it appears that the mechanisms of adaptation of the two interventions are similar. In the present study there was a significant reduction in the Δ[HHb+Mb]/$\Delta\dot{V}O_2$ ratios at the onset of exercise after 3 weeks of LVHIIT and MICT which suggests both interventions improved the local microvascular matching of O_2 delivery and utilisation. However, the mechanisms of this improvement in O_2 delivery remain unclear. Previous studies in T2DM have shown that both LVHIIT and MICT are effective at improving vascular function and endothelial health as measured by FMD (Maoirana *et al.* 2001; Schreuder *et al* 2015; Madsen *et al.* 2015; Francois *et al.* 2017) and that the mechanisms of this improvement in vascular function with exercise seem to be induced by an increased bioavailability of NO due to the chronic shear stress within the vasculature during exercise (Mitranun *et al*. 2014) and an exercise-induced reduction in local oxidative stress (Taddei *et al.* 2004). In addition, exercise training has shown to be effective at increasing skeletal muscle capillarisation which increases the total surface area for diffusion of O_2 into the myocyte (Hepple *et al.* 2000; Jensen *et al*. 2004). Despite this evidence, studies exploring vascular adaptations following LVHIIT or MICT during exercise in T2DM are lacking.

Although the present study has provided evidence for the enhancement of local O_2 delivery as the primary mechanism for the improvement in $\dot{V}O_2$ kinetics in T2DM, it is likely that improvements in mitochondrial oxidative capacity may have also contributed to these effects. For instance, it is evident that people with T2DM present with reduced mitochondrial function and protein content (Kelley *et al.* 2002; Ritov *et al*. 2005). Moreover, there is ample evidence to suggest that MICT is effective at increasing mitochondrial oxidative capacity, number and enzyme activity in T2DM (Toledo *et al*. 2007; Pheilix *et al*. 2010). More recently, Little *et al.* (2011) showed that 2 weeks of LVHIIT significantly increased CS activity in a group of individuals with uncomplicated T2DM (Little *et al.* 2011). Furthermore, studies from healthy populations have indicated that LVHIIT can increase the activity of PGC-1α (thought to be a key regulator of mitochondrial biogenesis) by up to 50% (Hood *et al.* 2011; Gibala *et al.* 2012). Therefore, we cannot exclude the possibility that changes in skeletal muscle mitochondria may have been, at least in part, responsible for the observed adaptations in $\dot{V}O_2$ kinetics in response to LVHIIT and MICT.

3.4.2. Effect of priming exercise on $\dot{V}O_2$ kinetics during moderate-intensity exercise.

Regarding baseline adaptations (i.e. week 0), in the present study priming exercise significantly reduced the $\tau\dot{V}O_{2P}$ of a subsequent bout of moderate-intensity exercise in the all three groups (MICT, 44 ± 12 s vs 31 ± 5 s; LVHIIT, 42 ± 8 s vs 31 ± 7s; CON, 43 ± 7 s vs 31 ± 5 s). The underlying mechanism of this improvement appears to be an improved matching of O_2 utilisation and delivery as reflected by a significant decrease in the Δ[HHb+Mb]/$\Delta\dot{V}O_{2P}$ ratio which is an index of the degree of O_2 extraction required for a given increase in $\dot{V}O_2$ (Murias *et al.* 2010; DeRoia *et al.* 2012). Moreover, at this baseline time point post-priming $\tau\dot{V}O_{2P}$ in all three groups was no longer significantly different than τ'[HHb+Mb] (during the 'unprimed' condition $\tau\dot{V}O_{2P}$ was significantly longer than τ'[HHb+Mb]) which is indicative of improved matching of O_2 utilisation and delivery.

The findings of the current study are in line with previous work from our laboratory that showed that in T2DM, PE significantly reduces the $\tau\dot{V}O_{2P}$ of a subsequent bout of moderate-intensity exercise which was accompanied by a near significant reduction in the $\Delta[HHb+Mb]/\Delta\dot{V}O_2$ ratio ($P = 0.06$) (Rocha *et al.* 2016). Moreover, the results of the present study are consistent with results from studies performed in young healthy individuals presenting with a 'slow' initial $\dot{V}O_2$ kinetics ($\tau\dot{V}O_{2P} > 25s$) (Murias *et al.* 2011) as well as sedentary older adults (DeLorey *et al.* 2004; DeRoia *et al.* 2012) that have reported a significant reductions in $\tau\dot{V}O_{2P}$ post-PE which were accompanied by a reduction in Δ $[HHb+Mb]/\Delta\dot{V}O_2$.

Among older adults, DeLorey *et al.* (2004) reported a significant reduction in $\tau\dot{V}O_{2P}$ following priming exercise which was accompanied by a shortening in the [HHb + Mb] TD and a lengthening of the τ [HHb + Hb] (DeLorey *et al.* 2004). This is indicative of an improved matching of O_2 utilisation and delivery in the area of interrogation at the onset of exercise. Furthermore, the $\tau\dot{V}O_{2P}$ of the participants in the study of DeLorey *et al.* (2004) was markedly faster post-priming than pre-priming [HHb + Hb]τ (30 s vs 51 s) which indicates that O_2 extraction proceeded at a slower rate than O_2 delivery following priming exercise. The findings of DeLorey *et al.* (2004) were confirmed in a larger study by De Roia *et al* (2012) who reported a significant reduction in $\tau\dot{V}O_{2P}$ as well as a shortening in the [HHb + Mb]TD and a lengthening of the [HHb + Hb]τ following priming exercise in 54 elderly males (De Roia *et al* 2012). De Roia *et al.* (2012) also reported an abolishment of the marked overshoot in the Δ $[HHb + Mb]/\Delta\dot{V}O_2$ at the onset of exercise which further strengthens the notion of an improved matching of O_2 delivery and utilisation with PE.

Regarding training adaptations, after 3 weeks of either LVHIIT or MICT, PE no longer had an effect on any parameter of the $\dot{V}O_2$ or the [HHb + Mb] kinetics response in the 2 groups. However, in the CON group PE continued to significantly reduce $\tau\dot{V}O_{2p}$ compared with the 'unprimed' $\tau\dot{V}O_{2p}$ at each time point. The underlying mechanism for the diminished effect of priming exercise after training remains unclear. However, with both types of training we observed a significant reduction in the unprimed Δ $[HHb + Mb]/\Delta\dot{V}O_2$ ratios so that they were similar to the post-priming Δ $[HHb + Mb]/\Delta\dot{V}O_2$ ratios from the 3rd week of training onwards which suggests that O_2 delivery and utilisation were well matched beyond 3 weeks of training. It has been suggested that PE is most effective when an impairment in O_2 delivery is apparent (DeLorey *et al.* 2004; Murias *et al.* 2011; Rocha *et al.* 2016) or when an O_2 delivery has been constrained by postural changes (Jones *et al.* 2006; Di Menna *et al.* 2010). Therefore, it appears that O_2 delivery following both LVHIIT and MICT was improved to such an extent that PE no longer enhanced local blood flow or O_2 delivery, and thus, did not manipulate the $\dot{V}O_2$ kinetics of subsequent bout of moderate-intensity cycling exercise.

3.4.3. Conclusion.

T2DM slows the adjustment of $\dot{V}O_2$ at the beginning of moderate-intensity exercise in young and middle-aged individuals resulting in exercise intolerance. This study demonstrates that after 3 weeks of a 12 week intervention, both LVHIIT and MICT significantly reduced $\tau\dot{V}O_{2P}$ during moderate-intensity exercise in individuals with T2DM and that the benefits were of a similar magnitude. This was accompanied by a significant reduction in the Δ [HHb+Mb]/$\Delta\dot{V}O_2$ ratios in both training groups which is suggestive of an improved matching of O_2 delivery and utilisation. Furthermore, both LVHIIT and MICT abolished the acute, beneficial effects of PE on oxidative metabolism. Faster $\dot{V}O_2$ kinetics are related to improvements in exercise tolerance that may increase the willingness of those with T2DM to participate in exercise and therefore result in an increased quality of life.

Chapter 4. *Effects of MICT vs LVHIIT on oxygen uptake and muscle deoxygenation kinetics during heavy-intensity exercise initiated from an elevated baseline in type 2 diabetes.*

4.1. Introduction.

The initiation of exercise from an elevated baseline (i.e., work-to-work) rather than from rest or an 'unloaded' baseline results in a lengthening (~60%↑) of the time constant of the primary component of the $\dot{V}O_2$ kinetics response ($\tau\dot{V}O_{2P}$) (Hughson & Morrisey, 1982; Brittain *et al.* 2001; Wilkerson *et al.* 2007; Jones *et al.* 2008; DiMenna *et al.* 2008; DiMenna *et al.* 2010; Williams *et al.* 2013; Nederveen *et al.* 2017). As activities of daily living comprise of abrupt increases in metabolic rate, an understanding of the mechanisms behind this elongated $\tau\dot{V}O_{2P}$ during work-to-work exercise and interventions that may improve $\dot{V}O_2$ kinetics during work-work transitions in T2DM require investigation.

In healthy individuals, the underlying mechanism of this elongated $\tau\dot{V}O_{2P}$ remains unclear but it is likely to be linked to the intrinsic properties of the skeletal muscle fibre types recruited during 'work to work' transitions. The Henneman size principle states that skeletal muscle fibres are recruited in an orderly fashion with smaller oxidative Type I fibres recruited first before larger Type II glycolytic fibres are required (Henneman & Mendell, 1981). Therefore, when exercise is initiated from a resting or unloaded state Type I fibres are recruited to meet the lower demand for muscular force production whereas when exercise is initiated from an elevated work rate Type I fibres have already been recruited thus necessitating the recruitment of the less efficient and less oxidative Type II muscle fibres. As Type II fibres are thought to have slower $\dot{V}O_2$ kinetics than Type I fibres the net result is thought to be a prolonged $\tau\dot{V}O_{2P}$ during 'work-to-work' transitions.

Wilkerson and Jones (2007), reported that $\tau\dot{V}O_{2P}$ increased by 60% when transitioning from a moderate- to severe-intensity exercise by 150% when transitioning from a heavy- to severe-intensity exercise when compared with transitions started from an unloaded baseline (Wilkerson and Jones 2007). Interestingly, increases in $\tau\dot{V}O_{2P}$ durations where accompanied by significant increases in iEMG activity during the transition to the higher intensity bouts, thus, suggesting an increase in motor unit recruitment. Furthermore, Jones *et al.*

(2008) reported a significant increase in the time course of PCr breakdown and higher fundamental gain of PCr during the work-to-work transition compared with that observed during transitions from rest i.e. there was a greater fall in PCr during the 'work-to-work' transition (Jones *et al.* 2008). This is indicative of a greater proportional involvement of muscle fibre types that are positioned higher in the recruitment hierarchy (Jones *et al.* 2006).

A limited number of published studies have investigated the effects of PE on $\dot{V}O_2$ kinetics parameters during a subsequent work to work transition in active healthy young individuals (Di Menna *et al.* 2008; DiMenna *et al*. 2010). Di Menna *et al.* (2008), reported no shortening of $\tau\dot{V}O_{2P}$ during a transition to high-intensity cycling from an elevated baseline post PE but, they did observe a significant decrease in the $\dot{V}O_{2SC}$ amplitude post-priming resulting in a significant decrease in the mean response time of the overall $\dot{V}O_2$ kinetics response (Di Menna *et al.* 2008). Later work by the same group reported a significant reduction in $\tau\dot{V}O_{2P}$ when high-intensity cycling exercise was initiated from a moderate-intensity baseline in the supine position subsequent to a bout of heavy-intensity PE (DiMenna *et al*. 2010). More recently, Gildea *et al.* (2018) reported that in individuals with uncomplicated T2DM, heavy PE significantly reduced the $\dot{V}O_{2SC}$ of a subsequent bout of heavy-intensity cycling exercise initiated from an elevated baseline which was accompanied with a substantial, but non-significant, reduction in $\tau\dot{V}O_{2P}$ (pre PE = 54 ± 14 s; post-PE = 42 ± 17 s) (Gildea *et al*. 2018). Therefore, the results of the studies by Di Menna *et al.* (2010) and Gildea *et al*. (2018) show that when a constrained O_2 delivery is present, PE is effective at speeding $\tau\dot{V}O_{2P}$ during a subsequent bout of heavy-intensity exercise initiated from an elevated baseline.

MICT, LVHIIT or repeated sprint training (RST) have all been shown to be effective at speeding $\tau\dot{V}O_{2P}$ and/or reducing the amplitude of the $\dot{V}O_{2SC}$ during single step-wise transitions in individuals with and without T2DM (Brandenburg *et al.* 1999; Berger *et al.* 2006; Bailey *et al.* 2009; McKay *et al.* 2009; Murias *et al.* 2011; MacAnaney *et al*. 2012). Although there is a dearth of studies looking at the effect of exercise training interventions in T2DM on the $\dot{V}O_2$ kinetics during 'work-to-work' transitions, there is evidence from healthy populations to suggest that exercise training can reduce $\tau\dot{V}O_{2P}$ during 'work-to-work' transitions. For instance, Williams *et al.* (2013) reported a significant 38%

reduction in $\tau\dot{V}O_{2P}$ during a work-to-work transition albeit within the moderate-intensity domain following 4 weeks of LVHIIT (8-12 x 60 s cycling bouts at 110% PO_{peak}) (Williams *et al.* 2013). More recently, Da Boit *et al.* (2014) reported a significant reduction in $\tau\dot{V}O_{2P}$ during a work-to-work transition from a moderate-intensity baseline to a severe intensity transition following 2 weeks of either sprint interval training (28% decrease in $\tau\dot{V}O_{2P}$, 4-6 'all out' sprints interspersed by 4 mins recovery) or MICT (22% decrease in $\tau\dot{V}O_{2P}$; 90% GET for 60-110 mins). However, they reported no changes in the amplitude of the $\dot{V}O_{2SC}$ or fundamental gain of $\dot{V}O_2$ (i.e., increase in $\dot{V}O_2$ per unit increase in power output) the post-training (Da Boit *et al.* 2014).

Accordingly, the purpose of the current study was to compare the effects of MICT with LVHIIT on the mechanisms and time course of adaptations in $\dot{V}O_2$ kinetics responses during heavy-intensity cycling exercise initiated from an elevated baseline in people living with uncomplicated T2DM. The secondary aim of this experiment was to investigate the effect of LVHIIT and MICT on the effects of priming exercise on $\dot{V}O_2$ kinetics during heavy-intensity exercise initiated from an elevated baseline. The specific hypotheses were that 1) MICT and LVHIIT would reduce $\tau\dot{V}O_{2P}$ and $\dot{V}O_{2SC}$ amplitude by a similar magnitude and within a similar timeframe while also speeding the overall $\dot{V}O_2$ MRT of the heavy-intensity exercise transition from an elevated baseline, 2) At baseline (i.e. week 0), PE would reduce $\tau\dot{V}O_{2P}$ and the $\dot{V}O_{2SC}$ amplitude and therefore the overall $\dot{V}O_2$ MRT of a subsequent bout of heavy-intensity exercise initiated from an elevated baseline, but that PE would not have an effect on $\tau\dot{V}O_{2P}$, the amplitude of $\dot{V}O_{2SC}$ or $\dot{V}O_2$ MRT beyond 3 weeks of LVHIIIT and MICT.

4.2. Methodology.

4.2.1. Participants.

Thirty-one participants entered the study, however, 2 participants from the MICT group were excluded from the end analysis. One participant was excluded due to poor quality data and the other participant did not tolerate the silicon mouth piece during data collection. In addition, one participant from the LVHIIT group was also excluded from the end analysis due to poor quality data. Therefore, 28 participants (17 men/11 women) with uncomplicated T2DM took part in the study (Table 4.1). Participant characteristics and medications are displayed in Table 4.1 and Table 4.2. Upon entering the study, the participants were randomised into one of three training groups; low-volume high-intensity interval training (LVHIIT; *n* = 8), moderate-intensity interval training (MICT; *n* = 11) or control (LVHIIT; *n* = 9). Five of the female participants were pre-menopausal (LVHIIT *n* = 1; MICT *n* = 1; CON *n* = 3) and 6 were post-menopausal not undergoing HRT (LVHIIT *n* = 1; MICT *n* = 3; CON *n* = 2). All the participants were non-smokers or had ceased smoking at least 12 months prior to commencing the study. The participants who partook in the present study also carried out the measurements shown in Chapter 2 and Chapter 3 of the present thesis.

4.2.1.1. Recruitment of study participants.

As per section 2.2.1.

4.2.1.2. Exclusion criteria.

As per section 2.2.1.1.

4.2.2. Study overview.

Each participant was required to visit the exercise testing facility in St. Colmcille's Hospital on an additional separate occasion (in addition to the visits described in Chapters 2 and 3) with testing visits separated by at least 48 hours (see Fig 4.X). In order to take part in this experiment, it was sufficient for participants to complete visit one described in Chapter 2. All premenopausal participants were tested during the mid-follicular phase (days 5-12) of the menstrual cycle which was determined by self-evaluation. All participants were requested to abstain from alcohol, caffeine and strenuous physical activity for at least 24 hours prior to any testing procedures. Each participant repeated both study visits at 3 week intervals during the exercise intervention, thus allowing for assessment of the time course of adaptation to exercise at 5 time points; weeks 0, 3, 6, 9 and 12 (see Fig. 4.1).

4.2.2.1. Visit 1 overview.

See section 2.2.4.2.

4.2.2.2. Visit 2 overview.

During this visit each participant completed 4 'work-to-work' exercise bouts. Each bout comprised of 3 minutes of cycling at 10W, followed by 6 minutes cycling at a moderate-intensity which was followed immediately by a stepwise increase to 6 minutes cycling at a high-intensity. From the ramp incremental cycling test (i.e. visit 1), the work rates required for this protocol were determined. A power output equivalent to 80% VT and a PO corresponding to halfway between VT and maximal power output; 50% Δ, were utilised for the moderate- and high-intensity exercise bouts respectively.

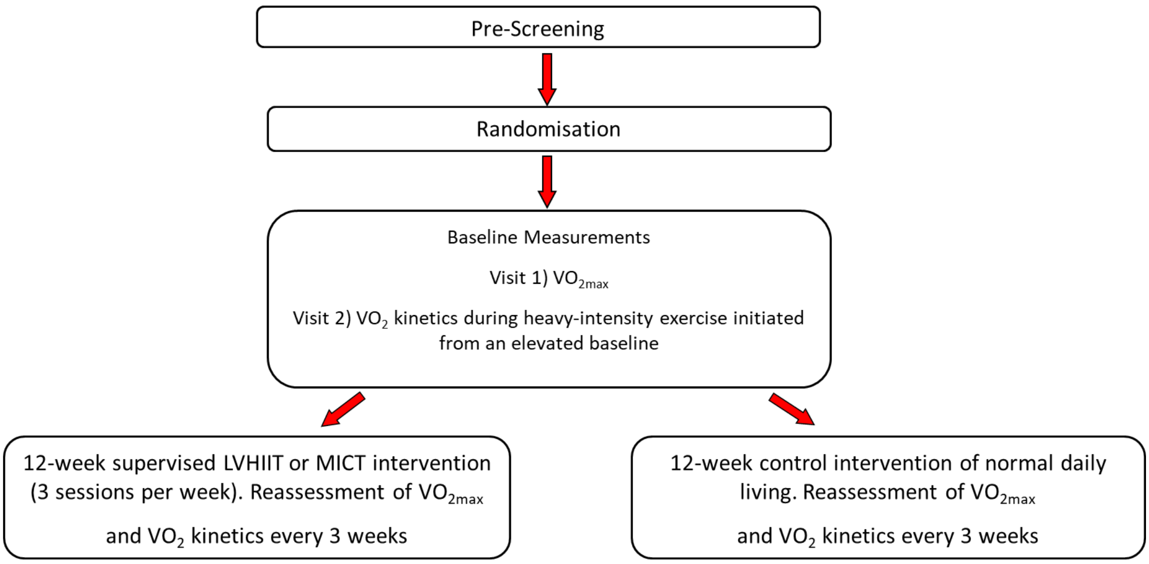


Figure 4.1 Study Overview

4.2.3. Exercise Training Interventions.

As per section 2.2.3.

4.2.3.1. Moderate-intensity continuous training.

As per section 2.2.3.1.

4.2.3.2. Low-volume high-intensity interval training.

As per section 2.2.3.2.

4.2.4. Laboratory measurements.

4.2.4.1. Pre-screening.

4.2.4.1.1. Exercise stress test.

As per section 2.2.4.1.1.

4.2.4.1.2. Evaluation of physical activity levels.

As per section 2.2.4.1.2.

4.2.4.1.3. Ankle: brachial index.

As per section 2.2.4.1.3.

4.2.4.1.4. Metabolic profile.

As per section 2.2.4.1.4.

4.2.4.2. Visits to the exercise physiology laboratory.

4.2.4.2.1 Visit 1

4.2.4.2.1.1. Anthropometric measurements.

As per section 2.2.4.2.1.

4.2.3.2.1.2. Maximal ramp incremental exercise test.

As per section 2.2.4.2.2

4.2.4.2.2. Visit 2.

4.2.4.2.2.1. Measurement of $\dot{V}O_2$ kinetics responses during heavy-intensity cycling exercise initiated from an elevated baseline with and without priming exercise.

Each participant completed 4 bouts of constant-load heavy-intensity cycling commencing from an elevated baseline on an electrically braked cycle ergometer (Excalibur Sport, LODE B.V., Groningen, The Netherlands) (Fig. 4.1). Each bout consisted of 3 min warm-up cycling at 10 W which was followed by 6 mins of moderate-intensity cycling (80% VT) which in turn was immediately followed by 6 mins of heavy-intensity cycling (50% Δ) (w-to-w). Two of these w-to-w bouts were completed without PE (w-to-w unprimed) and two bouts were preceded by a bout of PE (w-to-w primed). The unprimed w-to-w bout was used as PE. A pilot study carried out in this laboratory (*n* = 5) demonstrated that when a w-to-w bout was used as PE, its effect on subsequent w-to-w $\dot{V}O_2$ kinetics was not different compared with a condition where a single 6-min heavy-intensity bout (50% Δ) was used as PE (Appendix 7.7). Exercise was performed continuously with changes in PO initiated as a step function without a warning to the individual. There was a 12 min rest period between each of the cycling bouts, except following the first primed w-to-w bout whereby participants remained passively seated in a chair for the duration of a 45 minute period. This is the minimum time required for the physiological restoration of $\dot{V}O_2$, HR and blood lactate to resting levels following a bout of heavy intensity exercise (Burnley *et al.* 2006a).

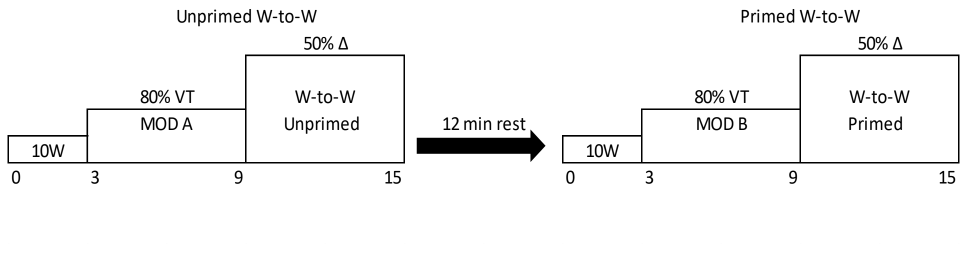


Figure 4.2. Representative figure of the study protocol. The protocol was repeated after a 45 min break following the completion of the primed w-to-w transition.

4.2.5. Laboratory equipment and measurement techniques

4.2.5.1. Cardio-metabolic unit.

As per section 2.2.5.1.

4.2.5.2. Heart rate.

As per section 2.2.5.2.

4.2.5.3 Muscle deoxygenation.

As per section 2.2.5.5.

4.2.6. Data Analysis.

4.2.6.1. Peak physiological responses during ramp exercise and determination of VT.

As per section 2.2.6.1.

4.2.6.2. Analysis of 80% VT component.

4.2.6.2.1. $\dot{V}O_2$ kinetics.

As per section 3.2.6.2.1.

4.2.6.2.2 Muscle deoxygenation kinetics.

As per section 3.2.6.2.2.

4.2.6.2.3. ∆ [HHb + Mb]/∆ $\dot{V}O_2$ ratios.

As per section 3.2.6.2.3.

4.2.6.2.4. Heart rate kinetics.

As per section 3.2.6.2.4.

4.2.6.3 Analysis of 50% ∆ component

4.2.6.3.1. $\dot{V}O_2$ kinetics.

Breath-by-breath $\dot{V}O_2$ data for each transition were linearly interpolated to give second-by-second values and time aligned such that time 0 represented the onset of exercise. Data from each transition were combined to yield a single, average response for each participant and further time-averaged into 5 s bins in order to yield a single mean response for each participant. The first 20 s of $\dot{V}O_2$ data after the onset of exercise were excluded in order to exclude data from the cardio-dynamic phase (Murias *et al*. 2011c). The model parameters of the $\dot{V}O_2$ kinetic response were therefore determined from 20 – 360 s of the step transition via a weighted least-squares nonlinear regression procedure (TableCurve 2D, Systat), in which the best fit was defined by minimization of the residual sum of squares. Data points lying outside the 95% prediction interval during the initial fit of a model were excluded. The averaged and smoothed responses for each participant were fitted using a bi-exponential function:

$$\dot{V}O_2\,(t) = \dot{V}O_{2baseline} + A_p[1- e^{-(t-TDp)/\tau p)}]\ F1 + A_{SC}[1 - e^{-(t - TDsc)/\tau sc)}]\ F2$$

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 $\dot{V}O_2$ measured over the final 60 s of the moderate-intensity cycling exercise component completed prior to the immediate transition to heavy-intensity cycling exercise; Ap and A_{SC}, are the amplitudes of the increase in $\dot{V}O_2$ for the primary and slow component phases respectively; TDp – TD_{SC} are the phase delays, and $\tau p – \tau_{SC}$ 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 of the primary and slow component phases respectively. The conditional expressions F1-F2 limit the fitting of the phase to the period at and beyond the time delay associated with that phase. The end-exercise $\dot{V}O_2$ was defined as the mean $\dot{V}O_2$ measured over the final 30 s of heavy-intensity exercise.

Finally, the mean response time (MRT) was calculated in order to measure the "overall" time course of the $\dot{V}O_2$ kinetic response during the heavy-intensity exercise bout, with no distinction made for the various phases of the response. This was calculated through the fitting of a mono-exponential curve from the onset to the end of the heavy-intensity exercise bout.

$$\dot{V}O_2\,(t) = \dot{V}O_{2baseline} + A\,[1- e^{-(t-TD)/\tau}]$$

Whereby $\dot{V}O_2$ (t) represents $\dot{V}O_2$ at a given time; $\dot{V}O_2$ baseline represents $\dot{V}O_2$ at time 0 at the commencement of the transition to the higher exercise intensity; A is the steady state amplitude of the increase in $\dot{V}O_2$. In this model $\dot{V}O_2$ is the time delay marking the beginning of the exponential rise and τ is the time constant of the response.

4.2.6.3.2. Muscle deoxygenation kinetics.

The Δ [HHb + Mb] data for each 'work-to-work' transition was linearly interpolated to provide second-by-second values and time aligned. Data were combined to provide a single, average response for each participant, and further time-averaged into 5 s bins to yield a single mean response per participant.

A time delay at the onset of exercise occurs in the [HHb + Mb] profile before it increases with an exponential like time course which has been suggested to reflect the matching between muscular O_2 uptake and local O_2 delivery at the onset of exercise (DeLorey *et al*. 2003; Grassi *et al.* 2003). This was determined in the present study by visual inspection as a systematic increase above the pre-transition level. [HHb + Mb] data were fitted from the first data point at the end of this TD to 360 s using the same bi-exponential model as described for the analysis of $\dot{V}O_2$ kinetics (see Equation 1, *section 4.2.5.3.1*) to determine the time course of muscle deoxygenation. The time course for the increase in Δ [HHb + Mb] can be described by the τΔ [HHb + Mb]. The overall time course of the total change of the Δ [HHb + Mb] for the primary response phase (known as the effective τΔ [HHb + Mb]) was determined from the sum of the time delay and τ [HHb + Mb] from the onset of exercise.

The final end amplitude of the response, referred to as absolute [HHb+Mb] end A, as the mean [HHb+Mb] measured over the final 30 s of heavy-intensity exercise.

Finally, the mean response time (MRT) was calculated to measure the "overall" time course of [HHb] kinetics during the heavy-intensity exercise bout, with no distinction made for the various phases of the response. This was calculated through the fitting of a mono-exponential curve (see *section 4.2.5.3.1*), from the onset to the end of the heavy-intensity exercise bout.

4.2.6.3.3. Heart rate kinetics.

Beat-by-beat heart rate data was linearly interpolated to provide second-by-second values and time-aligned. Data for each transition were ensemble-averaged to produce a single, average response for each participant.

Baseline HR (time 0) was determined to be the average of the last 60 s of the preceding moderate-intensity bout. The model parameters of the HR kinetic response were calculated from 0 – 360 s of the step transition via a weighted least-squares nonlinear regression procedure (TableCurve 2D, Systat), in which the best fit was defined by minimization of the residual sum of squares. Data points lying outside the 95% prediction interval during the initial fit of a model were excluded. As no clear slow component in HR kinetic was observed in the participants' responses it was decided that a mono-exponential model would best describe the HR kinetic response (see *section 3.2.5.2.2*). End exercise HR was determined as the average of the last 30 s of the HR response during the heavy-intensity exercise

4.2.7. Statistical Analysis.

Statistical analysis of the data was performed using SigmaPlot Version 12.0 software (Systat Software, Point Richmond, CA, USA) and DataDesk Version 8.0 software (Data Description). Normality of the data was assessed using the Shapiro-Wilk test. Non normal data and data that did not display equality of variance were transformed to resemble normal data. Baseline analysis of participant characteristics was completed with a one-way analysis of variance (ANOVA). The effect of priming exercise during the different time points of the intervention on $\dot{V}O_2$, HR and [HHb + Mb] kinetics parameters were completed using a 3-way repeated measures ANOVA (priming exercise vs time vs group). On the other hand, the effects of the different time points of the intervention on peak physiological responses, anthropometric data and unprimed $\dot{V}O_2$, HR and [HHb + Mb] kinetics parameters were analysed using a 2-way repeated measures ANOVA (group vs time). Post-hoc Tukey tests were performed in incidences of statistical significance. Statistical significance was set at $P < 0.05$. Data are displayed as mean ± standard (SD) unless otherwise stated.

The key variable in this study is the time constant of the primary component of $\dot{V}O_2$ kinetics; $\tau\dot{V}O_{2P}$, during the transition from an elevated baseline. Recently published studies investigating the effect of heavy priming exercise or exercise training on $\dot{V}O_2$ during exercise transitions from an elevated baseline in healthy individuals have reported an average $\tau\dot{V}O_{2P}$ of 45.8 ± 9.9 s (Mean ± SD) with the difference in $\tau\dot{V}O_{2P}$ pre- and post-intervention being ~14 s. Given that the estimated standard deviation (SD) of each population is 9.9 s, and that the minimum difference we wish to detect as significant would be ~14 s the minimum sample size needed to detect a significant effect at $\beta = 0.05$ and $\alpha = 0.05$ (70% power) for an ANOVA calculation design based on 3 groups, is 9 individuals.

4.3. Results.

4.3.1. Participants.

4.3.1.1. Recruitment of participants.

See section 2.3.1.1.

4.3.1.2. Participant physical characteristics, prescription medications and exercise adherence.

Participant characteristics and medications from the 28 participants who completed the study are displayed in Table 4.1 and Table 4.2. No significant differences in physical characteristics were among the 3 groups at baseline.

The mean exercise adherence was 97 ± 4% (range, 32-36 sessions) in the MICT group and 94 ± 6% (range 31-36 sessions) in the LVHIIT group. The average training intensity (PO) per session increased significantly after each retesting session (i.e., every 3 weeks) in both the MICT (weeks 1–3, 84 ± 33W; weeks 4–

6, 102 ± 39 W; weeks 7–9, 113 ± 43 W; weeks 10-12, 122 ± 44 W) and LVHIIT groups (weeks 1–3, 176 ± 35 W; weeks 4–6, 192 ± 37 W; weeks 7–9, 203 ± 38 W; weeks 10-12, 206 ± 40 W). No adverse effects to training were reported in either group.

Table 4.1. ***Participant baseline characteristics.***

	MICT (*n* = 11)	LVHIIT (*n* = 8)	Control (*n* = 9)	*Between Group P Value*
Age (years)	53.9 (10.0)	50.9 (10.2)	53.9 (9.4)	0.95
Male/female	7/4	6/2	4/5	
BMI (m.kg $^{-2}$)	31.0 (5.7)	28.8 (3.2)	30.5 (3.6)	0.57
Time since diagnosis (years)	6.6 (3.7)	6.8 (3.7)	6.6 (3.3)	0.42
Pre-exercise ABI (a.u.)	1.10 (0.10)	1.07 (0.04)	1.13 (0.07)	0.24
Post-exercise ABI (a.u.)	1.10 (0.10)	1.05 (0.10)	1.14 (0.08)	0.06
HbA_{1c} (%)	6.8 (0.5)	7.3 (0.5)	7.5 (1.3)	0.42
Fat layer of VL (mm)	7.9 (4.2)	6.5 (2.7)	8.6 (3.2)	0.22

Data are mean (SD). BMI, body mass index; ABI, ankle: brachial index; a.u., arbitrary units; VL, vastus lateralis.

Table 4.2. ***Prescriptive medications for individuals in each group.***

	MICT	LVHIIT	CON
Anti-hypertensives			
Angiotensin converting enzyme inhibitor		1	
Angiotensin II receptor blocker	1		1
Aspirin	3	1	2
Statins	5	3	3
Hypoglycaemic medications			
Oral hypo-glycaemic			
Metformin	5	5	5
Glucophage	2	2	1
Diamicron		2	2
Sitagliptin			2
Glicalzide	1	1	
Subcutaneous hypo-glycaemic			
Victoza	1		1

4.3.1.3. Physical activity levels.

Group mean averages for physical activity levels as measured by RT3 accelerometers (Table 4.3). No significant differences in physical activity were observed between the 3 groups.

Table 4.3. ***Mean group physical activity data expressed in hours per day as determined by RT3 accelerometers.***

	MICT (n = 8)	LVHIIIT (n = 7)	CON (n = 8)	*Between groups P value*
Inactive (h.day^{-1})	17.4 (1.6)	17.5(2.2)	18.2 (1.2)	0.44
Light (h.day^{-1})	5.2 (0.7)	5.3 (1.6)	4.8 (0.9)	0.65
Moderate (h.day^{-1})	1.2 (1.0)	1.0 (0.5)	0.8 (0.6)	0.42
Vigorous (h.day^{-1})	0.3 (0.3)	0.2 (0.2)	0.2 (0.3)	0.13

Data are mean (SD)

4.3.2. Time course of performance data during ramp exercise.

PO_{peak} and $\dot{V}O_{2max}$ responses throughout the training period are summarised in Table 4.5. In absolute terms (L.min^{-1}), $\dot{V}O_{2max}$ increased significantly beyond 3 weeks of MICT and beyond 6 weeks of LVHIIT until the completion of the intervention period. When $\dot{V}O_2$ measurements were normalised to body mass, a significant increase in $\dot{V}O_{2max}$ of a similar magnitude was observed in both the LVHIIT and MICT groups after 3 weeks of training which were maintained until the completion of the intervention period. In addition, normalised $\dot{V}O_{2max}$ in the LVHIIT and MICT groups were significantly different to CON beyond 3 weeks. PO_{peak} significantly increased by a similar magnitude at 3 weeks in both the LVHIIT and MICT groups and were maintained until the completion of the intervention period. In addition, there was a further significant increase in PO_{peak} after 6 weeks of LVHIIT and after 9 weeks of MICT. No increases in PO_{peak} were observed in the CON group at any stage during the intervention period (Table 4.4). Power outputs utilised during the priming exercise and moderate-intensity bouts are shown in Table 4.5.

Table 4.4. ***Peak physiological responses during the intervention period in the MICT, LVHIIT and CON groups.***

	Week 0	Week 3	Week 6	Week 9	Week 12	*P Value*		
$\dot{V}O_{2max}$ (L.min^{-1})						Time effect	Group effect	Time x Group
MICT	2.1 (0.7)	2.4 (0.7)*	2.6 (0.7)*#	2.5 (0.7)*#	2.5 (0.8)*#			
LVHIIT	2.4 (0.4)	2.6 (0.6)	2.6 (0.5)*#	2.7 (0.6)*#	2.7(0.5)*#	<0.001	0.13	0.003
CON	1.9 (0.5)	1.9 (0.6)	1.9 (0.6)	1.9 (0.6)	1.9 (0.5)			
$\dot{V}O_{2max}$ (mL.kg^{-1}.min^{-1})								
MICT	22.2 (4.6)	26.0 (5.7)*#	27.8 (5.1)*#	27.1 (5.9)*#	27.7 (5.5)*#			
LVHIIT	27.2 (3.5)	29.4 (3.4)*#	29.6 (3.5)*#	30.9 (4.2)*#	30.4 (3.7)*#	<0.001	0.007	<0.001
CON	21.5 (3.6)	22.1 (4.4)	21.6 (4.0)	22.2 (4.2)	22.0 (3.4)			
Peak PO (W)								
MICT	160 (54)	184 (63)*	191 (64)*	200 (65)*‡	201 (68)*‡†			
LVHIIT	198 (41)	216 (41)*	226 (45)*‡	229 (44)*‡	228 (47)*‡	<0.001	0.07	<0.001
CON	148 (49)	149 (52)	146 (55)	151 (51)	153 (50)			
TTF (s)								
MICT	665 (166)	750 (199)*	778 (203)*	811 (205)*‡	842 (251)*‡†			
LVHIIT	721 (90)	777 (93)	808 (97)*	819 (101)*	813 (100)*	0.03	0.11	021
CON	656 (123)	633 (127)	617 (125)	664 (123)	648 (116)			
Peak RER (a.u.)								
MICT	1.15 (0.10)	1.13 (0.06)	1.10 (0.07)	1.13 (0.07)	1.15 (0.10)			
LVHIIT	1.15 (0.04)	1.22 (0.06)	1.18 (0.07)	1.24 (0.09)	1.24 (0.09)	0.58	0.01	0.25
CON	1.13 (0.07)	1.10 (0.12)	1.11 (0.13)	1.10 (0.10)	1.11 (0.06)			

Data are mean (SD) * 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 CON ($P < 0.05$); $\dot{V}O_{2max}$, maximal oxygen uptake; PO, power output; TTF, time to failure; RER, respiratory exchange ratio.

Table 4.5. ***Power outputs for determination of $\dot{V}O_2$ kinetics and priming exercise.***

	MICT	LVHIIT	CON
PO @ VT (W)	91 (32)	115 (32)	83 (25)
% of PO_{peak} @ VT	59 (9)	62 (6)	57 (7)
PO @ 50% Δ	123 (43)	151 (41)	115 (36)
% of PO_{peak} @ 50% Δ	78 (3)	81 (3)	78 (3)

Data are mean (SD)

4.3.3. Effect of training on physiological responses during work-to-work exercise transitions.

4.3.3.1. $\dot{V}O_2$, [HHb+Mb], and HR data from heavy-intensity (50% Δ) exercise.

4.3.3.1.1. $\dot{V}O_2$ kinetics.

The group mean parameters of the $\dot{V}O_2$ kinetics response during heavy-intensity exercise initiated from an elevated baseline are shown in Table 4.6, representative individual response profiles are shown in Fig. 4.2., and group mean percentage changes in $\dot{V}O_{2SC}$ amplitude and $\tau\dot{V}O_{2P}$ are shown in Fig. 4.3. All individual response parameters can be found in Appendix 8.6. After 3 weeks of training, the amplitude of the $\dot{V}O_{2SC}$ was significantly reduced in both the LVHIIT and MICT groups by 40% and 44% respectively and maintained until the completion of the intervention, with no changes observed in the CON group. In addition, after 3 weeks of MICT and LVHIIT there were significant reductions in the $\dot{V}O_2$ MRT and $\tau\dot{V}O_{2P}$ in the MICT and LVHIIT and these reductions were maintained until the end of the intervention period.

Table 4.6. Time course changes in the group mean parameter estimates for $\dot{V}O_2$ kinetics during heavy-intensity exercise in the MICT, LVHIIT and CON groups.

	Week 0	Week 3	Week 6	Week 9	Week 12	*P value* Time effect	Group effect	Time x Group
$\dot{V}O_{2baseline}$ ($L.min^{-1}$)								
MICT	1.66 (0.43)	1.61 (0.40)	1.53 (0.40)	1.57 (0.41)	1.57 (0.35)			
LVHIIT	1.67 (0.67)	1.75 (0.19)	1.76 (0.22)	1.72 (0.20)	1.7 (0.23)	0.37	0.05	0.88
Control	1.39 (0.33)	1.34 (0.31)	1.36 (0.31)	1.34 (0.32)	1.43 (0.35)			
$\dot{V}O_2$ A ($L.min^{-1}$)								
MICT	0.50 (0.14)	0.45 (0.16)	0.53 (0.23)	0.53 (0.19)	0.59 (0.32)			
LVHIIT	0.55 (0.19)	0.52 (0.17)	0.55 (0.16)	0.55 (0.16)	0.56 (0.13)	0.03	0.60	0.62
Control	0.49 (0.21)	0.46 (0.23)	0.47 (0.22)	0.47 (0.23)	0.49 (0.22)			
$\tau\dot{V}O_{2P}$ (s)								
MICT	48 (10)	30 (8)*	30 (5)*	30 (6)*	27 (5)*			
LVHIIT	43 (13)	27 (6)*	33 (8)*	24 (11)*	28 (6)*	0.007	<.02	<0.001
Control	45(6)	41 (8)	39 (3)	40 (6)	43 (6)			
$\dot{V}O_2$ A_{SC} ($L.min^{-1}$)								
MICT	0.18 (0.08)	0.10 (0.05)*	0.09 (0.05)*	0.11 (0.06)*	0.10 (0.06)*			
LVHIIT	0.20 (0.07)	0.14 (0.06)*	0.15 (0.09)*	0.14 (0.07)*	0.12 (0.07)*	<0.001	0.25	0.005
Control	0.14 (0.05)	0.14 (0.08)	0.14 (0.06)	0.15 (0.07)	0.14 (0.06)			
$\dot{V}O_2$ MRT (s)								
MICT	80 (19)	61 (13)*	57 (15)*	57 (13)*	59 (14)*			
LVHIIT	73 (17)	60 (13)*	57 (11)*	55 (8)*	56 (7)*	<0.001	0.82	0.004
Control	67 (10)	65 (13)	61 (12)	64 (12)	62 (11)			

Data are mean (SD) $\dot{V}O_2$, oxygen uptake; A, amplitude; τ, time constant of the primary response; A_{SC}, slow component amplitude; MRT, mean response time * significantly different from week 0 (P < 0.05) .

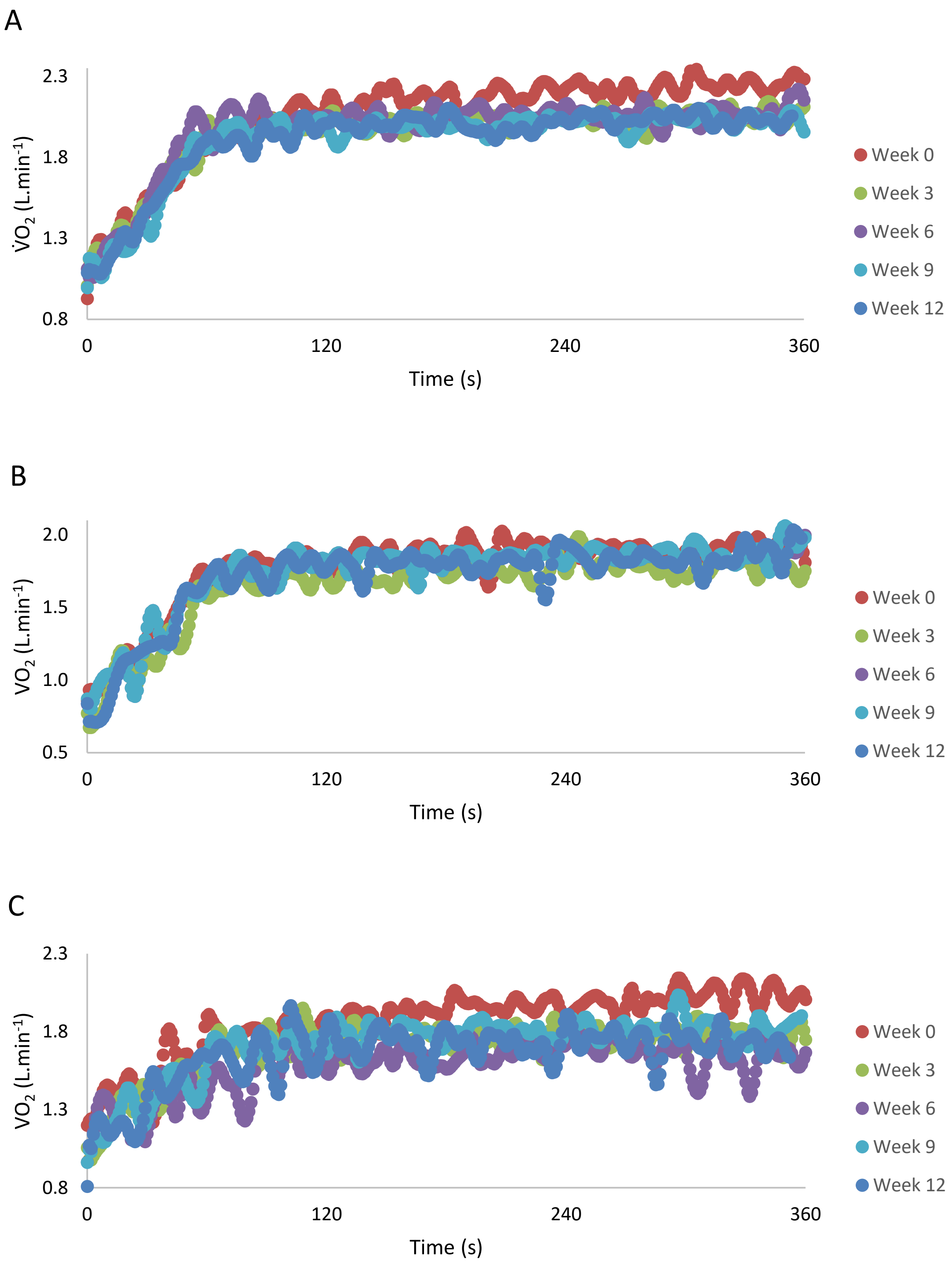
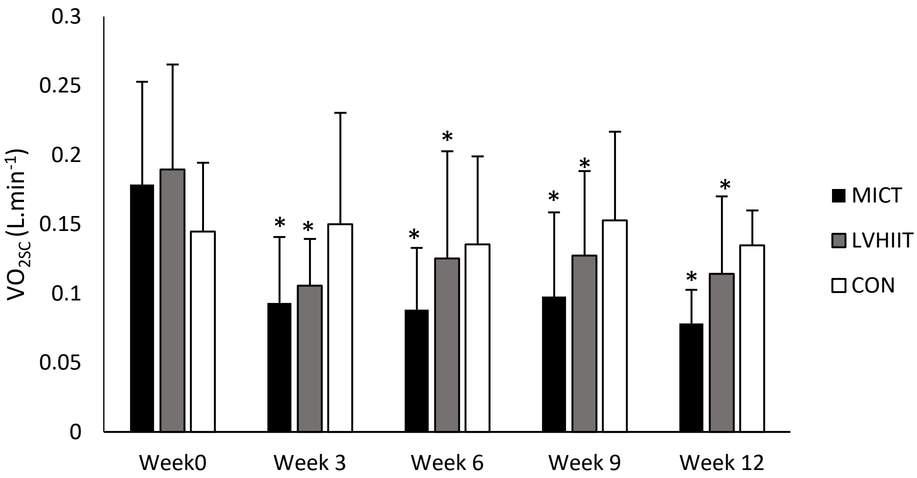


Figure 4.3. Representative plots of the $\dot{V}O_2$ kinetic response during heavy-intensity exercise initiated from an elevated baseline. Panels A, B and C represent individuals from the MICT, CON and LVHIIT groups respectively. Note the slower $\tau\dot{V}O_{2P}$ and larger $\dot{V}O_{2SC}$ amplitude at week 0 during MICT and LVHIIT.

A



B

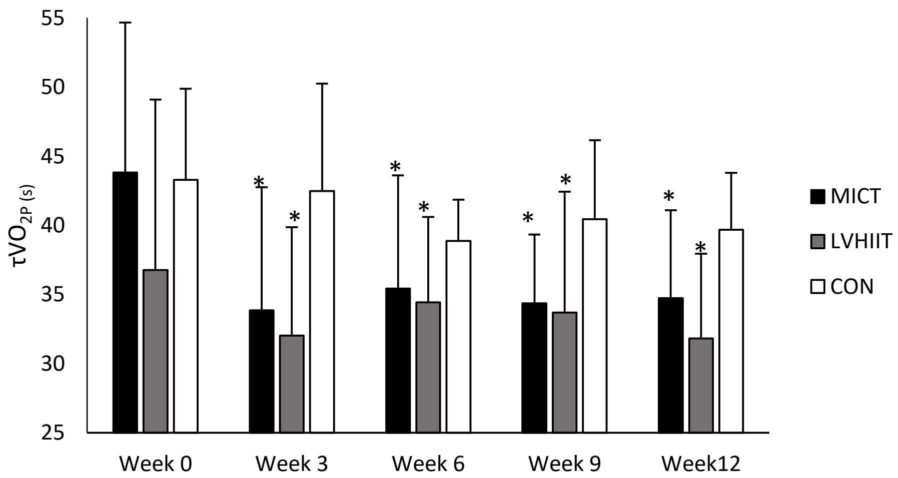


Figure 4.4. Illustration showing the time course effects of training on $\dot{V}O_{2SC}$ amplitude (Panel A) and $\tau\dot{V}O_{2P}$ (Panel B) in the LVHIIT, MICT and CON groups. *significantly different from Week 0 ($P < 0.05$). Error bars denote SD.

4.3.3.1.2. Muscle deoxygenation kinetics.

The group mean parameter responses of the [HHb + Mb] kinetic response during heavy-intensity exercise initiated from an elevated baseline are shown in Table 4.7 with representative [HHb +Mb] line of best fit plots shown in Fig. 4.4 and representative [HHb+Mb] MRT line of best fit plots shown in Fig. 4.5. All individual response parameters can be found in Appendix 8.6. Parameter estimates were not affected by any of the interventions.

Table 4.7. ***Time course changes in the group mean parameter estimates for [HHb + Mb] kinetics during heavy-intensity exercise in the MICT, LVHIIT and CON groups.***

	Week 0	**Week 3**	**Week 6**	**Week 9**	**Week 12**	*P value*		
TD[HHb +Mb] (s)						Time effect	Group effect	Time x Group
MICT	8 (6)	9 (4)	9 (5)	10 (6)	9 (4)			
LVHIIT	11 (9)	12 (9)	8 (3)	5 (3)	6 (4)	0.95	0.63	0.29
Control	10 (3)	6 (4)	16 (20)	12 (6)	16 (14)			
τ[HHb +Mb] (s)								
MICT	31 (18)	25 (10)	32 (14)	28 (9)	36 (8)			
LVHIIT	30 (15)	25 (11)	34 (23)	27 (8)	34 (16)	0.74	0.34	0.91
Control	18 (5)	22 (16)	20 (9)	20 (10)	15 (7)			
τ'[HHb +Mb] (s)								
MICT	39 (16)	34 (8)	41 (14)	38 (10)	45 (10)			
LVHIIT	41 (23)	38 (16)	42 (24)	32 (9)	41 (16)	0.72	0.15	0.96
Control	28 (6)	26 (14)	34 (22)	29 (14)	35 (20)			
[HHb +Mb] MRT (s)								
MICT	53 (29)	50 (23)	58 (25)	43 (20)	58 (18)			
LVHIIT	36 (20)	44 (29)	60 (37)	49 (16)	57 (40)	0.54	0.91	0.78
Control	57 (46)	44 (46)	38 (20)	45 (40)	63 (53)			

Data are mean (SD) [HHb +Mb], deoxygenated haemoglobin concentration; TD, time constant; τ, time constant of the primary response; τ' [HHb + Mb], effective time constant; MRT, mean response time. For [HHb+Mb] responses MICT n = 9, LVHIIT n = 7, CON n = 6.

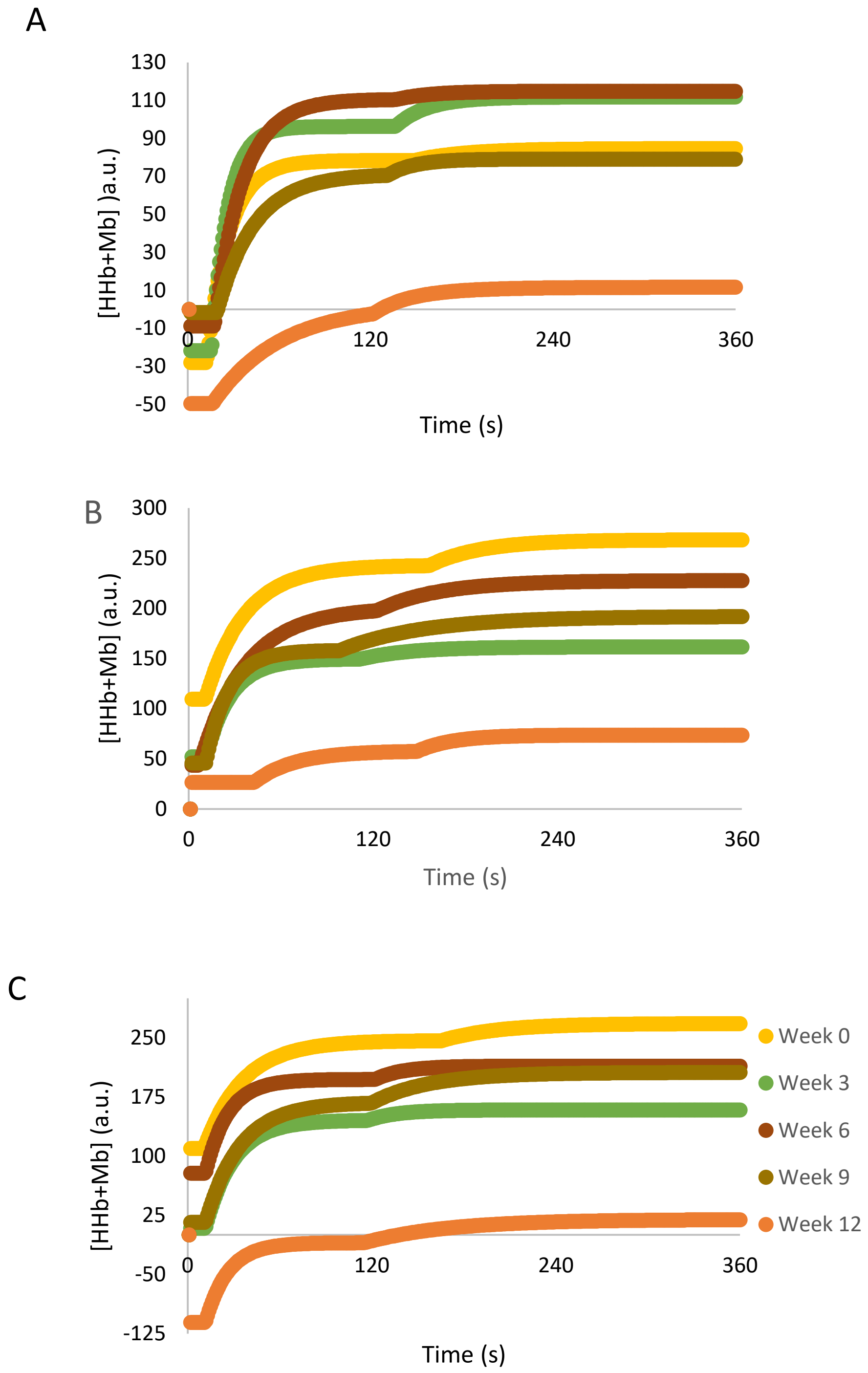


Figure 4.5. Panels A, B and C present the lines of best fit for individual representative [HHb + Mb] responses in the MICT, CON and LVHIIT groups respectively.

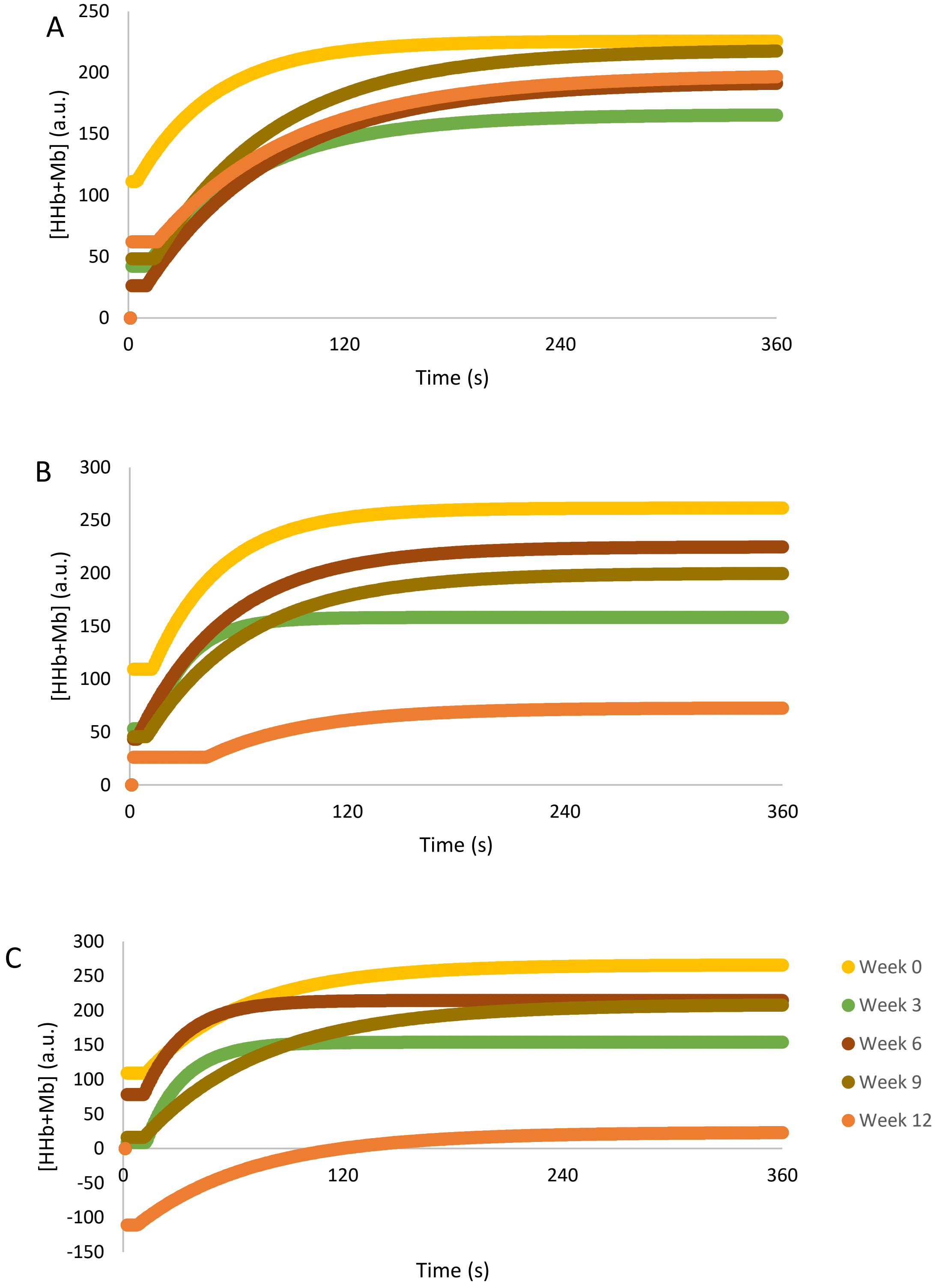


Figure 4.6. Panels A, B and C present lines of best fit for individual representative [HHb + Mb] MRT responses in the MICT, CON and LVHIIT groups respectively.

4.3.3.1.3. HR kinetics.

Group mean HR parameters for all three groups throughout the intervention are displayed in Table 4.8 and individual responses can be found in Appendix 8.6. There was no effect of exercise training on baseline HR or End-HR values in any group at any time point. After 6 weeks of training there was a significant reduction in τHR and HR amplitudes in the MICT group only. No changes in τHR and HR amplitudes were observed in the CON or LVHIIT groups at any time point

Table 4.8. ***Time course changes in the parameters of HR kinetics during heavy-intensity exercise in the MICT, LVHIIT and CON groups.***

	Week 0	**Week 3**	**Week 6**	**Week 9**	**Week 12**	*P value*		
Baseline HR (beats.min^{-1})						Time effect	Group effect	Time x Group
MICT	118 (27)	120 (13)	120 (16)	117 (14)	117 (12)			
LVHIIT	131 (21)	127 (13)	120 (10)	122 (8)	119 (9)	0.40	0.29	0.41
Control	127 (10)	124 (13)	122 (12)	114 (40)	121 (15)			
HR A (beats.min^{-1})								
MICT	27 (8)	25 (7)	20 (7)*	23 (8)*	21 (6)*			
LVHIIT	30 (7)	27 (4)	28 (5)	27 (4)	26 (4)	0.38	0.004	0.04
Control	31 (9)	33 (8)	34 (10)	32 (8)	35 (10)			
τHR (s)								
MICT	110 (23)	90 (17)*	80 (30)*	88 (25)*	77 (26)*			
LVHIIT	98 (30)	97 (13)	86 (13)	80 (35)	91 (16)	0.01	0.86	0.15
Control	95 (17)	95 (46)	92 (37)	85 (30)	100 (22)			
End-exercise HR (beats.min^{-1})								
MICT	145 (27)	145 (13)	140 (16)	140 (15)	138 (13)			
LVHIIT	161 (12)	154 (10)	148 (8)	149 (7)	146 (9)	0.39	0.45	0.40
Control	157 (10)	157 (12)	156 (12)	145 (38)	156 (13)			

Data are mean (SD) HR, heart rate; A, amplitude; τ, time constant of the primary response *different from week 0 ($P < 0.05$).

4.3.3.2 $\dot{V}O_2$, [HHb+Mb] and HR data from moderate-intensity (80% VT) exercise bouts.

4.3.3.2.1. $\dot{V}O_2$ kinetics.

The time course responses of the parameter estimates of $\dot{V}O_2$ kinetics during the moderate-intensity segment of the work-work transition without a prior bout of priming exercise (i.e. MOD A) are presented in Table 4.9. Individual parameter estimates are shown in Appendix 8.6. At baseline $\tau\dot{V}O_{2P}$ was similar across all groups. After 3 weeks of MICT and LVHIIT there was a significant reduction in the $\tau\dot{V}O_{2P}$ which was of a similar magnitude and was maintained throughout the training period. Moreover, $\tau\dot{V}O_{2P}$ was significantly faster in the LVHIIT and MICT groups than in the CON group beyond the 3 week time point. No changes $\tau\dot{V}O_{2P}$ were observed in the CON group at any time point.

Table 4.9. ***Time course changes in the group mean parameter estimates for $\dot{V}O_2$ kinetics during moderate-intensity exercise in the MICT, LVHIIT and CON groups.***

	Week 0	**Week 3**	**Week 6**	**Week 9**	**Week 12**	*P value*		
$\dot{V}O_2$ A ($L.min^{-1}$)						Time effect	Group effect	Time x Group
MICT	0.8 (0.3)	0.7 (0.3)	0.7 (0.3)	0.6 (0.2)	0.7 (0.2)			
LVHIIT	0.9 (0.3)	0.8 (0.2)	0.8 (0.2)	0.9 (0.3)	0.9 (0.2)	0.09	0.048	0.21
Control	0.5 (0.3	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)			
$\dot{V}O_2$ End A ($L.min^{-1}$)								
MICT	1.7 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)			
LVHIIT	1.8 (0.3)	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)	0.02	0.05	0.82
Control	1.4 (0.3)	1.4 (0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)			
$\tau\dot{V}O_{2P}$ (s)								
MICT	48 (7)	33 (5)*#	28 (7)*#	25 (3)*#	28 (5)*#			
LVHIIT	44 (9)	33 (4)*#	29 (4)*#	26 (4)*#	28 (4)*#	<0.001	<0.001	<0.001
Control	45 (8)	39 (9)	38 (7)	40 (10)	44 (7)			
$\dot{V}O_2$ gain ($mL.min^{-1}.W^{-1}$)								
MICT	10.9 (2.6)	9.6 (2.0)	10.1 (1.7)	9.3 (0.8)	10.5 (2.3)			
LVHIIT	10.5 (2.3)	9.3 (1.6)	9.1 (1.6)	9.5 (1.5)	9.6 (1.5)	0.62	0.5	0.79
Control	9.2 (2.0)	9.8 (1.1)	10.5 (1.1)	9.8 (0.5)	10.3 (0.9)			

Data are mean (SD). * Significantly different to week 0 (*P* <0.05); # significantly different from CON (*P*<0.05). $\dot{V}O_2$, oxygen uptake; A, amplitude; τ, time constant of the primary response

4.3.3.2.2. Muscle deoxygenation kinetics and Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratios.

Kinetic parameters for [HHb + Mb] response profiles are displayed in Table 4.10 and individual responses can be found in Appendix 8.6. There were no changes in any parameter of the [HHb + Mb] response profile in any group during the intervention period. The overall Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio responses for the MICT, CON and LVHIIT are shown in Table 4.11. After 3 weeks of LVHIIT and MICT the Δ [HHb+Mb]/Δ$\dot{V}O_2$ ratio was significantly lower than week 0 and remained so at weeks 6, 9 and 12. In the CON group, however, the Δ [HHb+Mb]/Δ$\dot{V}O_2$ ratio was not different at any time point.

Table 4.10. ***Time course changes in the group mean parameter estimates for [HHb + Mb] kinetics during moderate-intensity exercise in the MICT, LVHIIT and CON groups.***

	Week 0	**Week 3**	**Week 6**	**Week 9**	**Week 12**	*P value*		
[HHb+Mb] A (a.u)						Time effect	Group effect	Time x Group
MICT	76 (45)	101 (59)	84 (51)	97 (61)	83 (32)			
LVHIIT	153 (105)	159 (103)	151 (101)	169 (104)	160 (101)	0.44	0.03	0.50
Control	74 (63)	77 (64)	71 (54)	70 (51)	75 (50)			
[HHb+Mb] End A								
MICT	37 (87)	24 (84)	1 (46)	7 (99)	15 (74)			
LVHIIT	116 (117)	112 (81)	100 (114)	120 (101)	81 (109)	<0.001	0.51	<0.001
Control	35 (66)	31 (83)	16 (76)	47 (102)	13 (62)			
TD[HHb+Mb] (s)								
MICT	10 (7)	16 (7)	15 (8)	16 (5)	17 (4)			
LVHIIT	15 (4)	15 (4)	14 (2)	14 (4)	15 (8)	0.06	0.43	0.43
Control	16 (3)	14 (3)	13 (4)	15 (3)	19 (6)			
τ[HHb+Mb] (s)								
MICT	15 (7)	17 (9)	15 (10)	20 (18)	16 (5)			
LVHIIT	12 (6)	13 (6)	13 (9)	13 (6)	10 (5)	0.89	0.27	0.60
Control	12 (6)	11 (5)	18 (11)	17 (9)	20 (21)			
τ'[HHb+Mb] (s)								
MICT	25 (9)	33 (14)	30 (15)	36 (22)	33 (8)			
LVHIIT	27 (4)	28 (6)	26 (9)	26 (7)	26 (10)	0.24	<0.001	0.69
Control	28 (5)	24 (5)	30 (10)	32 (8)	39 (24)			

Data are mean (SD). [HHb+Mb], muscle deoxygenation; A, amplitude; TD, time delay, τ, time constant of the response; τ' [HHb + Mb], effective time constant of the response. For [HHb + Mb] responses MICT *n* = 10, LVHIIT *n* = 7, CON *n* = 8.

Table 4.11. ***Time course changes in the* Δ *[HHb + Mb]/*$\Delta\dot{V}O_2$** **ratios** ***during moderate-intensity exercise in the MICT, LVHIIT and CON groups.***

	Week 0	**Week 3**	**Week 6**	**Week 9**	**Week 12**		*P Value*	
Δ[HHb + Mb]/$\Delta\dot{V}O_2$	***MOD A***	***MOD A***	***MOD A***	***MOD A***	***MOD A***	Time effect	Group effect	Time x Group
MICT	1.19 (0.11)	1.10 (0.06)*	1.07 (0.06)*	1.05 (0.07)*	1.04 (0.05)*			
LVHIIT	1.17 (0.08)	1.09 (0.06)*	1.07 (0.09)*	1.05 (0.02)*	1.01 (0.05)*	0.001	0.007	0.007
CON	1.09 (0.09)	1.19 (0.14)	1.11 (0.10)	1.16 (0.07)	1.13 (0.07)			

Data are mean (SD). [HHb+Mb], muscle deoxygenation; $\dot{V}O_2$, oxygen uptake * significantly different to week 0 ($P < 0.05$). For Δ[HHb + Mb]/Δ $\dot{V}O_2$ responses MICT $n = 10$, LVHIIT $n = 7$, CON $n = 8$.

4.3.3.2.3 Heart rate kinetics.

Parameter estimates for HR kinetics during the moderate-intensity component of the work-work bout are shown in Table 4.12. Baseline HR was significantly reduced after 6 weeks in the LVHIIT group while no changes in baseline HR were observed in the MICT and CON groups. The amplitude of the HR response was significantly decreased after 6 weeks of MICT with no changes observed in the LVHIIT and CON groups. The end exercise HR amplitude was also significantly decreased beyond 6 weeks of LVHIIT and beyond 3 weeks of MICT. In terms of τHR, there was a significant reduction in τHR after 6 weeks of MICT and after 6 weeks of LVHIIT, while no changes in τHR were observed in the CON group throughout the study period.

Table 4.12. ***Time course changes in parameter estimates of HR kinetics during moderate-intensity exercise in the MICT, LVHIIT and CON groups.***

	Week 0	Week 3	Week 6	Week 9	Week 12	*P Value*		
HR baseline (beats.min^{-1})						Time effect	Group effect	Time x Group
MICT	102 (15)	98 (13)	99 (16)	97 (15)	98 (12)			
LVHIIT	101 (10)	97 (11)	93 (9)*	95 (10)*	94 (8)*	<0.001	0.86	0.53
Control	102 (100	99 (11)	97 (10)	99 (12)	94 (11)			
HR A (beats.min^{-1})								
MICT	25 (6)	22 (6)	20 (6)*	18 (5)*	18 (6)*‡			
LVHIIT	28 (7)	28 (3)	26 (7)	25 (5)	25 (6)	0.003	0.05	0.001
Control	23 (3)	24 (5)	23 (5)	26 (4)	24 (5)			
HR End A (beats.min^{-1})								
MICT	127 (15)	120 (14)*	119 (18)*	115 (14)*	115 (12)*			
LVHIIT	129 (11)	125 (10)	120 (9)*	120 (8)*	119 (8)*	<0.001	0.81	0.06
Control	125 (9)	123 (12)	120 (12)	124 (13)	118 (14)			
τHR (s)								
MICT	69 (19)	55 (18)	63 (46)*	49 (19)*	45 (19)*			
LVHIIT	72 (26)	69 (36)	48 (18)*‡	48 (14)*‡	49 (13)*‡	<0.001	0.58	0.005
Control	58 (29)	58 (23)	65 (30)	55 (23)	58 (17)			

Data are mean (SD). HR, heart rate; A, amplitude of phase II response; τ, time constant of the response * significantly different from week 0 ($P < 0.05$); ‡ significantly different from week 3 ($P < 0.05$).

4.3.4 Effect of priming exercise on physiological responses during work-to-work exercise transitions.

4.3.4.1. $\dot{V}O2$, [HHb+Mb], and HR data from heavy-intensity (50% Δ) exercise.

4.3.4.1.1 $\dot{V}O_2$ kinetics.

The group mean parameter responses of the $\dot{V}O_2$ kinetic response during heavy-intensity exercise initiated from an elevated baseline are shown in Table 4.13 while all individual response parameters can be found in Appendix 8.6. In addition, group mean $\tau\dot{V}O_{2P}$ responses before and after PE are shown in Fig. 4.6. At week 0, priming exercise significantly reduced the amplitude of the $\dot{V}O_{2SC}$ in the LVHIIT and MICT groups by 45% and 23% respectively while there was a non-significant ~8% reduction in the $\dot{V}O_{2SC}$ amplitude observed in the CON group. In addition, priming exercise significantly reduced $\tau\dot{V}O_{2P}$ and the $\dot{V}O_2$ MRT in all groups. PE ceased to have an effect on the amplitude of the $\dot{V}O_{2SC}$ after 3 weeks of training in the LVHIIT and MICT groups. PE continued to reduce the amplitude of the $\dot{V}O_{2SC}$ in the CON group by ~8% although this did not reach statistical significance. PE ceased to reduce the $\dot{V}O_2$ MRT after 6 weeks of LVHIIT and MICT while PE continued to reduce the $\dot{V}O_2$ MRT at all time points in the CON group by 15-25% ($P < 0.05$). PE no longer reduced $\tau\dot{V}O_{2P}$ after 3 weeks of LVHIIT and after 6 weeks of MICT but continued to significantly reduce the $\tau\dot{V}O_{2P}$ of the CON at all time points.

Table 4.13. Group mean parameter estimates for $\dot{V}O_2$ kinetics during heavy-intensity exercise in the MICT, LVHIIT and CON groups throughout the intervention period during the unprimed and primed bouts.

	Week 0		Week 3		Week 6		Week 9		Week 12		*P value*			
$\dot{V}O_{2baseline}$ (L.min^{-1})	***Unprimed***	***Primed***	***Unprimed***	***Primed***	***Unprimed***	***Primed***	***Unprimed***	***Primed***	***Unprimed***	***Primed***	Time effect	Group effect	Priming effect	T x G x P
MICT	1.66 (0.43)	1.70 (0.40)	1.61 (0.40)	1.60 (0.37)	1.53 (0.40)	1.55 (0.39)	1.57 (0.41)	1.53 (0.38)	1.57 (0.35)	1.60 (0.34)				
LVHIIT	1.67 (0.67)	1.84 (0.33)	1.75 (0.19)	1.82 (0.25)	1.76 (0.22)	1.78 (0.22)	1.73 (0.22)	1.73 (0.23)	1.7 (0.23)	1.73 (0.24)	0.83	<0.001	0.58	0.99
Control	1.39 (0.33)	1.40 (0.37)	1.34 (0.31)	1.36 (0.33)	1.36 (0.31)	1.38 (0.33)	1.34 (0.32)	1.37 (0.33)	1.30 (0.56)	1.38 (0.33)				
$\dot{V}O_2$ A (L.min^{-1})														
MICT	0.50 (0.14)	0.46 (0.13)	0.45 (0.16)	0.46 (0.21)	0.53 (0.23)	0.50 (0.19)	0.53 (0.19)	0.56 (0.22)	0.59 (0.32)	0.52 (0.18)				
LVHIIT	0.55 (0.19)	0.54 (0.18)	0.52 (0.17)	0.48 (0.16)	0.55 (0.16)	0.57 (0.18)	0.55 (0.16)	0.61 (0.14)	0.56 (0.13)	0.61 (0.14)	0.35	0.02	0.86	0.97
Control	0.49 (0.29)	0.46 (0.24)	0.46 (0.23)	0.46 (0.21)	0.47 (0.22)	0.47 (0.21)	0.47 (0.23)	0.45 (0.19)	0.49 (0.22)	0.49 (0.20)				
$\tau\dot{V}O_{2P}$ (s)														
MICT	48 (10)	28 (7)[c]	30 (8)*	28 (7)	30 (5)*	27 (6)	30 (6)*	29 (7)	27 (5)*	31 (3)				
LVHIIT	43 (13)	27 (8)[c]	27 (6)*	28 (8)	33 (8)*	27 (7)	24 (11)*	28 (7)	28 (6)*	30 (8)	<0.0001	<0.0001	<0.0001	0.043
Control	45(6)	31 (6)[c]	41 (8)	35 (4)	39 (3)	31 (8)	40 (6)	31 (6)[c]	43 (6)	33 (5)[c]				
$\dot{V}O_2$ A_{SC} (L.min^{-1})														
MICT	0.18 (0.08)	0.14 (0.08)[c]	0.10 (0.05)*	0.12 (0.05)	0.09 (0.05)*	0.11 (0.05)	0.11 (0.06)*	0.10 (0.04)	0.10 (0.04)*	0.11 (0.06)				
LVHIIT	0.20 (0.07)	0.11 (0.04)[c]	0.14 (0.06)*	0.12 (0.06)	0.15 (0.09)†	0.11 (0.04)	0.14 (0.07)*	0.11 (0.06)	0.12 (0.07)*	0.10 (0.04)	0.03	0.15	0.005	0.04
Control	0.14 (0.05)	0.13 (0.03)	0.14 (0.08)	0.13 (0.08)[d]	0.14 (0.06)	0.12 (0.09)	0.15 (0.07)	0.12 (0.07)[d]	0.14 (0.06)	0.10 (0.05)				
$\dot{V}O_2$ MRT (s)														
MICT	80 (19)	49 (18)[c]	61 (13)*	50 (17)[c]	57 (15)*	49 (13)	57 (13)*	50 (10)	59 (14)*	50 (10)				
LVHIIT	73 (17)	51 (11)[c]	60 (13)*	44 (12)[c]	57 (11)*	55 (13)	55 (8)*	49 (10)	56 (7)*	49 (10)	0.007	0.3	<0.0001	0.09
Control	67 (10)	52 (17)[c]	65 (13)	51 (18)[c]	61 (12)	52 (20)[c]	64 (12)	49 (16)[c]	62 (11)	50 (16)[c]				

Data are mean (SD) [c] significantly different from unprimed within the same time point * significantly different from week 0. $\dot{V}O_2$, oxygen uptake; A_p, amplitude of phase II response; τ, time constant of the response; A_{SC}, amplitude of the slow component; MRT, mean response time; G, group; T, time; P, priming.

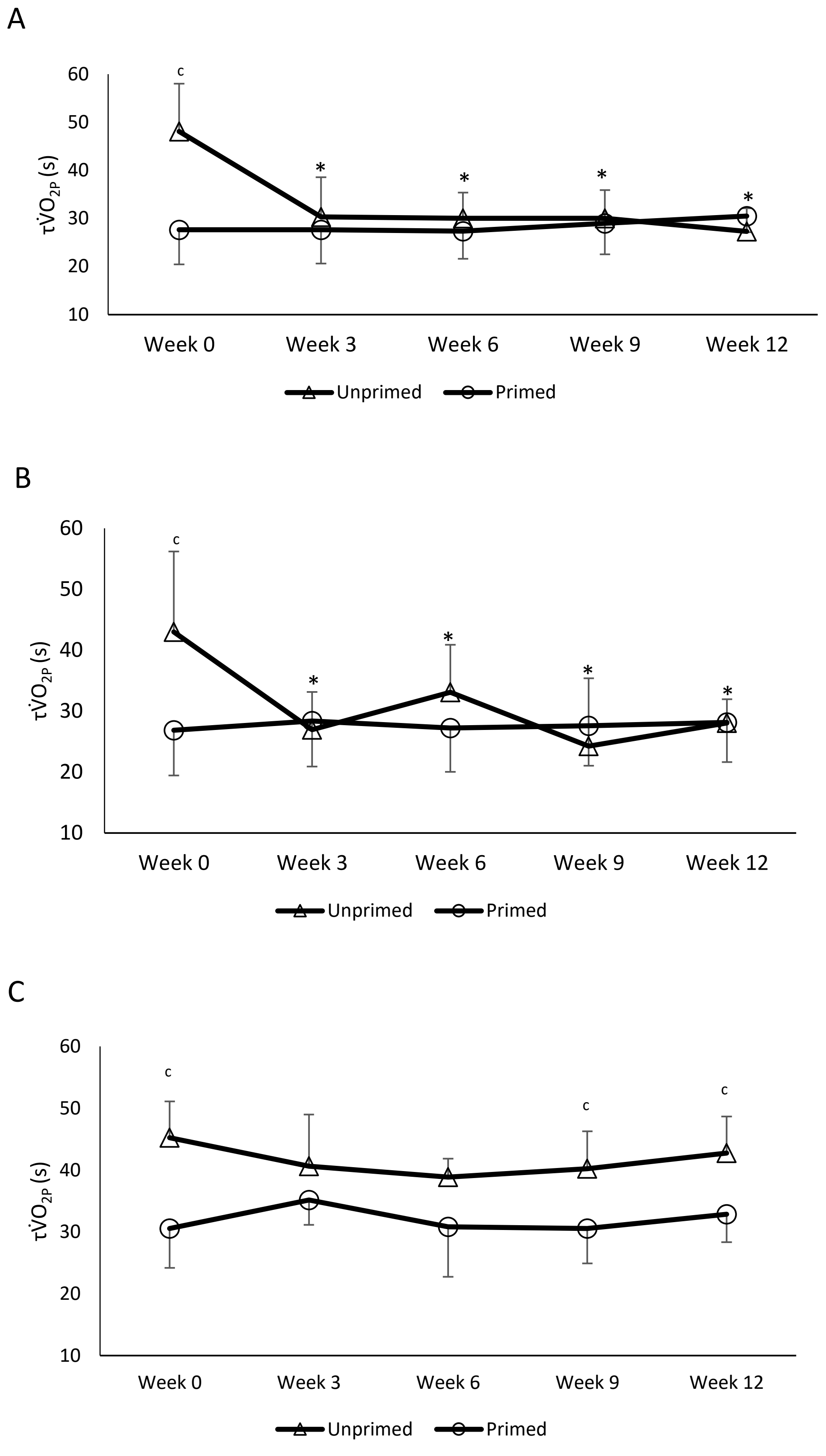


Figure 4.7 Panels A, B and C represent the time course changes in $\tau\dot{V}O_{2P}$ during unprimed and primed heavy-intensity exercise with training in the MICT, LVHIIT and CON groups respectively. [c] unprimed significantly different from primed ($P < 0.05$).*unprimed significantly different from week 0 ($P < 0.05$).

4.3.4.1.2. Muscle deoxygenation kinetics.

The group mean parameter responses of the [HHb + Mb] kinetic response during heavy-intensity exercise initiated from an elevated baseline are shown in Table 4.14 while all individual response parameters can be found in Appendix 8.6. Parameter estimates were similar across each of the 3 groups at week 0. PE had no effect on any parameter at any time point of the [HHb + Mb] response during heavy-intensity exercise initiated from an elevated baseline.

Table 4.14. ***Group mean parameter estimates for [HHb + Mb] kinetics during heavy-intensity exercise in the MICT, LVHIIT and CON groups throughout the intervention period during the unprimed and primed bouts.***

	Week 0		**Week 3**		**Week 6**		**Week 9**		**Week 12**		*P value*			
TD[HHb +Mb] (s)	***Unprimed***	***Primed***	***Unprimed***	***Primed***	***Unprimed***	***Primed***	***Unprimed***	***Primed***	***Unprimed***	***Primed***	Time effect	Group effect	Priming effect	T x G x P
MICT	8 (6)	12 (4)	9 (4)	8 (4)	9 (5)	9 (5)	10 (6)	9 (5)	9 (4)	8 (5)				
LVHIIT	11 (9)	13 (6)	12 (9)	9 (4)	8 (3)	13 (9)	5 (3)	8 (3)	6 (4)	8 (4)	0.81	0.48	0.14	0.37
Control	10 (3)	17 (8)	6 (4)	10 (2)	16 (20)	7 (5)	12 (6)	9 (4)	16 (14)	11 (11)				
τ[HHb +Mb] (s)														
MICT	31 (18)	20 (10)	25 (10)	24 (9)	32 (14)	27 (6)	28 (9)	30 (9)	36 (8)	32 (9)				
LVHIIT	30 (15)	18 (7)	25 (11)	21 (12)	34 (23)	21 (6)	27 (8)	30 (15)	34 (16)	24 (7)	0.87	0.004	0.58	0.59
Control	18 (5)	13 (3)	22 (16)	18 (7)	20 (9)	23 (4)	20 (10)	18 (9)	15 (7)	17 (3)				
τ'[HHb +Mb] (s)														
MICT	39 (16)	31 (9)	34 (8)	33 (8)	41 (14)	36 (10)	38 (10)	37 (10)	45 (10)	39 (9)				
LVHIIT	41 (23)	32 (12)	38 (16)	30 (14)	42 (24)	34 (11)	32 (9)	38 (16)	41 (16)	31 (5)	0.98	0.013	0.54	0.68
Control	28 (6)	32 (2)	26 (14)	27 (7)	34 (22)	38 (6)	29 (14)	25 (12)	35 (20)	29 (11)				
[HHb +Mb] MRT (s)														
MICT	53 (29)	43 (51)	50 (23)	41 (33)	58 (25)	48 (17)	43 (20)	38 (11)	58 (18)	56 (22)				
LVHIIT	35 (20)	28 (20)	44 (29)	34 (17)	60 (37)	43 (11)	49 (16)	45 (18)	57 (40)	41 (20)	0.45	0.41	0.002	0.99
Control	57 (46)	64 (59)	44 (46)	36 (24)	38 (20)	32 (10)	45 (40)	44 (44)	65 (53)	48 (35)				

Data are mean (SD). [HHb + Mb], deoxygenated haemoglobin concentration; TD, time delay, τ, time constant of the response; τ' [HHb + Mb], effective time constant; MRT, mean response time; G, group; T, time; P, priming. For [HHb +Mb] responses MICT n = 9, LVHIIT n = 7, CON n = 6.

4.3.4.1.3. Heart rate kinetics.

Group mean parameter HR responses for all 3 groups are displayed in Table 4.15 and individual responses can be found in Appendix 8.6. PE had no effect on baseline HR or End-HR values in any group at any time point. PE significantly reduced HR amplitude in the CON group at all time points. In the LVHIIT group, PE significantly reduced the HR amplitude at week 0 only.

Table 4.15. ***Group mean parameter estimates for HR kinetics during heavy-intensity exercise in the MICT, LVHIIT and CON groups throughout the intervention period during the unprimed and primed bouts.***

	Week 0		**Week 3**		**Week 6**		**Week 9**		**Week 12**		P Value			
Baseline HR (beats.min^{-1})	***Unprimed***	***Primed***	***Unprimed***	***Primed***	***Unprimed***	***Primed***	***Unprimed***	***Primed***	***Unprimed***	***Primed***	Time effect	Group effect	Priming effect	T x G x P
MICT	118 (27)	136 (15)	120 (13)	126 (13)	120 (16)	123 (17)	117 (14)	123 (14)	117 (12)	123 (14)				
LVHIIT	131 (21)	142 (10)	127 (13)	135 (11)	120 (10)	128 (7)	122 (8)	131 (7)	119 (9)	128 (10)	0.62	0.21	0.90	0.28
Control	127 (10)	137 (10)	124 (13)	133 (11)	122 (12)	135 (12)	114 (10)	137 (16)	121 (15)	131 (17)				
HR A (beats.min^{-1})														
MICT	27 (8)	23 (6)	25 (7)	21 (7)	20 (7)*	21 (7)	23 (8)*	19 (5)	21 (6)*	19 (6)				
LVHIIT	30 (7)	23 (5)^{c}	27 (4)	23 (3)	28 (5)	24 (5)	27 (4)	23 (3)	26 (4)	22 (4)	0.48	<0.0001	<0.0001	0.53
Control	31 (9)	23 (5)^{c}	33 (8)	27 (6)^{c}	34 (10)	22 (11)^{c}	32 (8)	26 (6)	35 (10)	22 (8)^{c}				
τHR (s)														
MICT	110 (23)	95 (41)	90 (17)*	90 (27)	80 (30)*	85 (34)	88 (25)*	82 (38)	77 (26)*	77 (25)				
LVHIIT	98 (30)	94 (19)	97 (13)	92 (10)	86 (13)	80 (15)	80 (35)	77 (16)	91 (16)	85 (21)	0.05	0.62	0.008	0.99
Control	95 (17)	76 (25)	95 (46)	80 (25)	92 (37)	79 (20)	85 (30)	77 (18)	100 (22)	78 (22)				
End-exercise HR (beats.min^{-1})														
MICT	145 (27)	159 (12)	145 (13)	147 (13)	140 (16)	144 (16)	140 (15)	142 (14)	138 (13)	142 (14)				
LVHIIT	161 (12)	165 (10)	154 (10)	158 (9)	148 (8)	153 (9)	149 (7)	154 (6)	146 (9)	150 (10)	0.65	0.09	0.57	0.31
Control	157 (10)	160 (10)	157 (12)	164 (14)	156 (12)	157 (14)	145 (30)	162 (16)	156 (13)	152 (22)				

Data are mean (SD) HR, heart rate; A, amplitude; TD, time delay, τ, time constant of the response* different from week 0 (P < 0.05). ^{c} significantly different from unprimed within the same time point (P < 0.05).

4.3.4.2. $\dot{V}O_2$, [HHb+Mb] and HR data from moderate-intensity (80% VT) exercise bouts.

4.3.4.2.1. $\dot{V}O_2$ kinetics.

The time course responses of the parameter estimates of $\dot{V}O_2$ kinetics during the moderate-intensity segment of the work-work transition with (MOD A) and without (MOD B) a prior bout of priming exercise are presented in Table 4.16. Individual parameter estimates are shown in Appendix 8.6. At baseline $\tau\dot{V}O_{2P}$ was similar across all groups but a prior bout of PE significantly reduced $\tau\dot{V}O_{2P}$ in all 3 groups. However, after 3 weeks of both LVHIIT and MICT training, PE no longer had an effect on any $\dot{V}O_2$ kinetic parameter during the moderate-intensity segment of the 'work-work' exercise in the LVHIIT and MICT groups. PE continued to significantly reduce $\tau\dot{V}O_{2P}$ in the CON group at all time points.

Table 4.16. ***Group mean parameter estimates for $\dot{V}O_2$ kinetics during moderate-intensity exercise in the MICT, LVHIIT and CON groups throughout the intervention period during the unprimed (MOD A) and primed (MOD B) bouts.***

	Week 0		**Week 3**		**Week 6**		**Week 9**		**Week 12**		*P Value*			
$\dot{V}O_2$ A_P (L.min^{-1})	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	Time effect	Group effect	Priming effect	T x G x P
MICT	0.8 (0.3)	0.71 (0.3)	0.66 (0.3)	0.62 (0.2)	0.68 (0.3)	0.68 (0.3)	0.64 (0.2)	0.65 (0.3)	0.70 (0.2)	0.64 (0.3)				
LVHIIT	0.94 (0.3)	0.80 (0.3)	0.83 (0.2)	0.81 (0.3)	0.81 (0.2)	0.83 (0.3)	0.86 (0.3)	0.75 (0.2)	0.85 (0.2)	0.81 (0.3)	0.87	<0.001	0.77	0.98
Control	0.54 (0.3	0.55 (0.2)	0.56 (0.2)	0.55 (0.2)	0.59 (0.2)	0.54 (0.2)	0.55 (0.2)	0.57 (0.2)	0.58 (0.2)	0.55 (0.2)				
$\dot{V}O_2$ End A (L.min^{-1})														
MICT	1.66 (0.4)	1.69 (0.4)	1.62 (0.4)	1.64 (0.4)	1.56 (0.4)	1.57 (0.4)	1.60 (0.4)	1.6 (0.4)	1.59 (0.4)	1.61 (0.4)				
LVHIIT	1.79 (0.3)	1.74 (0.4)	1.72 (0.2)	1.70 (0.3)	1.73 (0.2)	1.68 (0.3)	1.71 (0.2)	1.64 (0.3)	1.67 (0.2)	1.66 (0.3)	0.83	<0.001	0.49	1
Control	1.36 (0.3)	1.39 (0.3)	1.35 (0.3)	1.36 (0.3)	1.34 (0.3)	1.37 (0.3)	1.33 (0.3)	1.37 (0.3)	1.33 (0.3)	1.37 (0.3)				
$\tau\dot{V}O_{2P}$ (s)														
MICT	48 (7)	31 (5)^c	33 (5)*#	27 (4)	28 (7)*#	25 (2)	25 (3)*#	23 (2)	28 (5)*#	24 (3)				
LVHIIT	44 (9)	31 (7)^c	33 (4)*#	27 (3)	29 (4)*#	24 (5)	26 (4)*#	24 (4)	28 (4)*#	24 (3)	<0.0001	<0.0001	<0.0001	<0.001
Control	45 (8)	31 (5)^c	39 (9)	29 (4)^c	38 (7)	31 (6)^c	40 (10)	32 (6)^c	44 (7)	32 (6)^c				
$\dot{V}O_2$ gain (mL.min^{-1}.W^{-1})														
MICT	10.9 (2.6)	10.6 (1.8)	9.6 (2.0)	9.4 (1.5)	10.1 (1.7)	10.0 (1.3)	9.3 (0.8)	9.5 (1.5)	10.5 (2.3)	9.6 (1.5)				
LVHIIT	10.5 (2.3)	9.7 (1.9)	9.3 (1.6)	9.6 (1.6)	9.1 (1.6)	10 (1.4)	9.5 (1.5)	9.0 (0.9)	9.6 (1.5)	9.9 (0.9)	0.51	0.15	0.33	0.12
Control	9.2 (2.0)	9.8 (0.9)	9.8 (1.1)	9.8 (1.1)	10.5 (1.1)	9.5 (1.7)	9.8 (0.5)	10.0 (1.)	10.3 (0.9)	9.8 (0.7)				

Data are mean (SD). * Significantly different to week 0 (P < 0.05); ^{c} significantly different to MOD A within the same time point (P < 0.05). # significantly different from CON (P < 0.05). $\dot{V}O_2$, oxygen uptake; A, amplitude of the primary component; τ, time constant of the primary response; End A amplitude at the end of the exercise

4.3.4.2.2. Muscle deoxygenation kinetics and Δ [HHb + Mb]/Δ $\dot{V}O_2$ ratios.

Parameters for [HHb + Mb] response profiles are displayed in Table 4.17 and individual responses can be found in Appendix 8.6. There was no effect of PE on any [HHb + Mb] in any group throughout the training period. The overall Δ [HHb+Mb]/Δ$\dot{V}O_2$ ratio responses for the MICT, CON and LVHIIT are shown in Table 4.18. The Δ [HHb+Mb]/Δ$\dot{V}O_2$ ratio was significantly reduced with priming exercise at week 0 in all 3 groups. In the CON group this PE induced reduction in the Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio was maintained at all time points while in the LVHIIT and MICT groups the Δ [HHb + Mb]/Δ$\dot{V}O_2$ ratio of MOD A and MOD B were not significantly different at weeks 3, 6, 9, and 12.

Table 4.17. ***Parameter estimates for [HHb+ Mb] kinetics during moderate-intensity exercise in the MICT, LVHIIT and CON groups throughout the study period during the unprimed (MOD A) and primed (MOD B) bouts.***

	Week 0		Week 3		Week 6		Week 9		Week 12		*P Value*			
[HHb+Mb] A (a.u)	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	Time effect	Group effect	Priming effect	T x G x P
MICT	76 (45)	92 (60)	101 (59)	106 (54)	84 (51)	98 (42)	97 (61)	86 (51)	83 (32)	95 (36)				
LVHIIT	174 (94)	153 (150)	177 (96)	172 (123)	151 (101)	152 (118)	169 (104)	175 (141)	160 (101)	154 (124)	0.91	<0.0001	0.35	0.99
Control	74 (63)	77 (59)	77 (64)	89 (68)	71 (54)	77 (55)	70 (51)	76 (63)	75 (50)	75 (56)				
[HHb+Mb] End A														
MICT	37 (88)	73 (118)	24 (84)	32 (77)	1 (46)	149 (81)	7 (99)	20 (61)	15 (74)	167 (75)				
LVHIIT	141 (100)	161 (196)	127 (74)	159 (135)	109 (120)	97 (103)	133 (108)	155 (144)	101 (101)	128 (97)	0.38	<0.0001	0.02	0.99
Control	35 (66)	52 (84)	31 (83)	76 (84)	16 (76)	45 (65)	47 (102)	69 (76)	13 (62)	103 (50)				
TD[HHb+Mb] (s)														
MICT	10 (7)	12 (4)	16 (7)	14 (4)	15 (8)	14 (4)	16 (5)	15 (6)	17 (4)	15 (5)				
LVHIIT	14 (3)	13 (6)	15 (4)	12 (3)	13 (2)	13 (4)	13 (3)	12 (3)	13 (3)	13 (4)	0.24	0.08	0.053	0.87
Control	16 (3)	17 (8)	14 (3)	12 (3)	13 (4)	13 (3)	15 (3)	14 (4)	19 (6)	16 (8)				
τ[HHb+Mb] (s)														
MICT	15 (7)	20 (10)	17 (9)	12 (3)	15 (10)	17 (10)	20 (18)	15 (6)	16 (5)	18 (9)				
LVHIIT	11 (6)	19 (9)	12 (6)	15 (6)	13 (2)	14 (7)	13 (3)	12 (4)	11 (4)	14 (9)	0.97	0.01	0.43	0.98
Control	12 (6)	13 (3)	11 (5)	14 (3)	18 (11)	19 (10)	17 (9)	16 (6)	20 (21)	16 (4)				
τ ‘ [HHb+Mb] (s)														
MICT	26 (9)	32 (11)	33 (14)	33 (9)	30 (15)	30 (11)	36 (22)	31 (6)	33 (8)	33 (10)				
LVHIIT	26 (4)	32 (12)	27 (6)	26 (5)	25 (3)	27 (8)	24 (4)	24 (5)	22 (4)	27 (12)	0.69	0.002	0.81	0.98
Control	28 (5)	30 (6)	24 (5)	26 (5)	30 (10)	32 (9)	32 (8)	29 (8)	39 (24)	33 (9)				

Data are mean (SD) [HHb + Mb], deoxygenated haemoglobin concentration; $\dot{V}O_2$, oxygen uptake; A, amplitude; TD, time delay, τ, time constant of the response; τ’ [HHb + Mb], effective time constant; MRT, mean response time. For [HHb + Mb] responses MICT *n* = 10, LVHIIT *n* = 7, CON *n* = 8.

Table 4.18. Δ ***[HHb + Mb]/$\Delta\dot{V}O_2$ parameters for the MICT, LVHIIT and CON groups during the study period during the unprimed (MOD A) and primed (MOD B) bouts.***

	Week 0		**Week 3**		**Week 6**		**Week 9**		**Week 12**		*P Value*			
Δ[HHb + Mb]/$\Delta\dot{V}O_2$	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	Time effect	Group effect	Priming effect	T x G x P
MICT	1.19 (0.11)	1.06 (0.10)[c]	1.10 (0.06)*	1.01 (0.06)	1.07 (0.06)*	0.97 (0.10)	1.05 (0.07)*	1.03 (0.05)	1.04 (0.05)*	0.98 (0.07)				
LVHIIT	1.17 (0.08)	1.04 (0.06)[c]	1.09 (0.06)*	1.02 (0.06)	1.07 (0.09)*	1.04 (0.07)	1.05 (0.02)*	1.05 (0.03)	1.01 (0.05)*	1.05 (0.07)	0.003	<0.001	<0.001	0.02
CON	1.09 (0.09)	1.01 (0.06)[c]	1.19 (0.14)	1.08 (0.04)[c]	1.11 (0.10)	1.03 (0.08)[c]	1.16 (0.07)	1.03 (0.05)[c]	1.13 (0.07)	0.99 (0.15)[c]				

Data are mean (SD). [HHb + Mb], deoxygenated haemoglobin concentration;* significantly different to week 0 ($P < 0.05$); [c] significantly different from MOD A within the same time point ($P < 0.05$). For Δ[HHb + Mb]/Δ $\Delta\dot{V}O_2$ responses MICT n = 10, LVHIIT n = 7, CON n = 8.

4.3.4.2.3. Heart rate kinetics.

Parameter responses for HR kinetics during MOD A and MOD B are shown in Table 4.19. There was no effect of PE on any HR parameter at baseline or during the intervention period in any group during MOD A or MOD B.

Table 4.19. ***Group mean parameter estimates for HR kinetics during moderate-intensity exercise in the MICT, LVHIIT and CON groups throughout the study period during the unprimed (MOD A) and primed (MOD B) bouts.***

	Week 0		**Week 3**		**Week 6**		**Week 9**		**Week 12**		*P Value*			
HR baseline (beats.min^{-1})	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	***MOD A***	***MOD B***	Time effect	Group effect	Priming effect	T x G x P
MICT	102 (15)	116 (14)	98 (13)	106 (13)*	99 (16)	105 (15)*	97 (15)	105 (15)*	97 (11)	106 (13)*				
LVHIIT	101 (10)	113 (9)	97 (11)	108 (9)	93 (9)	101 (9)*	95 (10)*	104 (10)*	94 (8)*	101 (7)*	0.62	0.21	0.90	0.28
Control	102 (100	110 (9)	99 (11)	107 (9)	97 (10)	109 (8)	99 (12)	110 (15)	94 (11)	129 (17)				
HR A (beats.min^{-1})														
MICT	25 (6)	20 (5)	22 (6)	19 (6)	20 (6)*	18 (6)	18 (5)*	21 (15)	18 (6)*‡	15 (5)				
LVHIIT	28 (7)	27 (7)	28 (3)	25 (4)	26 (7)	26 (5)	25 (5)	25 (5)	25 (6)	24 (5)	0.48	<0.001	<0.001	0.53
Control	23 (3)	23 (4)	24 (5)	25 (5)	23 (5)	24 (5)	26 (4)	24 (5)	24 (5)	24 (7)				
End exercise HR (beats.min^{-1})														
MICT	127 (15)	136 (15)	120 (14)*	125 (13)*	119 (18)*	123 (15)*	115 (14)*	122 (14)*	115 (12)*	125 (13)*				
LVHIIT	129 (11)	139 (10)	125 (11)	133 (10)	120 (9)	127 (7)*	120 (8)*	129 (6)*	119 (9)*	125 (7)*	0.65	0.09	0.57	0.31
Control	125 (9)	134 (9)	123 (12)	131 (10)	120 (12)	133 (11)	124 (13)	135 (16)	118 (14)	129 (17)				
τHR (s)														
MICT	69 (19)	76 (19)	55 (18)	55 (22)*	63 (46)	53 (15)*	49 (19)*	50 (18)*	45 (19)*	50 (18)*				
LVHIIT	72 (26)	66 (21)	69 (36)	56 (14)	48 (18)	49 (15)*	48 (14)*‡	46 (13)*	49 (13)*‡	45 (14)*	0.05	0.62	0.008	0.99
Control	58 (29)	53 (13)	58 (23)	59 (21)	65 (30)	63 (21)	55 (23)	59 (23)	58 (17)	62 (21)				

Data are mean (SD). * Significantly different from week 0 ($P < 0.05$); ‡ significantly different from week 3 ($P < 0.05$); HR, heat rate; A, amplitude of the HR response; TD, time delay, τ, time constant of the response.

4.4. Discussion.

The current study primarily investigated the effects of LVHIIT and MICT on the $\dot{V}O_2$ kinetic responses during heavy-intensity exercise initiated from an elevated baseline in individuals with uncomplicated T2DM, while a secondary aim of this study was to assess the effects of LVHIIT and MICT on the effects of priming exercise on $\dot{V}O_2$ kinetics during heavy-intensity exercise initiated from an elevated baseline. The principal findings of this study were as follows;

1. Both LVHIIT and MICT significantly reduced $\tau\dot{V}O_{2P}$, $\dot{V}O_{2SC}$ amplitude and $\dot{V}O_2$ MRT by a similar magnitude after only 3 weeks of training and these changes were maintained until the end of the intervention.
2. At baseline (week 0), PE significantly reduced the $\dot{V}O_2$ MRT and τ $\dot{V}O_{2P}$ in all three groups, and $\dot{V}O_{2SC}$ amplitude in both training groups. However, beyond 3 weeks PE ceased to have any effect on these parameters in the MICT and LVHIIT groups while in the CON group, PE continued to have a positive effect on $\dot{V}O_2$ kinetics at all time points.
3. Training or PE had no effect on [HHb+Mb]. Thus, LVHIIT and MICT enhanced $\dot{V}O_2$ kinetics during heavy-intensity exercise initiated from an elevated baseline, were due to, at least in part, an increase in muscle blood flow and/or improved muscle perfusion to metabolic rate.

4.4.1. Effect of exercise training on $\dot{V}O_2$ and muscle deoxygenation kinetics during heavy-intensity cycling exercise initiated from an elevated baseline.

Exercise training is effective at accelerating the $\dot{V}O_2$ kinetics response during stepwise transitions from rest to moderate or heavy-intensity exercise in both individuals with T2DM and healthy peers (Brandenburg *et al.* 1999; Berger *et al.* 2006; Bailey *et al.* 2009; MacAnaney *et al.* 2012; Nevin *et al*. 2018). To our knowledge this is the first study to investigate whether LVHIIT and MICT accelerates $\dot{V}O_2$ kinetics during heavy-intensity exercise initiated from an elevated baseline in individuals with T2DM. In the present study, after 3 weeks of both LVHIIT and MICT there was a significant decrease in the $\dot{V}O_2$ MRT in both groups which was of a similar magnitude and was due to the combination of a reduced $\tau\dot{V}O_{2P}$ and a reduction in the amplitude of the $\dot{V}O_{2SC}$. After 3 weeks of MICT, $\tau\dot{V}O_{2P}$ was reduced by ~38% (P < 0.05) while the amplitude of the $\dot{V}O_{2SC}$ was reduced by ~25% (P < 0.05). In regard to LVHIIT, the amplitude of the $\dot{V}O_{2SC}$ reduced by~20% (P < 0.05) after 3 weeks of training and $\tau\dot{V}O_{2P}$ was reduced by ~37% (P < 0.05). This is clinically relevant in T2DM as activities of daily living involve transitions between different exercise intensities, thus an acceleration in VO_2 kinetics with training may increase the ease with which individuals with T2DM can complete daily functional tasks. The fact that both LVHIIT and MICT accelerated VO_2 kinetics within a similar timeframe and by a similar magnitude provides evidence that both types of exercise are effective at increasing submaximal exercise capacity when appropriately prescribed in T2DM.

These findings are in line with current research in healthy populations which has shown that both high-intensity training and MICT can improve $\dot{V}O_2$ kinetics during 'work-to-work' exercise bouts (Da Boit *et al*. 2014). Da Boit *et al*. (2014) reported a significant acceleration of $\tau\dot{V}O_{2P}$ during severe-intensity exercise initiated from an elevated baseline in a group of young healthy males and females following 2 weeks of either RST (4-6 'all-out' sprints interspersed by 4 mins of recovery) or MICT (60-100 mins cycling at 90% GET). The authors reported a significant reduction in the $\tau\dot{V}O_{2P}$ of the severe-intensity exercise bout in both the RST (-26%) and MICT (-22%) groups however, unlike the current study they did not observe any changes in the amplitude of the $\dot{V}O_{2SC}$.

The mechanisms of adaptation in $\tau\dot{V}O_{2P}$ during 'work-to-work' transitions are unclear. In healthy populations when 'work-to-work' transitions were performed within the moderate-intensity domain, it was shown that LVHIIT significantly reduces $\tau\dot{V}O_{2P}$ during the upper step of the transition (45%GET→90%GET) while also abolishing the overshoot in the $\Delta[HHb+Mb]/\Delta\dot{V}O_2$ ratio which is indicative of an improvement in O_2 delivery (Williams *et al.* 2013). It is reasonable to suggest that the underlying mechanism for the reduction in $\tau\dot{V}O_{2P}$ in the current study could at least in part be due to an improvement in O_2 delivery. At week 0 we observed that a prior bout of heavy-intensity exercise reduced the $\tau\dot{V}O_{2P}$ of a subsequent bout of heavy-intensity exercise during the 'work-to-work' transition in all three groups. However, the priming effect was no longer significant after 3 weeks of LVHIIT and MICT. Since priming exercise has only been shown to be effective in reducing subsequent $\tau\dot{V}O_{2P}$ during exercise initiated from an elevated baseline in conditions whereby O_2 delivery is impaired

(Di Menna *et al.* 2010; Gildea *et al.* 2018), it is tempting to suggest that the abolishment of the priming effect on subsequent reductions in $\tau\dot{V}O_{2P}$ with LVHIIT and MICT beyond 3 weeks of training is due to an improvement in microvascular blood flow delivery resulting in an improved matching of O_2 delivery and utilisation.

Alongside reductions in $\tau\dot{V}O_{2P}$ with training, we observed a significant reduction in the amplitude of the $\dot{V}O_{2SC}$ with LVHIIT and MICT after only 3 weeks of training. This is in contrast to the findings by Da Boit *et al.* (2014) in healthy participants who found no changes in the amplitude of the $\dot{V}O_{2SC}$ during work-to-work transitions after 2 weeks with either RST or MICT, although they did speculate that a longer duration training programme may allow for training induced adaptations in the $\dot{V}O_{2SC}$. Results from our laboratory and others have indicated that both MICT and LVHIIT can significantly reduce the amplitude of the $\dot{V}O_{2SC}$ during heavy-intensity exercise when it is initiated from a low baseline or resting conditions in both healthy populations and T2DM (Berger *et al.* 2006; Bailey *et al.* 2009; Nevin *et al.* 2018). Berger *et al.* (2006) reported a similar significant decrease in the amplitude of the $\dot{V}O_{2SC}$ after 6 weeks of LVHIIIT (20 x 60 s at 90% $\dot{V}O_{2peak}$ interspersed by 60s rest) or MICT (30 mins at 60% $\dot{V}O_{2peak}$) in young healthy individuals during transitions to severe-intensity exercise. More recently, Bailey *et al.* (2009) reported a significant decrease in the amplitude of the $\dot{V}O_{2SC}$ after just 2 weeks of RST (4-6 'all-out' sprints interspersed by 4 min rest) while 2 weeks of MICT (cycling at 90% for a duration that resulted in an equal work volume to RST) induced no changes in $\dot{V}O_{2SC}$ (Bailey *et al.* 2009). In addition, the τ [HHb + Mb] during severe-intensity exercise was significantly shorter with RST suggesting an improvement in muscle oxidative capacity (Bailey *et al.* 2009). In terms of T2DM, recent data obtained from participants who took part in the present intervention has shown that 12 weeks of MICT resulted in a significant reduction in the amplitude of the $\dot{V}O_{2SC}$ while 12 weeks of LVHIIT induced a tendency towards a reduction in the amplitude of the $\dot{V}O_{2SC}$ in transitions to a heavy-intensity from unloaded cycling ($P<0.10$) (Nevin *et al.* 2018).

The working skeletal muscle accounts for ~80% of the $\dot{V}O_{2SC}$ (Poole *et al.* 2008). Therefore it is reasonable to infer that exercise induced changes in the amplitude of the $\dot{V}O_{2SC}$ are as a result of adaptations in skeletal muscle properties and structure. However, muscle biopsies from the participants in the current study were not taken so therefore this hypothesis could not be tested.

Moderate-intensity exercise predominantly involves the recruitment of Type I oxidative muscle fibres (Krustrup *et al.* 2009) so it is unsurprising that chronic moderate-intensity exercise significantly increases Type I fibre capillarisation (Dudley *et al.* 1982) and local mitochondrial oxidative enzyme activity (Ingjer, 1979). Furthermore, there is evidence of duration-dependent Type II muscle fibre recruitment during moderate-intensity continuous exercise (Gollnick *et al*. 1974). Therefore, it cannot be excluded that MICT recruited and provoked training adaptations in Type II muscle in the present study. In fact, previous evidence has shown that chronic exercise training increases the capillarisation of Type II muscle fibres (Ingjer, 1979). Moreover, exercise training has been shown to convert Type IIx fibres to the more oxidative Type IIa (Anderson & Henriksson 1979) phenotype, and even Type II fibres to Type I fibres (Howald *et al*. 1985). In addition, MICT has been shown to significantly increase oxidative enzyme activity and mitochondrial size and protein content in individuals with T2DM (Toledo *et al.* 2007; Meex *et al.* 2010; Pheilix *et al.* 2010). Therefore, with the improvements in the oxidative capacity of Type I fibres and the phenotypical changes in Type II fibres observed with training it is possible that in the current study MICT increased the relative contribution of oxidative fibres to force production during higher-intensity exercise negating the need to recruit higher level glycolytic fibres and thus, reducing the amplitude of the $\dot{V}O_{2SC}$.

In regard to LVHIIT, it is also likely that adaptations in skeletal muscle structure and mitochondrial oxidative capacity induced the observed reductions in the amplitude of the $\dot{V}O_{2SC}$ in the present study. At exercise intervals performed near to or above $\dot{V}O_{2max}$ Type II muscle fibres are predominately recruited (Essen, 1978; Da Boit *et al*. 2014) and current evidence indicates that high-intensity training induces significant improvements in oxidative enzyme activity within Type II fibres (Gjovaag *et al.* 2008; Egan *et al*. 2010), improves Type II muscle fibre capillarisation (Jensen *et al*. 2004) and promotes the conversion of Type IIx fibres to Type IIa fibres (Allemeier *et al.* 1994). Moreover, 2 weeks of

LVHIIT increases CS activity (a marker of mitochondrial oxidative activity) in T2DM (Little *et al.* 2011) and, LVHIIIT has also been shown to be a potent stimulator of the activity of peroxisome-proliferator activated ϒ coactivator (PGC-1α), which is thought to be the master regulator of mitochondrial biogenesis (Gibala *et al.* 2012). Indeed, studies exploring the effect of LVHIIT on PGC-1α levels in healthy populations have indicated a ~50% increase in PGC-1α activity with LVHITT which is associated with significant increases in mitochondrial content and oxidative activity (Little *et al.* 2011b; Hood *et al.* 2011; Gibala *et al*. 2012).

4.4.2. Effect of exercise training on $\dot{V}O_2$ and muscle deoxygenation kinetics during moderate-intensity cycling exercise.

Consistent with the findings of Chapter 3, LVHIIT and MICT accelerated the $\dot{V}O_2$ kinetics during moderate-intensity exercise by a similar magnitude after 3 weeks of training while there was no change in any ‘unprimed’ $\dot{V}O_2$ parameters in the CON group throughout the intervention period. In addition, the Δ [HHb+Mb]/$\Delta\dot{V}O_{2P}$ overshoot observed during moderate-intensity exercise at week 0 was significantly reduced beyond 3 weeks of both LVHIIIT and MICT. This is suggestive of an improvement in the balance of O_2 delivery and utilisation being the underlying mechanism of the accelerated $\dot{V}O_2$ kinetics. These findings are consistent with those of Murias *et al*. (2010) who reported a significant reduction in $\tau\dot{V}O_{2P}$ in both healthy young and older men after 3 weeks of a 12 week MICT intervention which was accompanied by a significant reduction in the overshoot of the Δ[HHb+Mb]/$\Delta\dot{V}O_{2P}$ ratio (Murias *et al*. 2010).

As observed in Chapter 3, a loss of the priming-exercise induced reductions in $\tau\dot{V}O_{2P}$ on the subsequent bout of moderate-intensity exercise were evident beyond 3 weeks during both LVHIIT and MICT. Since, PE is most effective when there is a constrained O_2 delivery this adds further credence to the notion that both LVHIIT and MICT induced improvements in O_2 delivery resulting in an ameliorated matching of O_2 delivery to utilisation during moderate-intensity exercise.

4.4.3. Effect of priming exercise on $\dot{V}O_2$ and muscle deoxygenation kinetics during heavy-intensity cycling exercise initiated from an elevated baseline.

In the present study, completion of a prior bout of PE resulted in a significant reduction in $\tau\dot{V}O_{2P}$ during heavy-intensity exercise initiated from an elevated baseline in all 3 groups (MICT; -35%; LVHIIT; -25%; CON; -21%). These findings are in agreement with recent findings from our laboratory showing that a prior bout of PE significantly reduced the $\tau\dot{V}O_{2P}$ of a subsequent bout of heavy-intensity exercise initiated from an elevated baseline by ~22% in a group of individuals with uncomplicated T2DM including individuals relatively younger than those involved in the present study (46 ± 8 yr vs 53 ± 10 yr) (Gildea *et al.* 2018). Furthermore, Gildea *et al*. (2018) reported only a minimal 2% reduction in $\tau\dot{V}O_{2P}$ following a bout of prior PE in a group of sedentary but otherwise healthy controls. Typically, priming exercise only manipulates $\tau\dot{V}O_{2P}$ in the presence of an impairment in O_2 delivery. In this regard, impairments in microvascular blood flow during exercise are evident in T2DM (Bauer *et al.* 2007; Rocha *et al.* 2016). Thus, the results of the current study and those of Gildea *et al.* (2018), suggest that PE effectively enhances O_2 delivery therefore reducing $\tau\dot{V}O_{2P}$ during heavy-intensity exercise in individuals with T2DM. In addition, when O_2 delivery has been deliberately compromised in healthy populations, such as when moving from the upright to the supine cycling positions (i.e. reducing muscle perfusion pressure) there is further evidence that PE significantly reduces $\tau\dot{V}O_{2P}$ during a subsequent bout of heavy-intensity exercise. For instance, Di Menna *et al*. (2010) reported a 37% ($P < 0.05$) reduction in $\tau\dot{V}O_{2P}$ during a bout of severe-intensity cycling exercise in the supine position initiated from an elevated baseline subsequent to PE in a group of young active males (Di Menna *et al*. 2010) whereas no effect of PE on the $\tau\dot{V}O_{2P}$ were evident in the upright position (Di Menna *et al.* 2008).

In addition to the reductions in $\tau\dot{V}O_{2P}$ observed in the present study, significant reductions in the amplitude of the $\dot{V}O_{2SC}$ in the LVHIIT (-37%) and MICT (-27%) groups and a marked tendency for a reduction in the CON group (-20%) were also observed after PE. These findings are in line with previous work from our laboratory that showed a significant reduction in in the amplitude of the $\dot{V}O_{2SC}$ following PE in younger individuals with uncomplicated T2DM (Gildea *et al*. 2018). Furthermore, our findings are consistent with those from healthy populations who have shown a significant reduction in amplitude of the $\dot{V}O_{2SC}$ following PE but, unlike in T2DM in the absence of a change in $\tau\dot{V}O_{2P}$ (DiMenna *et al*. 2008; Bailey *et al.* 2009; Di Menna *et al*. 2010b).

As previously mentioned, it is thought that skeletal muscle accounts for 80% of the amplitude of the $\dot{V}O_{2SC}$ (Poole *et al.* 2008), therefore it is likely that the reduction in $\dot{V}O_{2SC}$ with PE observed in the current study and others is due to an alteration in motor unit recruitment patterns rather than an adaptation in O_2 delivery. In this regard, Di Menna *et al.* (2008) reported a significant reduction in the amplitude of the $\dot{V}O_{2SC}$ with PE during severe-intensity exercise in the upright position which was accompanied by reductions in iEMG activity between minute 2 and 6 of the primed severe-intensity bout (Di Menna *et al.* 2008). These results imply that the reduction in the amplitude of the $\dot{V}O_{2SC}$ was not due to a PE-induced enhancement in O_2 delivery but rather an alteration in motor unit recruitment pattern such that the requirement of further muscle recruitment and associated $\dot{V}O_2$ demand were reduced (Burnley *et al*. 2002; Di Menna *et al*. 2010). Further evidence for a priming-induced alteration in motor unit recruitment was reported by Di Menna *et al.* (2010b) who observed a significant reduction in iEMG activity during a high-intensity prone knee extension exercise subsequent to a bout of PE in young healthy males which was accompanied by significant reductions in the amplitude of the PCr slow component as well in PCr breakdown. The authors suggested that these results represented a delayed onset of muscle fibre recruitment in response to PE resulting in a reduction in the amplitudes of the PCr and $\dot{V}O_2$ slow components (Di Menna *et al.* 2010b).

In the present study, although a significant reduction in $\tau\dot{V}O_{2P}$ and an overall reduction in $\dot{V}O_2$ MRT with PE was observed, there were no changes in [HHb+Mb] kinetic responses. Since the [HHb+Mb] signal is accepted as a surrogate of O_2 extraction in the area of interrogation (DeLorey *et al.* 2004), it is tempting to infer that the reduction in $\tau\dot{V}O_{2P}$ observed with PE was as a result of an improvement in local O_2 delivery. Therefore, from the current study it can be concluded that PE positively manipulates the $\dot{V}O_2$ kinetic response of a subsequent bout of heavy-intensity exercise initiated from an elevated baseline.

As the acceleration of the $\dot{V}O_2$ MRT was due to a combination of a reduction in $\tau\dot{V}O_{2P}$ and the amplitude of the $\dot{V}O_{2SC}$ it can be inferred an improved O_2 delivery and an alteration in motor unit recruitment contributed to this effect.

4.4.4. Effect of priming exercise on $\dot{V}O_2$ and muscle deoxygenation kinetics during moderate-intensity cycling exercise.

Priming exercise significantly reduced the $\tau\dot{V}O_{2P}$ of the moderate-intensity component of the 'work-work' transition in all three groups at baseline by a similar magnitude (MICT, -35%; LVHIIT, -30%; CON, 31%). This is consistent with the results from Chapter 3 and from previous results from our laboratory and other laboratories demonstrating that in T2DM and in conditions whereby $\tau\dot{V}O_{2P}$ is constrained by impairments in O_2 delivery, a prior bout of PE is effective at accelerating subsequent $\dot{V}O_2$ kinetics responses (DeLorey *et al.* 2004; Murias *et al.* 2011; Rocha *et al.* 2016). In the present study PE did not affect [HHb+Mb] responses during a subsequent bout of moderate-intensity exercise in any of the 3 groups however, PE did abolish the overshoot of the Δ [HHb+Mb]/$\Delta\dot{V}O_2$ ratio that had been observed during the unprimed bout in all three groups at baseline.

In regards to training adaptations, beyond 3 weeks of either LVHIIT or MICT, PE no longer had an effect on any parameter of the $\dot{V}O_2$ kinetics response in the 2 groups. However, in the CON group PE continued to significantly reduce $\tau\dot{V}O_{2p}$ compared with the 'unprimed' $\tau\dot{V}O_{2p}$ at each time point. The underlying mechanism for the diminished effect of priming exercise after training remains unclear. However, with both types of training we observed a significant reduction in the unprimed Δ [HHb + Mb]/$\Delta\dot{V}O_2$ ratios so that they were similar to the post-priming Δ [HHb + Mb]/$\Delta\dot{V}O_2$ ratios from the 3rd week of training onwards which suggests that O_2 delivery and utilisation were well matched beyond 3 weeks of training. Thus, in agreement with the results from Chapter 3 the acceleration of the $\dot{V}O_2$ kinetics response during moderate-intensity exercise was attributed to a better matching of microvascular O_2 delivery to utilisation.

4.4.5. Conclusion.

In conclusion, both LVHIIT and MICT are safe and effective interventions that accelerate the $\dot{V}O_2$ kinetics response during heavy-intensity exercise initiated from an elevated baseline in individuals with uncomplicated T2DM. Both forms of training induced a reduction in the amplitude of the $\dot{V}O_{2SC}$ and an acceleration of $\tau\dot{V}O_{2P}$ which was accompanied by no changes in [HHb + Mb] kinetics responses. Improvements in O_2 delivery during exercise are likely to have contributed to the reduction in $\tau\dot{V}O_{2P}$ with training while, the reduction in the amplitude of the $\dot{V}O_{2SC}$ may have been caused by exercise induced changes in skeletal muscle properties and motor unit recruitment patterns. The disappearance of the effect of priming exercise on the subsequent speeding of $\dot{V}O_2$ MRT after 3 weeks of MICT and LVHIIT adds credence to the idea that training improved O_2 delivery resulting in an improved balance between O_2 delivery and utilisation.

Chapter 5: *General discussion.*

Individuals with uncomplicated T2DM present with an impairment in maximal and submaximal exercise capacity. The consistent reporting of a reduction in $\dot{V}O_{2max}$ in the region of 20% (Green *et al*. 2015) is of particular concern in this population as reductions in maximal exercise performance are strongly associated with increases in all-cause mortality (Wei *et al*. 2000). Recent work from our laboratory has shown that at submaximal levels middle-aged individuals with T2DM have a slower rate of pulmonary oxygen uptake kinetics than healthy controls (O'Connor *et al.* 2015; Rocha *et al.* 2016). These slowed $\dot{V}O_2$ kinetics result in an increased O_2 deficit thus, creating a dependency on anaerobic energy stores to produce ATP during the early stages of exercise. This consequently increases the accumulation of metabolic waste products resulting in earlier muscular fatigue and increased effort perception during exercise. Furthermore, individuals with T2DM report exercise as more strenuous than healthy controls even at low-intensities (Huebschmann *et al.* 2009) which is likely related to the exercise intolerance observed in individuals with T2DM at maximal and submaximal levels (Bauer *et al.* 2007; MacAnaney *et al.* 2012; Green *et al.* 2015).

Numerous studies have highlighted the benefits of regular MICT for individuals living with T2DM including improvements in glycaemic control (Balducci *et al.* 2012), lipid profiles (Sixt *et al.* 2010), body composition (Cuff *et al.* 2003), vascular function (Madsen *et al*. 2015) and exercise capacity at maximal and submaximal levels (MacAnaney *et al.* 2012). However, participation and adherence to exercise in this population remains low (Regensteiner *et al.* 2004). As a 'lack of time' is consistently identified as one of the key barriers of exercise participation in this population, time efficient interventions such as LVHIIT have come to the attention of clinicians and researchers.

5.1. Summary of main findings.

It has been shown that LVHIIT and MICT can both induce significant benefits in $\dot{V}O_{2max}$ in individuals with uncomplicated T2DM (MacAnaney *et al.* 2012; Mitranun *et al.* 2014; Francois *et al.* 2017) however, previous studies have not explored the mechanisms and time course of adaptation of these effects. In *Experiment 1* $\dot{V}O_{2max}$ was assessed using a ramp incremental cycling test to exhaustion (RI) every 3 weeks during a 12 week exercise intervention. During the RI tests the effects of exercise training on the profile of fractional muscle oxygen extraction, as estimated using the NIRS-derived deoxygenated haemoglobin signal ([HHb+Mb]), as well as Q_{max} responses using the modelflow method and inert gas rebreathing methods were assessed. After just 3 weeks of both LVHIIT and MICT and until the completion of the training interventions a significant increase in $\dot{V}O_{2max}$ which was accompanied by a significant reduction of the primary slope (S_1) of the bi-linear regression model of Δ [HHb+Mb] % vs $\%PO_{peak}$ was observed. This is indicative that one of the mechanisms underlying the improvement in exercise capacity in both training groups was an improved ability to deliver and/or redistribute O_2 to the exercising tissue resulting in a decreased reliance on O_2 extraction for a given increase in workload. It was observed that Q_{max} increased in the MICT and LVHIIT groups after 3 and 9 weeks respectively which suggests that adaptations in $\dot{V}O_{2max}$ were, at least in part, also due to adaptations in the central determinants of $\dot{V}O_{2max}$.

Pulmonary $\dot{V}O_2$ kinetics are profoundly slowed in middle-aged individuals with uncomplicated T2DM at the onset of moderate-intensity exercise (Regensteiner *et al.* 1998; Brandenburg *et al.* 1999; O'Connor *et al.* 2015). To the author's knowledge the study described in *Experiment 2* is the first to provide an insight into the time course and mechanisms of adaptation in $\dot{V}O_2$ kinetics in response to MICT and LVHIIT in individuals with uncomplicated T2DM. Through the measurement of the NIRS-derived [HHb+Mb] signal and $\dot{V}O_2$ responses the Δ [HHb+Mb]/Δ$\dot{V}O_2$ ratios were calculated in order to estimate the balance of microvascular O_2 delivery and utilisation during moderate-intensity exercise. The $\dot{V}O_2$ kinetics responses of the individuals in the LVHIIIT and MICT groups were significantly accelerated at 3 weeks of training with no further changes thereafter. In addition, the lack of adjustment in [HHb+Mb] profiles at any time point during training resulted in a significant reduction in the 'overshoot' of the Δ[HHb+Mb]/Δ$\dot{V}O_2$ ratios beyond 3 weeks of training, previously observed at baseline in the MICT and LVHIIT groups, thus reflecting a superior matching of microvascular O_2 delivery to utilisation.

In circumstances where the dynamic adjustment of $\dot{V}O_2$ is constrained by O_2 delivery, priming exercise has been shown to be effective at accelerating $\dot{V}O_2$

kinetics in both clinical and healthy populations (DeLorey *et al.* 2004; Murias *et al.* 2011; Rocha *et al.* 2016). In *Experiment 2,* it was shown that at week 0 PE significantly reduced the $\tau\dot{V}O_{2P}$ as well as the overshoot of the Δ [HHb + Mb]/$\Delta\dot{V}O_2$ ratio during a subsequent bout of moderate-intensity exercise in all 3 groups. However, there was no effect of PE on any of the $\dot{V}O_2$ parameters observed in the LVHIIT and MICT groups beyond 3 weeks of training. This finding further strengthens the evidence that both LVHIIT and MICT improved submaximal exercise capacity by improving the ability of the microvasculature to deliver or redistribute O_2 to the exercising muscle resulting in a decreased reliance on O_2 extraction for a given workload.

Since normal functional daily activities require constant transitions to different exercise intensities, it is of high relevance to investigate the effect of exercise training on $\dot{V}O_2$ kinetics during transitions from one exercise intensity to another. *Experiment 3* investigated the effects of LVHIIT and MICT on $\dot{V}O_2$ responses during heavy-intensity cycling exercise initiated from an elevated moderate-intensity baseline; a work-to-work transition. The results demonstrated that both LVHIIT and MICT accelerated the overall $\dot{V}O_2$ kinetics response or MRT during heavy-intensity exercise beyond 3 weeks of training through both speeding of the $\tau\dot{V}O_{2P}$ responses and a reduction in $\dot{V}O_{2SC}$ amplitude. The significant reduction in $\tau\dot{V}O_{2P}$ with MICT and LVHIIT in the presence of an unaltered [HHb + Mb] response profile indicates a likely improvement in O_2 delivery; whereas, the significant reduction in the $\dot{V}O_{2SC}$ amplitude after just 3 weeks of MICT and LVHIIT is indicative of exercise induced adaptations in the intrinsic properties of the skeletal muscle and alterations in motor unit recruitment patterns.

In regard to baseline (i.e. at week 0) adaptations, it was observed that PE significantly reduced the $\tau\dot{V}O_{2P}$ as well as $\dot{V}O_{2SC}$ amplitude during a subsequent bout of heavy-intensity exercise initiated from an elevated baseline in both training groups. However, there was no effect of PE on any of the $\dot{V}O_2$ parameters observed in the LVHIIT and MICT groups beyond 3 weeks of training. The significant reduction in $\tau\dot{V}O_{2P}$ with MICT and LVHIIT in the presence of an unaltered [HHb + Mb] response profile indicates a likely improvement in O_2 delivery; whereas, the significant reduction in the $\dot{V}O_{2SC}$

amplitude with PE is indicative of priming exercise induced adaptations in the intrinsic properties of the skeletal muscle and alterations in motor unit recruitment patterns.

Taken together, the results of the 3 experiments described within this thesis are in line with the current body of knowledge concerning the effect of exercise on submaximal and maximal exercise capacity in individuals with T2DM. The results contained in this thesis have provided for the first time an insight into the mechanisms and time course of adaptations in $\dot{V}O_{2max}$ in response to MICT and LVHIIT while, also showing for the first time that LVHIIT accelerates $\dot{V}O_2$ kinetics at moderate-intensity and heavy-intensity exercise domains in a similar fashion to MICT in individuals with uncomplicated T2DM. An overall overview of the study is shown in Fig 5.1

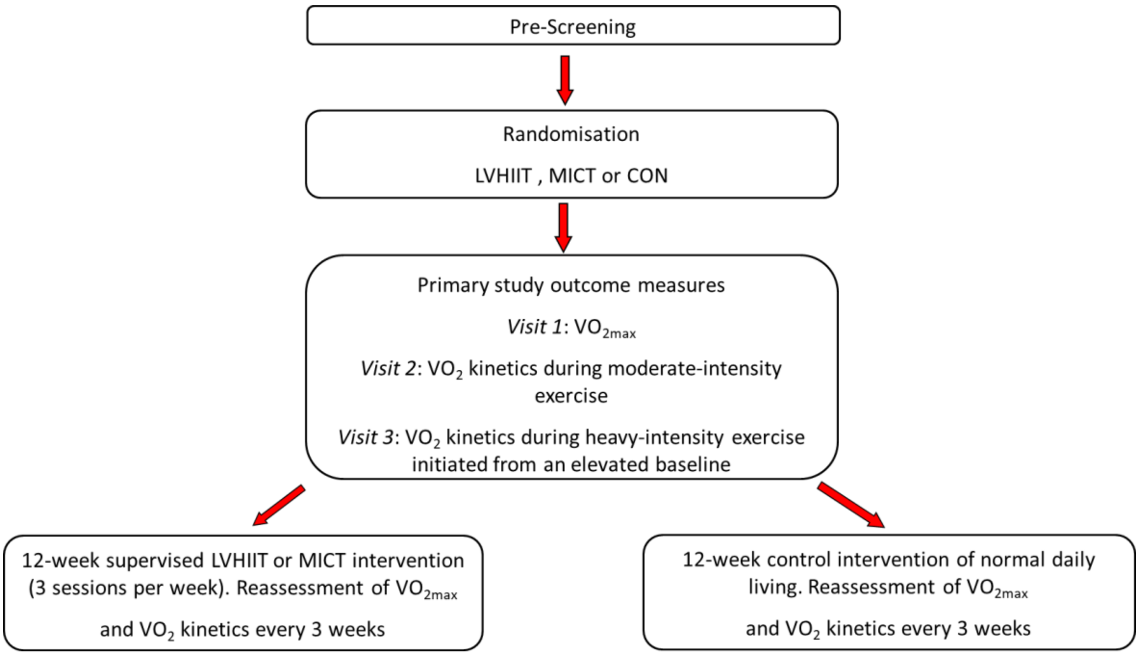


Figure 5.1. Overview of the entire study

5.2. Adaptations in maximal exercise capacity.

In the present study, after only 3 weeks of training a significant rightward shift in the primary slope of the bilinear regression model used to assess [HHb + Mb] during RI was evident in both training groups which is indicative of an improved peripheral blood flow and matching of O_2 delivery and utilisation within the microvasculature resulting in a reduction on the reliance on O_2 extraction. Moreover, significant improvements in Q_{max} after 3 weeks of MICT and 9 weeks of LVHIIT were also observed inferring that both central and peripheral adaptations occurred in order to enhance $\dot{V}O_{2max}$ in this cohort.

According to the Fick equation, $\dot{V}O_{2max}$ is determined by the body's ability to transport (as reflected by Q_{max}) and extract O_2 (as reflected by a-vO_2diff$_{max}$). This is the first study to show that both LVHIIT and MICT are effective at increasing Q_{max} in individuals with uncomplicated T2DM. This finding is consistent with studies from healthy populations that have reported significant improvements in Q_{max} with MICT and LVHIIT (Spina *et al.* 1993; Warburton *et al*. 2004; Murias *et al.* 2010; Astorino *et al.* 2017). For instance, Murias *et al.* (2011) reported a significant increase in Q_{max} in older and younger men after only 3 weeks of MICT (3 days per week, 45 mins at 70% $\dot{V}O_{2max}$) which accounted for 66% and 60% of the increase in $\dot{V}O_{2max}$ observed in the older and younger groups respectively. Furthermore, more recent work by Astorino *et al.* (2017) reported that 6 weeks of LVHIIT was effective at increasing Q_{max} in a group of young healthy individuals. Neither the present study nor the studies by Murias *et al.* (2010) and Astorino *et al.* (2017) reported a significant increase in HR_{max} with training, instead, all 3 studies reported a significant increase in SV_{max} which infers that changes in SV_{max} must be responsible for the training induced changes in Q_{max}.

Increases in SV_{max} with training could, at least in part, be linked to an enhanced left ventricular (LV) filling, increased LV contractility or a combination of both (Spina *et al.* 1993; Murias *et al.* 2010). Moreover, it has been postulated that training induced changes in Q_{max} are related to an increased diastolic filling because of a more compliant left ventricle (Levine, 2008) and an increase in blood volume which can lead to an increased SV via the Frank-Starling mechanism (Warburton *et al.* 2004; Murias *et al.* 2010). In healthy participants, Warburton *et al.* (2004) reported a significant increase in SV_{max} after 12 weeks of LVHIIT (2 min at 90% $\dot{V}O_{2max}$ interspersed by 2 mins active recovery for a duration equivalent to that required to match the work completed during a MICT session) and MICT (30-48 mins at an intensity equivalent to 1% below VT) of a similar magnitude, which was a result of an increase in blood volume (measured using radionuclide ventriculography) (Warburton *et al.* 2004). The authors suggested that this led to an increase in peak LV filling rate inducing an improvement in end-diastolic volume. Since this improvement in diastolic function occurred in the absence of major changes in cardiac contractility, Warburton *et al.* (2004) inferred that the consequent increase in SV_{max} was due to an increased ability to utilise the Frank-Starling mechanism (Warburton *et al*. 2004).

There is strong evidence to suggest that endurance trained individuals have an increased ability to utilise the Frank-Starling mechanism to enhance SV during exercise compared to sedentary individuals (Gledhill *et al.* 1994; Hagberg *et al.* 1998; Warburton *et al*. 1999). Therefore, it is possible that changes in SV_{max} and consequently Q_{max} in response to LVHIIT and MICT observed in the present study happened as a result of changes in blood volume leading to an increased ability to utilise the Frank-Starling mechanism.

In addition, ~21% of changes in $\dot{V}O_{2max}$ with MICT were due to a widening of the $a\text{-}vO_2diff_{max}$ in the present study, which is similar to the 33% contribution of $a\text{-}vO_2diff_{max}$ to changes in $\dot{V}O_{2max}$ observed in the study by Murias *et al.* (2011) in older men. However, no changes in $a\text{-}vO_2diff_{max}$ were evidenced after LVHIIT.

There is much evidence to suggest that both MICT and LVHIIT can induce significant adaptations in skeletal muscle properties and structure. For instance, both LVHIIT and MICT significantly increase Type I and Type II fibre capillarisation (Ingjer, 1979; Dudley *et al.* 1982; Jensen *et al*. 2004) and there is evidence of duration-dependent Type II muscle fibre recruitment during moderate-intensity continuous exercise (Gollnick *et al*. 1974). Therefore, it cannot be excluded that MICT and LVHIIT provoked training adaptations in Type I and Type II muscle fibres resulting in a more oxidative phenotype overall. Moreover, both MICT and LVHIIT have been shown to be highly effective at increasing mitochondrial number and oxidative capacity and at increasing the activity of key oxidative enzymes in individuals with uncomplicated T2DM (Toledo *et al.* 2007; Meex *et al.* 2010; Pheilix *et al*. 2010; Little *et al*. 2011).

In order to assess peripheral muscle adaptations, NIRS was utilised to measure changes in tissue deoxygenation (Δ [HHb + Mb]) within the microvasculature of the vastus lateralis muscle during the RI tests. As changes in Δ[HHb + Mb] are considered a surrogate for microvascular O_2 extraction (DeLorey *et al.* 2003), it was hypothesised that a reduced reliance on local muscle fractional O_2 extraction would contribute to the improvement in $\dot{V}O_{2max}$ with LVHIIT and MICT in uncomplicated T2DM. After 3 weeks of LVHIIT and MICT a pronounced rightward shift of the primary slope of the bi-linear regression model used to fit the Δ [HHb + Mb] % vs Δ%PO_{peak} profile was evident. This is most likely due to an enhancement in local microvascular blood flow in the area of NIRS interrogation and subsequent reduction in the reliance on O_2 extraction. To the knowledge of this investigator, no other previous studies have explored this adaptation following training. However, based on experiments using acute exercise modes this is consistent with the notion that a reduced perfusion pressure and thus, reduced local O_2 delivery leads to a reduction in $\dot{V}O_{2max}$ (Hughson *et al.* 1996). In fact studies involving participants with reduced muscle perfusion pressure as a result of disease state or manipulation of O_2 delivery during exercise through postural alterations, have shown that they demonstrate reductions in $\dot{V}O_{2max}$ and a slowing of $\dot{V}O_2$ kinetics (Jones *et al.* 2006; Bauer *et al.* 2007; Di Menna *et al*.2010a; Di Menna *et al*. 2010b; Gildea *et al*. 2016; Rocha *et al.* 2016).

For instance, Di Menna *et al*. (2010) reported a significant leftward shift of the sigmoidal Δ[HHb + Mb]% vs Δ%PO_{peak} profile when ramp exercise was performed in a supine position compared with an upright cycling position in young healthy males. In fact the primary slope of the Δ[HHb + Mb]% vs Δ%PO_{peak} profile was almost doubled during the RI test performed in the supine position which was accompanied by a significant 8% reduction in $\dot{V}O_{2peak}$ in the supine compared to the upright position (Di Menna *et al*. 2010). On the other end of the spectrum, Boone *et al.* (2009) reported that elite trained male cyclists displayed a significant rightward shift of the Δ[HHb + Mb]% vs Δ%PO_{peak} sigmoidal profile compared with recreationally active males (Boone *et al.* 2009). More recent work by the same group has also shown that when Δ[HHb + Mb]% vs Δ%PO_{peak} profiles are modelled using the bi-linear regression model as utilised in the present study, elite trained male cyclists continued to display a significant rightward shift of the Δ[HHb + Mb]% vs Δ%PO_{peak} profile compared to recreationally active males (Boone *et al.* 2015). These alterations in the parameters of the Δ[HHb+Mb]% vs Δ%PO_{peak} profile are indicative of an enhanced matching of muscle blood flow to oxygen utilisation in the area of

NIRS interrogation with increased aerobic fitness. Boone *et al*. (2009, 2015) attributed these findings to an increased oxidative capacity of the skeletal muscle mitochondria in combination with training induced adaptations in skeletal muscle fibre phenotype (Boone *et al.* 2009; Boone *et al.* 2015).

Although the present study has provided evidence for improvements in central O_2 delivery as reflected by an increase in Q_{max} and estimated active muscle (i.e. VL) microvascular blood flow with LVHIIT and MICT, peripheral limb conduit artery blood flow responses were not measured in order to estimate their contribution to the changes in $\dot{V}O_{2max}$. In this regard, previous studies in individuals with T2DM have suggests an improvement in macrovascular function with both LVHIIT and MICT. Flow-mediated dilation (FMD) is a reliable non-invasive assessment of endothelium-dependent vasodilation and reflects the response of the endothelial cells to shear stress which typically results in the release of NO, prostacyclin and other vasodilatory factors (Clifford & Hellsten, 2004; Harley & Tanka 2010; Stoner *et al.* 2012). Previous studies in individuals with uncomplicated T2DM have shown that both MICT and LVHIIT are effective at improving vascular function as measured with FMD which accompanies a significant improvement in maximal exercise capacity (Maiorana *et al.* 2007; Mitranun *et al*. 2014; Madsen *et al*. 2015b; Francois *et al.* 2017a). Potential physiological mechanisms underlying this improvement in FMD include an increase in NO bioavailability, an increased NO sensitivity of the smooth muscle cells and a reduction of oxidative stress within the vasculature (Maiorana *et al*. 2001; Ribeirio *et al*. 2010; Mitranun *et al.* 2014). Recent work from our laboratory has shown a significant reduction in the peak hyperaemic responses during an incremental intermittent calf plantar flexion exercise accompanied with a significant reduction in peak performance in uncomplicated T2DM compared with healthy controls (Kiely *et al.* 2014). It is tempting to suggest that LVHIIT and MICT may improve the hyperaemic response during maximal cycling exercise, but studies measuring blood flow responses during cycling exercise are needed to elucidate this.

5.3. Adaptations in submaximal exercise capacity.

Experiments 2 and *3* focused on the time course and mechanisms of adaptation in submaximal exercise capacity in response to LVHIIT and MICT in uncomplicated T2DM. The results of *Experiment 2* showed that both LVHIIT and MICT significantly accelerated $\dot{V}O_2$ kinetics during moderate-intensity exercise in the presence of an improved matching of O_2 delivery to utilisation as reflected by a reduction in the Δ [HHb + Mb]/$\Delta\dot{V}O_2$ ratio. The results of *Experiment 3* showed that both MICT and LVHIIT were effective at speeding the $\dot{V}O_2$ kinetics during heavy-intensity exercise initiated from an elevated baseline through the acceleration of $\tau\dot{V}O_{2P}$ and a reduction in $\dot{V}O_{2SC}$ amplitude. This suggests that in addition to changes in O_2 delivery, training induced adaptations in the intrinsic properties of skeletal muscle and alterations in motor unit recruitment patterns were likely following LVHIIT and MICT.

The locus of control of $\dot{V}O_2$ kinetics is thought to lie within the skeletal muscle mitochondria particularly when O_2 delivery is not constrained (Poole & Jones, 2005). However, when O_2 delivery to the skeletal muscle is constrained such as when muscle perfusion pressure is manipulated through postural changes (Di Menna *et al.* 2010), in disease states such as T2DM (Bauer *et al.* 2007; Rocha *et al.* 2016) or in deconditioned/sedentary individuals (DeLorey *et al.* 2004; Murias *et al.* 2011), the locus of control shifts from the mitochondria to the ability of the cardiovascular system to adequately supply O_2 to the working muscles. In fact, recent work suggests that there is a 'tipping point' ($\tau\dot{V}O_{2P}$ > 25s) above which $\dot{V}O_2$ kinetics are predominantly determined by O_2 delivery (DeLorey *et al.* 2004; Gurd *et al*. 2005; Murias *et al*. 2011; Poole & Jones 2017). This notion has garnered further credence from the evidence that a bout of prior heavy-intensity priming exercise significantly accelerates the $\dot{V}O_2$ kinetics of a subsequent bout of moderate-intensity exercise in individuals who present with initially 'slow' kinetics (DeLorey *et al.* 2004; Murias *et al.* 2011; Rocha *et al.* 2016). Moreover priming exercise has been shown to also significantly reduce the Δ [HHb+Mb]/$\Delta\dot{V}O_2$ ratio during a subsequent bout of moderate-intensity exercise which is indicative in an improved matching in O_2 delivery and utilisation.

In *Experiment 2* it was observed that after 3 weeks of LVHIIT and MICT, $\tau\dot{V}O_{2P}$ was accelerated and the Δ[HHb + Mb]/$\Delta\dot{V}O_2$ ratios were reduced to the extent that PE no longer had an effect on a subsequent bout of moderate-intensity exercise in either the LVHIIT or MICT group. This is indicative that the amelioration in the matching of O_2 delivery to utilisation was so great that the primary locus of control for $\dot{V}O_2$ kinetics in these individuals had shifted back to within the skeletal muscle mitochondria. Our results are in line with previous studies that have shown that LVHIIT and MICT can rapidly improve $\dot{V}O_2$ kinetics and reduce the reliance on O_2 extraction during moderate-intensity exercise in young heathy men and women with initial 'slow' $\dot{V}O_2$ kinetics (McKay *et al*. 2009; Murias *et al*. 2010b; Murias *et al*. 2011).

Improved O_2 delivery to the microvasculature appears to be the underlying mechanism for the acceleration in $\dot{V}O_2$ kinetics observed with MICT and LVHIIT. However, Q amplitudes during submaximal moderate-intensity exercise have been shown to be unaffected by T2DM (Baldi et al. 2003; O'Connor et al. 2015). In regard to training adaptations in Q during submaximal exercise, MacAnaney *et al.* (2012) reported a significantly faster rate of increase in Q during moderate-intensity exercise following 12 weeks of MICT in a group of people with uncomplicated T2DM (MacAnaney *et al.* 2012).

Regarding local blood flow during exercise in T2DM, leg vascular conductance responses, leg blood flow and microvascular blood flow responses during steady-state exercise appear to be blunted in T2DM (Kingwell *et al.* 2002; Bauer *et al.* 2007; Lalande *et al.* 2008;McAnaney *et al.* 2011; Kiely *et al.* 2014) although these findings are not universal (Poitras *et al.* 2018). Furthermore, evidence of microvascular impairments in T2DM have also been exhibited in human (Baeur *et al*. 2007) and rodent models (Padilla *et al.* 2007). Padilla *et al.* (2007), reported markedly reduced microvascular PO_2 (P_MV_{O2}) values at rest and an alteration in P_MV_{O2} kinetics during contractions in Goto-Kakizaki (GK) rats with T2DM compared to healthy animals. P_MV_{O2} is representative of the driving force for O_2 diffusion from the blood to the working muscle and a lower P_MV_{O2} is indicative of an O_2 delivery impairment. The authors postulated that altered red blood cell haemodynamics within the capillaries in addition to impairments in endothelial dependent and independent vasodilatory mechanisms resulted in these abnormal P_MV_{O2} kinetics in rats. Therefore, it is possible that in a similar manner to *Experiment 1,* the possible mechanisms for the increase in O_2 delivery and distribution in the *Experiment 2* may also be an exercise induced improvement in vascular function due to an increase in NO bioavailability, an increased NO sensitivity of the smooth muscle cells and a reduction of oxidative stress within the microvasculature (Maiorana *et al*. 2001; Ribeirio *et al*. 2010; Mitranun *et al.* 2014). Increased NO bioavailability would in turn result in improved microvascular O_2 delivery and distribution; leading to the significant reduction in Δ[HHb+Mb]/$\Delta\dot{V}O_2$ ratios and accelerated $\dot{V}O_2$ kinetics with training observed in the present study.

Adaptations in active skeletal muscle in response to MICT and LVHIIT are also likely contributory factors for the acceleration in $\dot{V}O_2$ kinetics observed in *Experiment 2* and *Experiment 3*. For instance, reduced skeletal muscle capillary density and baseline membrane thickening (Williamson & Kojo, 1983; He *et al*. 2001) as well as significant mitochondrial dysfunction have been found in the skeletal muscle of individuals with T2DM (Kelley *et al*. 2002; Ritov *et al.* 2005). In turn, interval and continuous training have been shown to increase capillarisation in Type I and Type II muscle fibres (Jensen *et al.* 2004) which would increase the surface area for O_2 diffusion into the myocyte; and in addition, both LVHIIT and MICT have also been shown to be effective at increasing mitochondrial oxidative capacity and number in T2DM (Toledo *et al.* 2007; Meex *et al.* 2010; Pheilix *et al.* 2010; Little *et al*. 2011).

In *Experiment 3* a significant reduction in the $\dot{V}O_{2SC}$ amplitude was observed during heavy-intensity exercise initiated from an elevated baseline after 3 weeks of MICT and LVHIIIT. Since the skeletal muscle accounts for over 80% of the amplitude of the $\dot{V}O_{2SC}$, this shows that in addition to improvements in O_2 delivery, adaptations in skeletal muscle properties and motor unit recruitment patterns probably contributed to the acceleration in $\dot{V}O_2$ kinetics observed in *Experiment 3*. For instance, MICT has been shown to recruit predominantly Type I fibres and recruit Type II fibres with increasing exercise duration while higher-intensity exercise is thought to specifically recruit Type II fibres (Gollnick *et al*. 1974; Essen, 1978; Da Boit *et al*. 2014). Moreover, both MICT and interval training have been shown to increase the oxidative capacity of Type I fibres while also converting Type II fibres to a more oxidative phenotype. Therefore, if the oxidative ability of lower order skeletal muscle fibres increases with training it would reduce the necessity for the recruitment of higher order fibres, ultimately cutting the O_2 cost of exercise which may have led to the reduction of the amplitude of the $\dot{V}O_{2SC}$ in the present study and thus, the reduction in the overall response time of $\dot{V}O_2$ kinetics in Experiment 3.

Collectively, the finding of *Experiment 2* and *Experiment 3* have shown that LVHIIIT and MICT are effective at improving submaximal exercise tolerance in T2DM. During moderate-intensity exercise $\dot{V}O_2$ kinetics are accelerated as a result of an amelioration of O_2 delivery while during heavy-intensity exercise adaptations in skeletal muscle in combination with enhanced O_2 delivery appear to be the mechanism for the reduction in the overall response time in $\dot{V}O_2$ kinetics. The functional implication of these findings are that by reducing the O_2 deficit accrued at the onset of exercise, time to exhaustion during submaximal exercise may increase. This in its turn may result in a reduced feeling of exertion and ultimately an improved willingness to increase exercise participation.

5.4. Limitations.

The author acknowledges that the modelflow algorithm might exhibit bias relative to a standard method especially during periods of changing metabolic demand (Tam *et al.* 2004; Faisal *et al.* 2009). To minimise this, Q_{max} values were determined during the 85% PO constant load confirmatory bout and the Q_{max} values obtained using the model flow algorithm were found to correlate strongly with those obtained using the inert gas rebreathing method (r = 0.93, P <0.001).

The author acknowledges the limitations that lie within the use of NIRS. However, in humans, NIRS remains the only laboratory method that can give inferences in local responses in fractional oxygen extraction and thus microvascular blood flow during exercise. In addition, the lack of ability to discriminate between muscle fibre types should be acknowledged. The area of interrogation used in the current study was the vastus lateralis as it has been postulated to be a primary locomotor muscle during cycling exercise, but there is evidence to suggest that the vastus lateralis of healthy individuals has a higher fraction of type II fibres and a lower blood flow than other regions in the quadriceps femoris (Kalliokoski *et al*. 2006). Therefore, data pertaining to fractional O_2 extraction in the present study may have arisen from Type II muscle fibres, whereas exercise performed in the moderate-intensity domain would typically result in the preferential recruitment of Type I fibres. The fact that disparities may exist between and within muscles may have an influence on the findings of the present study. Finally, adipose tissue layer thickness at the site of measurement has the potential to influence NIRS measurements through its effect on the scattering properties of the tissue (Elwell, 1995). However, the 3 groups in the present study were well matched in terms of adipose layer thickness as we determined the thickness of the skin and adipose tissue layer at the site of the interrogation via 2D ultrasound operating in B-mode and no differences were found between groups.

The 3 groups contained a mix of males and females and this may have had an influence on the results presented in this thesis. It is evidenced that in healthy men and women exercise training improves $\dot{V}O_{2max}$ by different mechanisms. In men the main contributing factor is Q_{max}, while in women, improvements in $\dot{V}O_{2max}$ seem to be induced mostly due to a widening of the a-vO_2diff$_{max}$ (Spina *et al.* 1993; Murias *et al.* 2011). In addition, due to the small numbers in each group the risk of Type I or Type II statistical errors must be acknowledged. However, a power calculation for the repeated measures ANOVAs used in each study was performed and each was found to be powered to perform repeated measures ANOVAs.

The failure to measure differentiated RPE for the legs and chest to reflect both central and local fatigue is a limitation of this study. This would have greatly added to the practical application of the findings of an improved objective exercise tolerance in people with T2DM. Finally, it would have been of interest to investigate the barriers to regular exercise participation in this cohort prior to the start of the intervention. Since lack of time is used as a justification for the use of HIIT it would have been worthwhile investigating if it was a barrier in this small cohort.

5.5. Future research.

The current study reported on the significant improvements in $\dot{V}O_{2max}$ and $\dot{V}O_2$ kinetics and their time course and mechanisms of adaptation following 12 weeks of MICT and LVHIIT in T2DM. Although it was inferred that an improved microvascular blood flow distribution may be responsible for these improvements as reflected by a reduced S_1 during the RI test and a reduced Δ[HHb + Mb]/$\Delta\dot{V}O_{2P}$ ratio during submaximal exercise, the effects of LVHIIT and MICT on the time course adaptations in peak and submaximal leg blood flow responses were not assessed. As these responses have been consistently reported to be impaired in middle aged individuals with T2DM (Lalande *et al*. 2008; MacAnaney *et al*. 2011; Kiely *et al*. 2014) the effects of training on these responses is warranted.

As yet, no study has looked at longer term (6-12 months) effects of independent LVHIIT vs MICT after a supervised period is completed on subsequent $\dot{V}O_2$ kinetics and exercise adherence rates in individuals with T2DM. Such future studies utilising the exercise protocol outlined in the current study should aim to incorporate a resistance training element given its added benefits in glycaemic control in T2DM (Colberg *et al.* 2016).

5.6 Clinical relevance of findings

A reduction in maximal exercise capacity is associated with an increased risk of all-cause morbidity and mortality. *Experiment 1* shows that VO_{2max} in T2DM can be significantly improved after 3 weeks of either LVHIIT or MICT due to both central and peripheral adaptations. This has important clinical relevance because it can now be said that structured exercise training can have a significant influence on maximal exercise capacity in T2DM within a relatively short space of time. This can be used as an important motivating factor as a clinician can provide evidence to their patient with T2DM that within 3 weeks of completing either MICT or LVHIIT, as prescribed in this thesis, they could expect to see a 13-24% increase in their VO_{2max} and therefore a significant reduction in their risk of all-cause mortality. Moreover, as both interventions induced significant benefits within a similar time frame it allows for further individualisation of exercise prescription as the patient now has a choice between different exercise modes that may better suit their lifestyle.

Experiments 2 and *3* show that both LVHIIT and MICT induce significant improvements in VO_2 kinetics responses during submaximal exercise after only 3 weeks of training due to likely changes in skeletal muscle properties and an improved matching of O_2 delivery and utilisation. The reduced effect of priming exercise after 3 weeks of training also indicates to an enhanced O_2 delivery due to training. These findings can again be used as an important motivating factor to increase exercise participation because after just three weeks of training, exercise completed in the moderate- and high- intensity exercise domains, such as some activities of daily living, was physiologically speaking, easier to complete.

Although positive improvements in submaximal and maximal exercise capacity were observed in the experiments contained in this thesis the long term sustainability of these two interventions was not assessed. In fact, after the completion of the intervention period each participant was encouraged to maintain their training regime and was invited back to the laboratory after 6 weeks of training after the completion of the supervised training intervention. To the best of this investigator's knowledge only 2 participants from the MICT group were still training 6 weeks after the intervention period was finished, while none of the LVHIIT group had continued to train.

5.7. Overall conclusion and implications of findings.

The main conclusion of this study is that LVHIIT and MICT improve exercise tolerance in individuals with uncomplicated T2DM by a similar magnitude and within a similar timeframe and that the mechanisms of adaptation in both modes of exercise appear to be similar. The present work has shown that LVHIIT is as efficient as MICT at improving exercise intolerance in T2DM. This is highly significant as 'lack of time' is consistently presented as one of the primary barriers to exercise participation in this population. LVHIIT requires ~50% less time commitment than MICT; it may, therefore, be an attractive option for people living with T2DM who wish to increase their exercise participation.

Given that decreased exercise capacity and physical activity levels are associated with an increase in all causes of morbidity and mortality, the functional significance of the rapid improvement in exercise intolerance observed in the present study cannot be overlooked. As has been shown previously, slowed $\dot{V}O_2$ kinetics are associated with an increased perception of effort and possibly exercise avoidance. Therefore, improvements in these parameters may lead to increased exercise tolerance and ultimately an improved quality of life in this clinical population.

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7. Appendices

Appendix 7.1. Recruitment flyer

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Participants needed for a research study on cardiorespiratory & exercise capacity in type 2 diabetes

We are looking to recruit men and women with type 2 diabetes aged between 18 and 70 years who **do not** exercise regularly for the possibility to undertake a 12-week supervised training intervention designed by trained exercise physiologists.

If interested in receiving more information, please contact:

Norita Gildea: gildean@tcd.ie

Adam McDermott: mcdermad@tcd.ie

Appendix 7.2. Patient Information Leaflet

ELM PARK, DUBLIN 4

Department of endocrinology and diabetes mellitus

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: The effect of age and sex on the time course and mechanisms of adaptation in cardiovascular and metabolic health with exercise training in type 2 diabetes.

NAME OF PRINCIPAL INVESTIGATOR:

Prof Donal O'Shea
Dr. Ronan Canavan
Mr. Adam McDermott
Ms Norita Gildea
Dr Joel Rocha
Prof Simon Green
Dr Mikel Egaña

You are being invited to participate in a research study. Thank you for taking time to read this.

WHAT IS THE PURPOSE OF THIS STUDY?

The aim of the study is to measure the initial responses of blood flow and oxygen consumption during a calf-exercise and cycling-exercise before, during and after a 12-week period. During the 12-week period some participants will complete a supervised exercise training programme training 3 times per week under supervision at the Loughlinstown Leisure Centre, Co. Dublin and the others will continue with their normal lifestyle.

WHY HAVE I BEEN CHOSEN?

You have Type 2 Diabetes Mellitus and as therapy to improve your condition we want to investigate the time course of adaptation in cardiovascular and metabolic health with exercise training.

WHAT WILL HAPPEN IF I VOLUNTEER?

Your participation is entirely voluntary. If you initially decide to take part you can subsequently change your mind without difficulty. This will not affect your future treatment in any way. Furthermore your doctor may decide to withdraw you from this study if he/she feels it is in your best interest.

If you agree to participate, before the commencement of the project you will be requested to provide 2 blood samples (approx. 2.5 tsp.) and you will undergo a screening visit to determine if your current health status meets the inclusion criteria for this study. Upon receiving medical clearance to participate in this, you will be randomly allocated into one of the EXERCISE (continuous or interval training) or CONTROL (non-exercise) groups. Participants in the EXERCISE groups will perform a 12-week supervised exercise training programme. Participants in the CONTROL group will continue normal life for the following 12-weeks (If you are allocated to the control group you will be offered the possibility to undertake the 12-week supervised exercise programme only after you finish the 12-weeks of your usual daily routine). Regardless of your group you will, at week 0 and 12, undergo four testing days (three at the human laboratory in the Biotechnology Building, Department of Physiology, Trinity College Dublin, and one at St Columcille's Hospital) at least 48 hours apart, where you will perform the necessary calf ergometer and cycling testing (see below). In addition, you will be asked to give a blood sample and wear a continuous glucose monitor system once during each assessment week (i.e. Weeks 0, 3, 6, 9, 12) and record your energy intake (by filling 3-day food diaries) and physical activity (using a questionnaire and accelerometer). From this point assessments will be undertaken during 2 visits every 3 weeks (i.e. weeks 3, 6 and 9) at TCD. Please note that preparation for the testing days will entail abstinence from caffeine, alcohol, nutritional supplements and strenuous physical activity for 24 hours prior to testing. In addition, we ask that you do not consume any food during the 3 hours preceding the tests.

Below we have included all the information regarding where each visit will be, what will be required from you and how long will it take to complete the individual tests and whole visit.

Visit before the start of the study

Screening visit (Location: St. Columcille's Hospital)				
Name of test	**What it does**	**What is required**	**Total test time (min)**	**Total visit time (min)**
Blood sampling	Allows measurement of the sugar and fats in your blood.	You will need to provide 2 blood samples (approx. 2.5 tsp.).	5	80
Ankle-Brachial Index (ABI)	Allows assessment of the risk of having narrowed or blocked arteries in your legs or arms.	You will need to initially rest and then do 30 heel raises so that your resting and post-exercise blood pressure can be measured at the ankle and in the arm.	15	
Exercise stress test	Allows detection of possible problems in the heart during exercise.	You will need to walk on a treadmill whilst connected to a heart monitoring device to see how far you walk and if you develop chest pain or changes in the activity of your heart.	60 (approx. 15 min of exercise)	

Visits during assessment weeks 0 and 12

Visit 1 (Location: St. Collumcille's Hospital)				
Name of test	**What it does**	**What is required**	**Total test time (min)**	**Total visit time (min)**
Pulse wave velocity (PWV)	Allows the measurement of how stiff your arteries are.	You will need to rest whilst the arteries in your neck and groin are monitored using an external pressure sensor.	20	70
Body measurements	Allows the measurement of your physical characteristics.	You will need to stand still and relaxed whilst measures of height, weight, neck, hip and waist circumferences and body fat are taken.	10	
Maximal cycling capacity test	Allows the measurement of the maximum amount of oxygen you can use during a maximal cycling effort.	You will need to cycle in the seated position where the resistance felt on the pedals will go up until you cannot rotate them. During this test you will be required to increase your level of effort until you cannot cycle any further.	30 (approx. 12 min of exercise)	
Cardiac output exercise test	Allows the estimation of the maximum blood your heart can pump during each minute	You will need to cycle at a high-intensity until you cannot rotate the pedals.	10 minutes (approx. 4 min of exercise)	

Visit 2 (Location: Trinity College Dublin)				
Name of test	**What it does**	**What is required**	**Total test time (min)**	**Total visit time (min)**
Fat tissue thickness by Ultrasound	Allows the measurement of the fat layer above your muscles in the leg.	You will need to rest whilst the fat layer in your leg is measured using an ultrasound machine.	10	175
Calf and quadriceps NIRS occlusion	Allows the assessment of the ability of the muscles of the back of your lower leg and front of the upper thigh to use oxygen.	You will need to be in a lying position whilst a blood pressure cuff is inflated to a high pressure of 250mmHg for up to 7 min for each muscle.	25	
Flow-mediated dilation (FMD)	Allows the assessment of the ability of the artery at the back of your knee to widen and increase the amount of blood that goes to the muscles of the lower leg.	You will need to be in a lying position whilst a blood pressure cuff is inflated around the lower leg to a high pressure of 250mmHg for 5 min.	20	
Calf exercise	Allows the measurement of the amount of blood that goes to the muscles of the lower leg during moderate-intensity exercise.	You will need to push your toes against a force plate that measures the strength of your lower leg. Each push will last 1 second, followed by a 2 second rest and this exercise will continue for 6min. This exercise will then need to be repeated two more times but you will have a 10-minute rest between each 6 min session.	80 (18 min of exercise)	
Constant-load cycling test at moderate-intensity	Allows the measurement of how much oxygen your muscles use during	You will need to cycle for 9 min (including 3min warm-up) in the seated position whilst the resistance felt on the pedals will be of a	40 (18 min of exercise)	

	moderate-intensity cycling exercise.	constant moderate-intensity for 6 min. This will be repeated once but you will have 12 min of rest in between.		

Visit 3 (Location: Trinity College Dublin)				
Name of test	**What it does**	**What is required**	**Total test time (min)**	**Total visit time (min)**
Constant-load cycling test at high-intensity	Allows the measurement of how much oxygen your muscles use during high-intensity cycling exercise.	You will need to cycle for 9 min (including 3 min of warm-up) in the seated position whilst the resistance felt on the pedals will be of a constant high-intensity for 6 min. This will be repeated three more times but there will be a total rest period of 69 min	115 (36 min of exercise)	115

Visit 4 (Location: Trinity College Dublin)				
Name of test	**What it does**	**What is required**	**Total test time (min)**	**Total visit time (min)**
Constant-load cycling test at moderate and high intensity	Allows the measurement of how much oxygen your muscles use during moderate and high intensity cycling exercise.	You will need to cycle for 15 min (including 3 min of warm-up) in the seated position whilst the resistance felt on the pedals will be of a moderate-intensity for the first 6 min and a high-intensity for the last 6 min. This will be repeated three more times but there will be a total rest period of 69 min	139 (60 min of exercise)	139

Visits during the remaining assessment weeks (Weeks 3, 6 and 9)

Visit 1 (Location: Trinity College Dublin)				
Name of test	**What it does**	**What is required**	**Total test time (min)**	**Total visit time (min)**
Pulse wave velocity (PWV)	Allows the measurement of how stiff your arteries are.	You will need to rest whilst the arteries in your neck and groin are monitored using an external pressure sensor.	20	169
Body measurements	Allows the measurement of your physical characteristics.	You will need to stand still and relaxed whilst measures of height, weight, neck, hip and waist circumferences and body fat are taken.	10	
Constant-load cycling test at moderate and high intensity	Allows the measurement of how much oxygen your muscles use during moderate and high intensity cycling exercise.	You will need to cycle for 15 min (including 3 min of warm-up) in the seated position whilst the resistance felt on the pedals will be of a moderate-intensity for the first 6 min and a high-intensity for the last 6 min. This will be repeated three more times but there will be a total rest period of 69 min	139 (60 min of exercise)	

Visit 2 (Location: Trinity College Dublin)				
Name of test	**What it does**	**What is required**	**Total test time (min)**	**Total visit time (min)**
Fat tissue thickness by Ultrasound	Allows the measurement of the fat layer above your muscles in the leg.	You will need to rest whilst the fat layer in your leg is measured using an ultrasound machine.	10	159
Flow-mediated dilation (FMD)	Allows the assessment of the ability of the artery at the back of your knee to widen and increase the amount of blood that goes to the muscles of the lower leg.	You will need to be in a lying position whilst a blood pressure cuff is inflated around the lower leg to a high pressure of 250mmHg for 5 min.	20	
Calf exercise	Allows the measurement of the amount of blood that goes to the muscles of the lower leg during moderate-intensity exercise.	You will need to push your toes against a force plate that measures the strength of your lower leg. Each push will last 1 second, followed by a 2 second rest and this exercise will continue for 6min. This exercise will then need to be repeated two more times but you will have a 10-minute rest between each 6 min session.	80 (18 min of exercise)	
Constant-load cycling test at moderate-intensity	Allows the measurement of how much oxygen your muscles use during moderate-intensity cycling exercise.	You will need to cycle for 9 min (including 3min warm-up) in the seated position whilst the resistance felt on the pedals will be of a constant moderate-intensity for 6 min.	19 (9 min of exercise)	
Maximal cycling capacity test	Allows the measurement of the maximum amount of oxygen you can use during a maximal cycling effort.	You will need to cycle in the seated position where the resistance felt on the pedals will go up until you cannot rotate them. During this test you will be required to increase your level of effort until you cannot cycle any further.	30 (approx. 12 min of exercise)	

Please note that you will need to provide 1 fasted blood sample (approx. 1.25 tsp.) during each assessment week.

Summary of all visits over the 3 month period			
Week	**Number of visits**	**Location of visits**	**Total time per visit (min)**
Screening	1	St. Columcille's Hospital	80
0	4	St. Columcille's Hospital (1) Trinity College Dublin (3)	70 175 115 139
3	2	Trinity College Dublin (2)	169 159
6	2	Trinity College Dublin (2)	169 159
9	2	Trinity College Dublin (2)	169 159
12	4	Trinity College Dublin (4)	70 175 115 139
		Total (min)	**2062**
		Total (hours)	**34.4**

As indicated in the above table this study will take 3 months to be completed and will involve approximately 34 hours of testing during this period.

- Supervised exercise training programme (Exercise groups only):

During the 12 week exercise training period you will perform three exercise sessions per week of either moderate-intensity continuous training (MICT) or high-intensity interval training (HIIT) depending on which group you were randomised to. Cycling will be the main exercise mode for both groups and all sessions will be supervised by a qualified Personal Trainer.

If you are in the MICT group sessions will last a total of 60 minutes consisting of 10 minutes for warm-up/cool-down (5 min each) and 50 minutes at a moderate training intensity.

If you are in the HIIT group sessions will last a total of 30 minutes consisting of 10 minutes for warm-up/cool-down (5 min each) and an interval training protocol of 10x1min sessions at a high-intensity separated by 10x1min recovery periods at a low-intensity.

The exercise intensities for both groups will be recalculated every 3 weeks to reflect changes in fitness. The programme will be performed in Loughlinstown Leisure Centre, Co. Dublin.

You will have your blood glucose levels measured before and after training. If blood glucose before exercise is <6.8mmmol/l a snack with 25 g carbohydrate and 7 g protein will be provided to you. You will also need to keep a glucose monitoring log sheet, which will be regularly checked by the research team.

During the exercise session you will wear a heart rate monitor and be asked how the exercise feels to ensure adherence with the intensity of training. Blood pressure will also be monitored before and after the exercise sessions.

ARE THERE ANY BENEFITS FROM MY PARTICIPATION?

You may or may not benefit from taking part in this study.

ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?

There are a number of minor risks associated with this study.

Blood sampling: Blood sampling may make some volunteers feel uneasy, or prove painful to some. Some may experience slight bruising or discomfort around the sampling area. Occasional dizziness and nausea, and bruising are also potential risks. The risks will be minimized or eliminated by having only trained personnel to draw blood. Additionally, you will be monitored while blood is being obtained in a lying down position. All blood samples will be taken in the laboratory under sterile conditions using "one-time use" needles and containers. Proper procedures will be followed for the protection and safety of all people involved, and for the disposal of biohazardous waste in line with College/Faculty policy and best laboratory practices.

Ultrasound: The risk of using ultrasound is minimal. You may experience minor redness at the point where the ultrasound probe is pressed against your skin. This redness is due to the pressure on your skin from the probe. The redness is temporary and dissipates quickly.

Cuff occlusion: A cuff will be inflated in the calf and quadriceps at a pressure of 250 mmHg for up to 7 minutes. The risks associated with this occlusion include slight bruising, tingling and numbness, moderately elevated blood pressure, minor elevation of heart rate, and discomfort from the cuff pressure. The discomfort caused by the cuff pressure quickly disappears after the test. Women on oestrogen replacement therapy have an increased risk of developing blood clots and occlusion of leg blood flow may increase this risk. However, to our knowledge, there have been no actual cases of blood clots reported in studies involving blood flow occlusion. So far, over 1000 tests have been performed in our laboratory both in young and older individuals with no adverse outcomes.

Maximal and constant load cycling tests: The study involves both maximal and constant load cycling tests to determine the ability of your muscles to use oxygen. Due to its nature, all participants will experience physical tiredness which may cause some discomfort such as temporary muscle fatigue and shortness of breath. These feelings go away very quickly once the exercise session has finished. It is possible that you may also experience light headedness, chest discomfort, cramping in the legs and irregular heartbeats during this test. With a maximal exercise test there is a very slight risk that participants may suffer a heart attack To minimise the risk prior to performing the maximal exercise tests, a stress test using 12-lead ECG and blood pressure measurements will be carried out at St Columcille's hospital.

Exercise training (Exercise groups only): Exercise training may result in muscle tightness, soreness, fatigue and rarely a pulled muscle. However, these will be minimised by a proper warm-up, familiarisation procedure, and a cool-down. In addition, the intensity of exercise will be closely monitored and a qualified personal trainer will supervise each session. The risk of a coronary event, although very minor, does exist.

WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?

If you decide not to participate in this study your treatment will not be affected in any way.

CONFIDENTIALITY

Your identity will remain confidential. A study number will identify you. Your name will not be published or disclosed to anyone.

COMPENSATION

Your doctors are adequately insured by virtue of their participation in the clinical indemnity scheme.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

This study is a collaborative study between Prof Donal O'Shea (consultant endocrinologist, St Vincent's University) and Dr Mikel Egana (Assistant Professor in Physiology, Trinity College Dublin) and has been funded by the Health Research Board of Ireland.

Will I be paid for taking part in this study? No

Will my expenses be covered for taking part in this study? Yes, expenses related to transport will be covered.

HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?

The St. Vincent's Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

CONTACT DETAILS

You can get more information or answers to your questions about the study, your participation in the study, and your rights, from any of the investigators: Mr. Adam McDermott (mcdermad@tcd.ie), Ms. Norita Gildea (gildean@tcd.ie), Dr Joel Rocha (borgespj@tcd.ie) or Dr Mikel Egaña, (01-8961770/ megana@tcd.ie). If the study team learns of important new information that might affect your desire to remain in the study, you will be informed at once.

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the Participant Information. YES ☐ NO ☐

- I have had the opportunity to ask questions and discuss the study. YES ☐ NO ☐

- I have received satisfactory answers to all my questions. YES □ NO □

- I have received enough information about this study. YES □ NO □

- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care. YES □ NO □

- I understand that relevant sections of any of my data collected during the study will be processed and may be looked at by responsible individuals of the research team, where it is relevant to my taking part in this research. I give permission for these individuals to have access to and process this data. YES □ NO □

- I understand that the data or material will be retained after the study is completed, however, this material will not be used in future unrelated studies without further specific permission being obtained. YES □ NO □

- I agree to provide blood samples or for the research team to use blood samples (or part of a blood sample) which are taken for clinical reasons. YES □ NO □

- I freely and voluntarily agree to be part of this research study. YES □ NO □

Participant's Signature: ___________________________________

Date: ____________________

Participant's Name in print: ______________________________

Investigator's Signature: ________________________________

Date: ____________________

Investigator's Name in print: _____________________________

Appendix 7.3. Exercise log book

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Name: ___________________________

Please read through this page before starting to fill your exercise log.

We would like you to fill in this exercise log book during each exercise session. Specific details of how to complete this exercise log book are shown below

Please record the following in the allocated spaces for each exercise session:

- Date.
- Start and finishing time.
- Mode of exercise chosen.
- Heart rate before and after each part of the session.
- Intensity or level of exercise undertaken for each part of the session.
- Duration of time spent exercising in each mode (for the main phase only).
- How you felt during each part of the session using the scale on the back of this booklet.

Note: Use the comments section to report any unusual symptoms experienced in the session/day.

Please feel free to contact us with any questions.

Adam McDermott	01 896 1937	mcdermad@tcd.ie
Norita Gildea	01 896 1937	gildean@tcd.ie

Exercise Log Sheet

Week: X Session X Date: ____________ Time session started: __________ Time session finished: __________ Training HR range:________________

Part of Session	Mode of Exercise	Pre-exercise Heart Rate	Intensity / Level	Duration	Post-exercise Heart Rate	How did the exercise feel?
Warm-up	Treadmill			5 min		
Main phase	Bike					
Cool down	Treadmill			5 min		
	Stretching			30 s per stretch		

Comments:
____
____

Rating of exercise difficulty

6	least effort
7	very, very light
8	
9	very light
10	
11	fairly light
12	
13	somewhat hard
14	
15	hard
16	
17	very hard
18	
19	very, very hard
20	maximum effort

Appendix 7.4. Experiment 1 raw data.

Participant baseline characteristics

LVHIIT	Sex		Age	Time since diagnosis	ABI Pre Exercise	ABI Post Exercise	Stature (m)	Body Mass (kg)	BMI (kg.m2)	RT3 SED	RT3 Light	RT3 MOD	RT3 VIG	Fat Layer VL (mm)
26	F		62.3	12	1.05	1.02	1.60	66.5	25.98	16.70	6.12	1.08	0.10	8.10
34	M		50.96	X	1.1	1	1.88	99.0	28.01	14.25	7.49	1.98	0.29	5.3
35	M		58.8	11.2	1.02	1	1.78	79	24.93	20.06	3.55	0.37	0.02	3.20
36	M		59.1	4.2	1.03	1.13	1.75	95	31.02	17.41	5.31	0.85	0.43	5.70
38	F		60.2	5.2	1.07	1.05	1.65	74.5	27.36	X	X	X	X	6.10
45	M		56.1	3.2	1.1	1.1	1.88	100.4	28.41	17.65	4.84	1.18	0.34	5.3
47	M		46.1	8.0	1.12	1.02	1.82	96.4	29.10	15.83	6.85	1.05	0.27	4.1
48	F		42.0	5.7	1.08	1.11	1.50	79.1	35.16	20.28	3.12	0.52	0.07	11.6
49	M		32.3	3.1	1.02	0.98	1.83	94	28.10	X	X	X	X	8.4
Males	**6**	**Mean**	52.0	6.6	1.07	1.05	1.74	87.10	28.67	17.45	5.33	1.00	0.22	6.42
Females	**3**	**S.D.**	10.1	3.5	0.04	0.1	0.1	12.4	3.0	2.2	1.6	0.5	0.2	2.6
		SEM	2.2	0.8	0.0	0.0	0.0	2.7	0.7	0.5	0.4	0.1	0.0	0.6

MICT	Sex		Age	Time since diagnosis	ABI Pre Exercise	ABI Post Exercise	Stature (m)	Body Mass (kg)	BMI (kg.m2)	RT3 SED	RT3 Light	RT3 MOD	RT3 VIG	Fat Layer VL (mm)
4	M		52.1	5.5	1.1	1.2	1.83	116.5	34.79	17.61	4.58	1.60	0.21	5.40
7	M		59.8	7.1	1.13	0.99	1.78	95	29.98	X	X	X	X	6.00
8	F		62.5	8.3	1.34	1.2	1.70	60	20.76	18.26	5.29	0.39	0.05	7.60
15	M		41.4	3	0.97	0.99	1.74	115	37.98	17.09	6.06	0.80	0.05	5.80
17	F		62.9	8.3	1.1	1.1	1.65	92	33.79	X	X	X	X	18.20
20	M		64.8	7.8	1.3	1.3	1.69	90	31.51	15.99	6.16	1.45	0.40	4.53
23	F		63.9	5.9	1.25	1.1	1.63	75.7	28.67	14.14	5.39	3.38	1.09	12.50
24	F		36.9	13.9	1.08	1.1	1.70	116	40.14	19.30	4.12	0.48	0.11	X
28	M		54.1	9.1	1.1	1.2	1.74	94.7	31.28	X	X	X	X	7.30
30	M		52.7	0.1	0.98	0.95	1.88	94.1	26.62	18.39	5.24	0.31	0.06	6.10
32	M		48.2	X	1.1	1.2	1.77	116.7	37.25	X	X	X	X	5.90
39	M		42.2	3.3	1	1.2	1.70	72.5	25.09	18.12	4.72	0.88	0.28	5.90
43	F		43.8	10.8	1.2	1.2	1.58	59	23.63	17.35	5.91	0.74	0.00	7.50
Males	**8**	**Mean**	**52.7**	**6.9**	**1.1**	**1.1**	**1.72**	**92.1**	**30.9**	**17.4**	**5.3**	**1.1**	**0.3**	**7.7**
Females	**5**	**S.D.**	9.6	3.7	0.1	0.1	0.1	20.6	5.9	1.5	0.7	1.0	0.3	3.9
Total	**13**	**SEM**	1.5	0.6	0.0	0.0	0.0	3.3	0.9	0.2	0.1	0.2	0.1	0.6

Control	Sex		Age	Time since diagnosis	ABI Pre Exercise	ABI Post Exercise	Stature (m)	Body Mass (kg)	BMI (kg.m2)	RT3 SED	RT3 Light	RT3 MOD	RT3 VIG	Fat Layer VL (mm)
3	M		55.2	9.3	1.14	1.26	1.74	94.5	31.21	17.70	5.91	0.39	0.00	7.80
10	F		71.3	8.2	1.19	1.12	1.61	73	28.16	16.72	4.72	1.75	0.81	12.30
12	M		48.3	5.7	1.2	1.1	1.82	108.8	32.85	X	X	X	X	5.00
18	F		42.8	10.8	1.2	1.2	1.58	65	26.04	17.35	5.91	0.74	0.00	7.50
21	F		51.4	2.9	1.1	1.2	1.58	76	30.44	19.03	4.70	0.25	0.01	9.90
22	F		63.1	2.9	1	1	1.55	86	35.80	18.98	4.86	0.14	0.02	12.70
31	M		55.8	11.1	1.2	1.2	1.86	92.5	26.74	17.85	4.63	1.37	0.15	5.60
33	M		55.4	3.2	1.1	1.1	1.88	99	28.01	17.65	4.84	1.18	0.34	4.70
41	F		42.0	5.7	1.08	1.11	1.50	79.1	35.16	20.28	3.12	0.52	0.07	11.60
Males	**4**	**Mean**	**53.9**	**6.6**	**1.13**	**1.14**	**1.68**	**85.99**	**30.49**	**18.19**	**4.84**	**0.79**	**0.18**	**8.57**
Females	**5**	**S.D.**	9.4	3.3	0.07	0.08	0.15	13.97	3.56	1.15	0.87	0.58	0.28	3.17
Total	**9**	**SEM**	1.5	0.5	0.0	0.0	0.0	2.2	0.6	0.2	0.1	0.1	0.0	0.5

Peak physiological responses during ramp incremental exercise at week 0

	Oxygen Uptake						Power Output			
MICT DSP ID	Peak (L.min)	Peak (mL.kg.min)	RCP (L.min)	RCP (mL.kg. min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
4	3.2	27.3	3.0	25.6	2.2	19.0	231	207	133	1004
7	2.1	21.6	1.7	18.4	1.4	14.3	162	130	88	728
8	1.5	25.2	1.5	24.4	1.2	20.4	116	97	60	544
15	3.2	28.0	3.0	25.7	2.6	22.2	245	190	150	825
17	1.5	16.5	1.4	15.5	1.2	12.6	85	66	40	420
20	2.4	26.7	2.1	23.8	1.9	20.6	152	130	105	688
23	1.5	20.2	1.4	18.4	1.1	14.7	121	98	73	562
24	2.1	17.8	2.0	17.3	1.8	15.8	155	140	93	700
28	1.8	18.9	1.7	18.1	1.4	15.1	186	157	90	648
30	2.4	26.0	2.3	24.3	1.6	17.0	213	191	124	729
32	X	X	X	X	X	X	246	X	X	828
39	1.2	15.9	1.1	14.9	1.0	13.7	96	72	59	465
43	1.2	21.0	1.1	19.2	0.9	16.1	103	88	82	492
MEAN	**2.0**	**22.1**	**1.9**	**20.5**	**1.5**	**16.8**	**162**	**130**	**91**	**664**
SD	**0.7**	**4.4**	**0.6**	**4.0**	**0.5**	**3.1**	**57**	**48**	**32**	**166**

	Oxygen Uptake						Power Output			
LVHIIT DSP ID	Peak (L.min)	Peak (mL.kg. min)	RCP (L.min)	RCP (mL.kg. min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
26	1.9	29.2	1.7	25.3	1.59	23.9	159	143	115	716
34	2.1	21.5	2.0	20.5	1.50	15.1	179	165	112	627
35	2.3	28.7	2.2	27.8	1.68	21.2	176	159	112	618
36	2.6	26.8	2.5	26.0	2.17	22.5	198	152	119	684
38	1.5	20.2	1.5	19.5	1.06	14.2	97	93	49	642
45	2.8	27.9	2.7	27.0	1.91	19.0	252	223	142	846
47	2.8	29.0	2.6	27.4	2.07	21.4	232	206	146	786
48	1.8	22.4	1.7	20.7	1.34	16.6	144	131	92	656
49	3.0	31.8	2.8	29.8	2.23	23.7	247	225	152	831
MEAN	**2.3**	**26.4**	**2.2**	**24.9**	**1.7**	**19.7**	**187**	**166**	**115**	**712**
SD	**0.5**	**4.0**	**0.5**	**3.7**	**0.4**	**3.7**	**51**	**44**	**32**	**88**

	Oxygen Uptake						Power Output			
CON DSP ID	Peak (L.min)	Peak (mL.kg. min)	RCP (L.min)	RCP (mL.kg. min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
3	1.8	19.0	1.6	16.4	1.3	14.1	139	108	81	636
10	1.2	16.6	1.1	15.1	0.9	12.3	101	80	55	484
12	2.4	23.2	2.2	20.1	1.4	12.8	200	168	87	690
18	1.4	21.6	1.4	21.6	1.1	17.1	107	100	70	508
21	1.7	21.8	1.4	18.4	1.2	15.7	120	83	65	780
22	1.6	18.0	1.4	16.6	1.1	13.0	120	95	65	780
31	2.3	24.8	2.1	22.8	1.7	18.6	175	159	108	615
33	2.8	28.2	2.7	27.7	1.8	18.5	247	238	133	830
41	1.6	20.3	1.4	18.2	1.2	15.1	126	110	80	584
MEAN	**1.9**	**21.5**	**1.7**	**19.6**	**1.3**	**15.3**	**148**	**127**	**83**	**656**
SD	**0.5**	**3.6**	**0.5**	**3.9**	**0.3**	**2.4**	**49**	**52**	**24**	**123**

Peak physiological responses during ramp incremental exercise at week 3

	Oxygen Uptake						Power Output			
MICT DSP ID	Peak (L.min)	Peak (mL.kg.min)	RCP (L.min)	RCP (mL.kg.min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
4	3.4	29.2	2.9	24.8	1.9	16.4	278	255	195	1192
7	2.2	22.8	2.0	20.7	1.5	15.4	175	149	100	780
8	1.9	32.6	1.8	30.2	1.4	24.4	133	104	71	612
15	3.4	30.8	3.0	26.9	2.5	22.8	289	214	176	957
17	1.5	16.4	1.4	15.5	1.3	13.8	100	80	68	480
20	3.1	33.8	2.8	31.2	2.1	22.7	188	174	129	832
23	1.8	24.1	1.8	23.8	1.3	16.7	134	125	80	616
24	2.1	18.6	2.0	17.6	1.7	15.1	156	139	101	704
28	2.4	26.3	2.2	23.8	1.8	19.6	208	174	116	714
30	2.8	29.7	2.6	27.6	1.9	20.4	236	210	137	798
32	X	X	X	X	X	X	275	X	X	915
39	1.7	22.0	1.5	19.7	1.2	15.7	122	103	77	569
43	1.4	24.2	1.3	22.1	1.1	19.3	122	108	82	568
MEAN	**2.3**	**25.9**	**2.1**	**23.7**	**1.6**	**18.5**	**186**	**153**	**111**	**749**
SD	**0.7**	**5.5**	**0.6**	**4.8**	**0.4**	**3.5**	**66**	**53**	**42**	**195**

	Oxygen Uptake						Power Output			
LVHIIT DSP ID	Peak (L.min)	Peak (mL.kg.min)	RCP (L.min)	RCP (mL.kg.min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
26	2.2	32.9	2.1	31.8	1.6	24.7	183	146	105	812
34	2.4	25.1	2.3	23.4	1.8	18.2	192	171	122	665
35	2.3	29.0	2.1	27.1	1.8	23.3	189	157	123	657
36	2.6	28.0	2.6	27.3	2.3	24.3	223	194	156	758
38	1.6	21.4	1.4	18.6	1.2	15.8	110	86	69	720
45	3.2	31.9	2.8	28.0	2.2	21.7	270	231	164	900
47	3.3	32.3	2.9	29.2	2.3	22.4	267	232	168	891
48	2.0	24.2	2.0	23.7	1.5	18.4	160	142	98	720
49	2.9	32.0	2.2	23.5	2.0	22.4	241	207	153	813
MEAN	**2.5**	**28.5**	**2.3**	**25.9**	**1.9**	**21.3**	**204**	**174**	**129**	**771**
SD	**0.6**	**4.2**	**0.5**	**3.9**	**0.4**	**3.1**	**52**	**47**	**34**	**90**

	Oxygen Uptake						Power Output			
CON DSP ID	Peak (L.min)	Peak (mL.kg.min)	RCP (L.min)	RCP (mL.kg.min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
3	1.8	18.7	1.5	16.2	1.3	14.0	137	116	78	628
10	1.1	14.4	1.0	13.5	0.8	11.4	80	65	49	402
12	2.7	24.8	2.4	22.5	1.6	14.8	208	171	106	714
18	1.4	23.3	1.3	22.2	1.1	18.4	107	91	75	508
21	1.5	19.1	1.4	17.8	1.3	16.1	119	96	76	556
22	1.8	20.4	1.6	18.7	1.3	14.7	120	103	73	778
31	2.7	27.8	2.4	25.1	1.7	17.7	206	176	100	707
33	2.8	27.8	2.4	24.0	1.8	17.6	230	185	113	780
41	1.8	22.3	1.6	19.9	1.3	16.2	136	124	81	624
MEAN	**1.9**	**22.1**	**1.7**	**20.0**	**1.4**	**15.6**	**149**	**125**	**83**	**633**
SD	**0.6**	**4.4**	**0.5**	**3.8**	**0.3**	**2.2**	**52**	**43**	**20**	**127**

Peak physiological responses during ramp incremental exercise at week 6

	Oxygen Uptake						Power Output			
MICT DSP ID	Peak (L.min)	Peak (mL.kg.min)	RCP (L.min)	RCP (mL.kg. min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
4	3.9	34.0	3.4	28.9	2.5	21.8	295	267	193	1260
7	2.4	25.3	2.2	22.5	1.7	17.6	180	139	109	800
8	2.0	33.3	1.8	30.8	1.6	26.5	141	123	81	644
15	3.7	33.0	3.4	31.0	2.9	26.5	293	258	206	969
17	1.8	19.6	1.7	18.3	1.6	17.1	115	91	76	540
20	2.9	32.0	2.7	30.2	2.4	27.2	191	173	142	844
23	1.9	25.8	1.9	24.8	1.4	19.4	149	132	94	676
24	2.4	21.1	2.3	19.9	2.0	17.0	154	134	100	698
28	2.6	28.3	2.5	26.6	2.0	21.4	206	178	130	708
30	2.8	30.2	2.5	27.7	2.1	22.4	248	215	166	834
32	X	X	X	X	X	X	289	X	X	957
39	1.7	23.1	1.6	21.2	1.3	17.8	126	115	82	584
43	1.4	25.1	1.3	23.2	1.2	21.3	122	109	93	569
MEAN	**2.5**	**27.6**	**2.3**	**25.4**	**1.9**	**21.3**	**193**	**161**	**123**	**776**
SD	**0.8**	**5.0**	**0.7**	**4.4**	**0.5**	**3.8**	**68**	**58**	**45**	**201**

	Oxygen Uptake						Power Output			
LVHIIT DSP ID	Peak (L.min)	Peak (mL.kg. min)	RCP (L.min)	RCP (mL.kg. min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
26	2.1	31.6	2.0	29.9	1.6	23.7	183	166	134	813
34	2.4	25.0	2.3	24.2	2.0	20.5	192	175	139	667
35	2.3	29.8	2.3	29.1	1.7	21.4	207	189	127	711
36	2.6	28.1	2.5	26.2	2.1	22.3	233	178	141	789
38	1.9	25.9	1.6	21.5	1.3	17.3	138	120	77	888
45	3.0	29.6	2.8	27.7	2.4	23.6	274	222	192	912
47	3.5	34.4	3.2	31.5	2.6	25.6	298	247	188	957
48	2.1	25.1	2.0	23.9	1.6	19.2	172	141	112	768
49	3.0	33.3	2.8	30.8	2.4	26.0	251	226	168	843
MEAN	**2.5**	**29.2**	**2.4**	**27.2**	**1.9**	**22.2**	**216**	**185**	**142**	**816**
SD	**0.5**	**3.5**	**0.5**	**3.5**	**0.4**	**2.9**	**52**	**41**	**37**	**94**

	Oxygen Uptake						Power Output			
CON DSP ID	Peak (L.min)	Peak (mL.kg. min)	RCP (L.min)	RCP (mL.kg. min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
3	1.5	16.3	1.4	14.8	1.2	12.8	100	96	76	480
10	1.3	18.3	1.2	19.7	0.9	13.0	98	81	60	472
12	2.4	22.0	2.2	19.7	1.7	15.3	207	172	112	711
18	1.4	23.1	1.2	21.0	1.0	17.3	109	92	67	516
21	1.6	20.6	1.6	19.6	1.3	16.3	116	98	77	543
22	1.5	17.5	1.4	16.1	1.1	12.5	107	95	65	702
31	2.6	27.0	2.3	24.1	1.7	17.7	178	154	101	624
33	2.8	28.0	2.7	27.5	1.9	19.5	251	220	143	843
41	1.8	22.1	1.6	19.8	1.3	16.7	146	128	86	663
MEAN	**1.9**	**21.6**	**1.7**	**20.2**	**1.4**	**15.7**	**146**	**126**	**87**	**617**
SD	**0.6**	**4.0**	**0.5**	**3.8**	**0.3**	**2.5**	**55**	**47**	**27**	**125**

Peak physiological responses during ramp incremental exercise at week 9

	Oxygen Uptake						Power Output			
MICT DSP ID	**Peak (L.min)**	**Peak (mL.kg.min)**	**RCP (L.min)**	**RCP (mL.kg. min)**	**VT (L.min)**	**VT(mL.kg.min)**	**Peak (W)**	**RCP (W)**	**VT (W)**	**TTF (s)**
4	3.9	33.6	3.4	29.9	3.0	26.0	310	245	205	1320
7	1.9	19.8	1.8	18.7	1.6	16.9	181	158	117	804
8	2.1	36.4	2.0	35.2	1.8	30.4	153	136	104	692
15	3.5	32.0	3.5	31.6	3.0	27.3	306	260	219	1008
17	1.7	18.5	1.6	17.5	1.5	16.3	116	97	73	544
20	2.4	27.8	2.4	27.3	2.1	24.2	181	163	137	804
23	1.8	23.7	1.6	21.3	1.2	16.4	152	126	83	686
24	2.4	21.3	2.1	18.9	1.9	17.1	176	144	123	784
28	2.7	28.6	2.6	27.0	2.0	21.1	235	222	154	795
30	2.8	30.8	2.3	25.1	2.0	22.3	243	199	170	819
32	X	X	X	X	X	X	288	X	X	954
39	1.9	25.4	1.8	24.0	1.5	20.2	146	134	108	664
43	1.4	24.2	1.3	22.4	1.1	20.0	128	112	88	592
MEAN	**2.4**	**26.8**	**2.2**	**24.9**	**1.9**	**21.5**	**201**	**166**	**132**	**805**
SD	**0.8**	**5.7**	**0.7**	**5.5**	**0.6**	**4.6**	**68**	**53**	**47**	**202**

	Oxygen Uptake						Power Output			
LVHIIT DSP ID	**Peak (L.min)**	**Peak (mL.kg. min)**	**RCP (L.min)**	**RCP (mL.kg. min)**	**VT (L.min)**	**VT(mL.kg.min)**	**Peak (W)**	**RCP (W)**	**VT (W)**	**TTF (s)**
26	2.3	34.2	2.1	31.7	2.0	30.1	195	158	131	860
34	2.6	27.6	2.5	26.5	1.9	20.1	207	193	153	711
35	2.3	30.0	2.2	28.4	1.8	23.0	204	177	127	702
36	2.6	27.7	2.5	26.9	2.1	22.4	230	196	144	780
38	1.8	24.5	1.7	22.9	1.4	18.6	144	124	93	924
45	3.5	35.0	3.2	31.6	2.7	26.5	290	258	202	960
47	3.3	33.3	3.2	32.2	2.4	24.3	283	242	170	939
48	2.0	24.2	1.9	23.2	1.6	19.4	168	147	113	740
49	3.2	35.3	3.0	32.9	2.3	25.7	257	233	178	861
MEAN	**2.6**	**30.2**	**2.5**	**28.5**	**2.0**	**23.3**	**220**	**192**	**145**	**831**
SD	**0.6**	**4.4**	**0.6**	**3.9**	**0.4**	**3.7**	**50**	**46**	**34**	**100**

	Oxygen Uptake						Power Output			
CON DSP ID	**Peak (L.min)**	**Peak (mL.kg. min)**	**RCP (L.min)**	**RCP (mL.kg. min)**	**VT (L.min)**	**VT(mL.kg.min)**	**Peak (W)**	**RCP (W)**	**VT (W)**	**TTF (s)**
3	1.8	19.4	1.7	17.9	1.1	12.1	138	116	64	632
10	1.3	17.7	1.2	16.0	0.9	13.0	97	86	59	468
12	2.6	23.3	2.3	20.7	1.6	14.5	211	180	95	723
18	1.3	22.7	1.3	21.5	1.1	18.0	105	99	70	500
21	1.5	19.5	1.4	18.5	1.2	15.6	118	89	63	771
22	1.6	18.3	1.5	17.2	1.1	12.2	119	102	63	774
31	2.5	26.2	2.1	21.8	1.7	17.7	180	130	105	630
33	3.1	30.8	2.9	28.7	2.0	19.5	246	217	136	829
41	1.8	22.2	1.7	21.1	1.4	18.0	142	115	85	648
MEAN	**1.9**	**22.2**	**1.8**	**20.4**	**1.3**	**15.6**	**151**	**126**	**82**	**664**
SD	**0.6**	**4.2**	**0.6**	**3.7**	**0.3**	**2.8**	**51**	**44**	**26**	**123**

Peak physiological responses during ramp incremental exercise at week 12

	Oxygen Uptake						Power Output			
MICT DSP ID	Peak (L.min)	Peak (mL.kg.min)	RCP (L.min)	RCP (mL.kg. min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
4	3.7	32.6	3.5	30.7	2.8	24.0	295	245	200	1260
7	1.9	20.5	1.8	19.5	1.7	18.4	196	150	133	864
8	1.8	31.3	1.7	30.3	1.5	25.8	142	111	75	648
15	3.7	33.7	2.4	21.7	2.8	26.2	310	234	192	1320
17	1.8	19.4	1.7	19.0	1.4	14.9	112	88	70	528
20	2.7	31.7	2.6	30.6	2.4	28.3	203	180	154	892
23	1.8	24.4	1.6	22.0	1.4	19.1	147	137	108	668
24	2.4	21.5	2.1	19.4	1.8	16.7	175	157	125	780
28	3.0	32.5	2.5	26.8	2.2	23.3	244	199	155	822
30	2.9	31.0	2.5	27.2	2.1	22.8	259	218	169	867
32	X	X	X	X	X	X	279.0	X	X	90
39	1.9	25.8	1.6	22.2	1.5	20.2	132	119	94	608
43	1.5	25.8	1.4	24.4	1.3	22.5	127	111	92	588
MEAN	**2.4**	**27.5**	**2.1**	**24.5**	**1.9**	**21.9**	**202**	**162**	**131**	**764**
SD	**0.8**	**5.2**	**0.6**	**4.5**	**0.6**	**4.1**	**69**	**52**	**44**	**314**

	Oxygen Uptake						Power Output			
LVHIIT DSP ID	Peak (L.min)	Peak (mL.kg. min)	RCP (L.min)	RCP (mL.kg. min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
26	2.1	32.3	2.0	30.8	1.9	28.3	187	161	130	828
34	2.6	27.4	2.3	24.9	2.1	21.9	210	182	152	720
35	2.5	32.1	2.2	28.2	1.8	23.3	220	183	130	750
36	2.5	27.0	2.4	25.6	2.0	21.7	230	196	143	780
38	1.8	25.2	1.6	21.6	1.4	19.1	130	112	83	840
45	3.2	32.2	2.9	29.3	2.6	26.5	292	253	227	966
47	3.2	31.7	2.8	28.3	2.3	23.0	280	235	181	930
48	2.0	24.6	1.9	23.0	1.6	19.4	150	137	106	680
49	3.3	35.9	3.0	32.1	2.2	23.9	252	219	177	846
MEAN	**2.6**	**29.8**	**2.3**	**27.1**	**2.0**	**23.0**	**217**	**187**	**148**	**816**
SD	**0.5**	**3.9**	**0.5**	**3.5**	**0.4**	**3.0**	**55**	**46**	**43**	**94**

	Oxygen Uptake						Power Output			
CON DSP ID	Peak (L.min)	Peak (mL.kg. min)	RCP (L.min)	RCP (mL.kg. min)	VT (L.min)	VT(mL.kg.min)	Peak (W)	RCP (W)	VT (W)	TTF (s)
3	1.9	20.9	1.7	18.5	1.4	15.4	139	118	98	634
10	1.4	19.0	1.4	18.6	1.1	14.8	103	88	54	492
12	2.2	20.4	2.1	18.8	1.4	12.8	193	164	94	669
18	1.2	21.0	1.1	19.2	0.9	16.1	103	88	65	492
21	1.6	20.3	1.5	19.4	1.2	15.3	129	105	76	595
22	1.7	19.1	1.6	17.9	1.3	14.9	119	101	76	774
31	2.7	27.5	2.4	25.1	1.9	19.8	195	166	113	675
33	2.8	27.9	2.7	27.0	1.9	19.2	252	214	142	846
41	1.8	22.4	1.7	20.7	1.3	16.6	144	122	92	656
MEAN	**1.9**	**22.0**	**1.8**	**20.6**	**1.4**	**16.1**	**153**	**130**	**90**	**648**
SD	**0.5**	**3.4**	**0.5**	**3.2**	**0.3**	**2.2**	**50**	**43**	**27**	**116**

Muscle deoxygenation parameters during ramp incremental exercise at week 0

MICT NIRS HHb VL% v's PO(%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
4	-8.00	1.29	1.22	81.80	0.08	0.99
7	-71.28	1.77	1.55	65.97	0.22	0.35
8	10.87	1.37	1.31	56.88	0.06	0.92
15	0.00	1.25	0.92	64.25	0.33	0.96
20	-13.00	1.72	1.08	49.81	0.64	0.97
23	-40.00	2.42	2.35	44.88	0.14	0.87
24	-40.00	2.34	2.09	58.96	0.24	0.95
28	-4.30	1.55	1.57	64.66	-0.02	0.99
30	-6.10	2.01	1.46	32.94	0.07	0.92
32	-10.10	1.28	1.17	80.05	0.11	0.96
39	-49.00	1.73	1.24	84.58	0.30	0.88
43.000	-14.00	1.32	0.85	77.73	0.74	0.94
MEAN	**-20.41**	**1.67**	**1.40**	**63.54**	**0.24**	**0.89**
SD	**24.10**	**0.41**	**0.45**	**15.94**	**0.24**	**0.18**

LVHIIT NIRS HHb VL% v's PO (%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
26	-3.09	1.66	1.53	56.02	0.13	0.96
34	-20.24	2.02	1.78	52.13	0.24	0.93
35	-53.00	1.50	0.01	99.90	1.49	0.87
36	-7.00	1.38	2.12	77.84	-0.74	0.97
38	-70.91	1.66	1.40	96.20	0.26	0.42
45	-31.00	1.45	1.46	91.65	-0.01	0.94
47	-74.90	2.17	2.25	81.65	-0.08	0.84
48	37.31	1.49	2.34	37.83	-0.85	0.76
49	-11.04	1.24	1.22	89.96	0.03	0.98
MEAN	**-25.99**	**1.62**	**1.57**	**75.91**	**0.05**	**0.85**
SD	**33.85**	**0.28**	**0.67**	**20.76**	**0.63**	**0.17**

Control NIRS HHb VL% v's PO (%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
3	-21.000	1.419	1.040	70.880	0.380	0.889
10	41.999	1.050	0.605	92.999	0.445	0.360
12	-6.000	1.206	1.337	85.197	-0.131	0.961
18	-20.000	1.310	1.150	90.702	0.160	0.975
21	-13.600	1.460	1.511	66.460	-0.051	0.944
22	-75.883	1.820	1.477	95.618	0.343	0.557
31	5.900	1.768	1.703	51.933	0.065	0.917
33	0.761	1.160	1.544	86.000	-0.383	0.992
41	-4.070	1.210	1.740	86.000	-0.530	0.821
MEAN	**-10.21**	**1.38**	**1.35**	**80.64**	**0.03**	**0.82**
SD	**31.02**	**0.27**	**0.36**	**14.48**	**0.34**	**0.22**

Muscle deoxygenation parameters during ramp incremental exercise at week 3

MICT NIRS HHb VL% v's PO(%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
4	-3.10	1.37	1.17	65.93	0.20	0.99
7	-24.00	1.27	0.43	77.30	0.84	0.97
8	-14.00	1.17	0.85	98.00	0.34	0.95
15	-6.10	1.28	1.07	73.58	0.21	0.93
20	-6.00	1.61	1.92	57.91	-0.31	0.95
23	9.90	1.30	1.08	55.20	0.22	0.93
24	-4.65	1.23	0.88	69.00	0.35	0.98
28	-0.90	1.64	1.38	51.97	0.26	0.97
30	-5.10	1.40	1.06	66.08	0.35	0.98
32	-8.00	1.17	0.99	87.82	0.18	0.98
39	-23.00	1.36	1.05	83.57	0.31	0.97
43.000	-32.00	1.69	1.40	69.78	0.32	0.88
MEAN	**-9.75**	**1.38**	**1.11**	**71.34**	**0.27**	**0.96**
SD	**11.59**	**0.18**	**0.36**	**13.66**	**0.25**	**0.03**

LVHIIT NIRS HHb VL% v's PO (%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
26	2.00	1.09	1.40	68.81	-0.31	0.96
34	3.10	1.45	1.22	57.09	0.23	0.99
35	-3.10	1.37	1.21	69.16	0.16	0.98
36	-0.98	1.21	1.22	82.00	-0.01	0.98
38	-5.60	1.35	0.83	54.71	0.52	0.95
45	-3.10	1.06	1.11	94.98	-0.05	0.99
47	-1.90	1.36	1.28	68.00	0.08	0.98
48	-32.00	1.36	4.97	86.91	-3.61	0.92
49	-0.50	0.87	0.47	83.38	0.41	0.94
MEAN	**-1.28**	**1.24**	**1.16**	**71.12**	**0.09**	**0.98**
SD	**3.33**	**0.16**	**0.19**	**15.25**	**0.26**	**0.02**

Control NIRS HHb VL% v's PO(%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
3	-6.450	1.728	1.729	55.900	-0.001	0.716
10	-3.900	1.080	1.790	99.000	-0.710	0.897
12	-23.830	1.309	1.590	81.030	-0.281	0.990
18	-41.020	1.844	2.094	60.240	-0.250	0.951
21	-24.000	1.640	1.230	65.720	0.410	0.899
22	-48.000	1.453	1.466	96.370	-0.013	0.748
31	-28.000	1.699	1.258	57.371	0.441	0.974
33	-14.000	1.221	1.226	90.679	-0.005	0.985
41	-17.000	1.282	3.310	80.900	-2.028	0.845
MEAN	**-22.91**	**1.47**	**1.74**	**76.36**	**-0.27**	**0.89**
SD	**14.71**	**0.27**	**0.66**	**17.00**	**0.75**	**0.10**

Muscle deoxygenation parameters during ramp incremental exercise at week 6

MICT NIRS HHb VL% v's PO(%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
4	-3.10	1.37	1.31	68.92	0.06	0.95
7	-14.00	1.17	0.11	79.50	1.05	0.97
8	-9.00	1.34	0.80	62.48	0.54	0.97
15	-6.00	0.98	0.68	74.53	0.30	0.86
20	-24.00	1.92	2.04	57.23	0.15	0.96
23	-51.00	1.62	1.40	81.78	0.22	0.98
24	-8.99	1.44	1.06	67.10	0.38	0.97
28	-2.89	1.80	1.46	49.97	0.34	0.99
30	0.16	1.17	1.13	79.47	0.04	0.96
32	-2.28	1.08	0.80	89.17	0.28	0.99
39	-4.00	1.21	1.13	81.17	0.08	0.95
43	-4.10	1.85	1.62	39.99	0.23	0.97
MEAN	**-10.77**	**1.41**	**1.13**	**69.28**	**0.31**	**0.96**
SD	**14.26**	**0.32**	**0.50**	**14.63**	**0.28**	**0.03**

LVHIIT NIRS HHb VL% v's PO (%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
26	2.00	1.38	1.38	69.00	0.00	0.97
34	-0.35	1.37	0.97	64.83	0.40	0.96
35	-11.00	1.38	1.26	77.95	0.12	1.00
36	-4.78	1.40	0.90	65.69	0.50	0.98
38	-8.00	0.99	0.60	93.24	0.39	0.86
45	-5.22	1.13	1.06	86.25	0.07	0.99
47	5.90	1.04	0.98	83.68	0.06	0.99
48	20.44	1.43	1.99	35.05	-0.56	0.10
49	-4.10	0.87	0.27	91.83	0.60	0.97
MEAN	**-0.57**	**1.22**	**1.05**	**74.17**	**0.18**	**0.87**
SD	**9.39**	**0.21**	**0.49**	**18.17**	**0.35**	**0.29**

Control NIRS HHb VL% v's PO(%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
3	1.950	1.610	1.550	25.990	0.060	0.826
10	49.990	1.460	2.060	27.430	-0.600	0.240
12	-12.000	1.395	1.812	70.899	-0.417	0.994
18	-30.000	1.380	0.637	41.260	0.743	0.968
21	-14.170	1.500	2.214	72.220	-0.714	0.820
22	-68.000	1.558	1.470	97.010	0.088	0.558
31	-22.000	2.250	2.284	51.750	-0.034	0.973
33	-6.006	1.160	1.470	88.931	-0.310	0.992
41	1.000	0.913	2.162	72.000	-1.249	0.110
MEAN	**-11.03**	**1.47**	**1.74**	**60.83**	**-0.27**	**0.72**
SD	**31.22**	**0.36**	**0.52**	**25.62**	**0.57**	**0.34**

Muscle deoxygenation parameters during ramp incremental exercise at week 9

MICT NIRS HHb VL% v's PO(%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
4	-9.12	1.29	1.08	79.49	0.21	0.98
7	-12.00	1.07	0.62	87.83	0.45	0.98
8	-6.90	1.36	0.91	62.03	0.46	0.93
15	-0.10	1.13	0.93	75.00	0.20	0.98
20	-34.00	1.04	1.04	59.54	0.00	0.90
23	-21.99	1.29	1.42	75.87	-0.13	0.93
24	-15.99	1.47	1.66	78.12	-0.19	0.99
28	-1.98	1.67	1.54	55.38	0.13	0.99
30	-2.90	1.35	0.90	66.01	0.45	0.99
32	-3.30	1.10	0.90	89.57	0.19	0.99
39	-9.00	1.17	0.96	90.79	0.21	0.99
43	-2.00	1.47	1.22	56.63	0.26	0.94
MEAN	**-9.94**	**1.28**	**1.10**	**73.02**	**0.19**	**0.97**
SD	**9.97**	**0.19**	**0.31**	**12.86**	**0.21**	**0.03**

LVHIIT NIRS HHb VL% v's PO (%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
26	-15.51	1.29	0.75	78.74	0.54	0.92
34	13.45	1.32	1.12	44.21	0.20	0.98
35	-3.96	1.25	0.98	76.99	0.27	0.98
36	1.80	1.29	1.30	74.02	-0.01	0.99
38	-4.20	1.59	1.05	44.10	0.54	0.97
45	-4.00	1.09	0.70	87.73	0.39	1.00
47	1.90	1.20	1.13	77.94	0.07	0.98
48	-2.99	1.16	2.76	87.20	-1.60	0.99
49	-0.10	0.87	0.76	83.97	0.11	0.98
MEAN	**-2.07**	**1.23**	**0.98**	**67.63**	**0.32**	**0.97**
SD	**9.47**	**0.16**	**0.23**	**18.75**	**0.22**	**0.03**

Control NIRS HHb VL% v's PO(%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
3	-18.000	1.208	1.234	76.610	-0.026	0.940
10	9.000	0.966	1.660	75.390	-0.694	0.850
12	-20.000	1.449	2.321	74.050	-0.872	0.973
18	-9.974	1.363	1.389	78.160	-0.026	0.987
21	0.999	1.088	2.081	85.770	-0.993	0.923
22	-14.000	1.212	1.194	89.730	0.018	0.872
31	-16.000	2.316	2.726	49.000	-0.410	0.966
33	-12.000	1.264	0.957	83.187	0.307	0.991
41	-104.570	1.950	6.323	84.340	-4.373	0.003
MEAN	**-20.50**	**1.42**	**2.21**	**77.36**	**-0.79**	**0.83**
SD	**32.89**	**0.44**	**1.65**	**11.87**	**1.42**	**0.32**

Muscle deoxygenation parameters during ramp incremental exercise at week 12

MICT NIRS HHb VL% v's PO(%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
4	-24.00	1.36	1.29	85.30	0.08	0.96
7	-0.99	1.21	0.90	72.07	0.31	0.98
8	-15.51	1.37	1.31	67.91	0.05	0.96
15	-3.26	0.81	0.59	58.00	0.22	0.99
20	-46.08	1.51	0.79	79.87	0.72	0.97
23	-29.00	1.51	2.74	85.99	0.53	0.97
24	-9.10	1.45	1.46	73.02	-0.01	0.99
28	-2.69	1.45	0.98	57.01	0.47	0.99
30	1.09	1.05	1.10	90.78	-0.05	0.98
32	-26.44	1.67	2.34	58.00	-0.66	0.90
39	-47.30	1.69	1.79	85.98	-0.10	0.94
43.000	-9.60	1.09	0.50	86.51	0.59	0.98
MEAN	**-17.74**	**1.35**	**1.31**	**75.04**	**0.18**	**0.97**
SD	**16.88**	**0.26**	**0.68**	**12.49**	**0.38**	**0.03**

LVHIIT NIRS HHb VL% v's PO (%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
26	-5.00	1.46	2.67	71.08	-1.21	0.97
34	0.02	1.26	0.95	70.52	0.31	0.99
35	0.00	1.36	1.06	67.01	0.30	0.99
36	-2.10	1.22	1.27	82.96	-0.05	0.98
38	-9.00	1.24	1.32	77.23	-0.08	0.97
45	-8.00	1.14	1.15	92.53	-0.01	1.00
47	7.92	1.36	1.37	72.99	-0.01	0.94
48	16.96	0.82	0.77	95.96	0.05	0.85
49	-7.00	1.22	1.14	84.04	0.08	0.98
MEAN	**-0.69**	**1.23**	**1.30**	**79.37**	**-0.07**	**0.96**
SD	**8.44**	**0.18**	**0.55**	**10.18**	**0.45**	**0.02**

Control NIRS HHb VL% v's PO(%) (Double-Linear)						
ID	Intercept	Slope 1	C	Breakpoint	Slope 2	r^2
3	-46.000	1.437	1.477	74.640	-0.040	0.898
10	-136.640	0.971	2.687	75.130	-1.716	0.370
12	0.000	1.404	2.903	69.514	-1.498	0.946
18	-40.000	1.320	0.576	47.000	0.744	0.95
21	-14.000	1.974	1.831	49.130	0.143	0.95
22	-63.000	1.848	1.883	89.944	-0.035	0.314
31	-34.000	2.360	2.514	55.840	-0.154	0.931
33	-31.000	1.288	1.298	91.648	-0.010	0.943
41	41.000	1.490	2.960	27.000	-1.470	0.730
MEAN	**-35.96**	**1.57**	**2.01**	**64.43**	**-0.32**	**0.78**
SD	**48.36**	**0.42**	**0.81**	**21.36**	**0.84**	**0.26**

Peak cardiac responses throughout the intervention period

Qpeak (L.min)					
MICT	WK0	WK3	WK6	WK9	Wk12
4	23.0	27.5	25.2	26.4	30.9
7	12.2	15.6	14.4	13.2	12.3
8	10.5	12.5	13.2	13.2	13.2
15	19.7	21.1	22.8	25.6	25.6
17	10.4	11.3	11.7	10.6	10.7
20	15.7	17.1	17.2	16.5	16.3
23	10.8	11.0	11.3	12.5	11.2
24	14.3	14.6	14.9	14.8	15.2
28	14.0	14.6	15.5	16.2	17.0
30	19.0	19.4	21.7	21.6	21.5
39	12.1	14.2	13.0	14.6	16.0
43	11.1	10.8	11.7	12.3	12.4
Mean	14.4	15.8	16.4	16.8	16.9
SD	4.2	4.9	4.7	5.3	6.2

Qpeak (L.min)					
LVHIIT	WK0	WK3	WK6	WK9	Wk12
26	12.0	13.1	13.1	13.2	14.2
34	13.5	14.7	15.7	14.1	15.0
35	13.5	14.4	15.1	15.3	14.1
36	19.8	19.9	20.4	20.1	20.1
38	10.0	10.6	12.0	12.0	12.3
45	18.5	20.0	20.3	19.6	19.5
47	20.8	23.1	21.6	21.7	21.8
48	11.0	12.2	12.7	14.0	13.2
49	21.93	21.9	20.2	24.2	24.1
Mean	15.7	16.7	16.4	16.2	17.1
SD	4.6	4.6	3.9	3.6	4.3

Qpeak (L.min)					
CON	WK0	WK3	WK6	WK9	Wk12
3	14.9	14.0	13.7	12.8	13.1
10	8.8	8.9	9.1	9.5	10.00
12	18.8	19.3	16.2	18.6	18.8
18	10.0	10.5	10.7	10.4	9.6
21	14.6	12.1	13.4	14.1	14.3
22	10	11.8	10.1	10	10.00
31	18.0	18.2	18.0	15.4	16.3
33	20.8	20.7	20.8	19.9	23.0
41	9.9	10.52	13.1	13.1	12.00
Mean	13.98	14.00	13.9	13.8	14.13
SD	4.50	4.32	3.86	3.70	4.55

A-VO2 diffmax (mL O2 per 100 mL)					
MICT	WK0	WK3	WK6	WK9	Wk12
4	13.8	12.4	15.7	14.7	12.1
7	16.8	14.0	16.9	14.1	15.3
8	14.4	15.4	14.8	16.1	13.6
15	16.4	16.2	16.1	13.8	14.3
17	14.6	13.3	15.3	16.1	16.5
20	15.3	17.9	16.6	14.6	16.5
23	14.1	16.5	17.1	14.3	16.0
24	14.5	14.7	16.3	16.0	15.6
28	12.8	16.6	17.0	16.8	17.8
30	12.9	14.3	12.7	13.1	13.4
39	9.5	11.6	13.2	12.7	11.8
43	11.2	12.9	12.2	11.3	11.9
Mean	13.9	14.6	15.6	14.7	14.6
SD	2.1	1.9	1.5	1.3	2.0

A-VO2 diffmax (mL O2 per 100 mL)					
LVHIIT	WK0	WK3	WK6	WK9	Wk12
26	16.2	16.6	16.1	17.3	15.0
34	15.8	16.5	15.1	18.6	17.2
35	16.8	15.9	15.5	15.2	17.7
36	13.1	13.2	12.9	13.0	12.6
38	15.1	14.7	15.8	15.1	15.0
45	15.1	15.9	14.6	18.1	16.4
47	13.4	14.1	16.0	15.3	14.5
48	16.4	16.5	16.3	14.2	15.3
49	13.6	13.4	15.0	13.2	13.8
Mean	15.1	15.2	15.3	15.6	15.3
SD	1.4	1.4	1.0	2.0	1.6

A-VO2 diffmax (mL O2 per 100 mL)					
CON	WK0	WK3	WK6	WK9	Wk12
3	12.0	12.6	11.1	14.3	14.9
10	13.8	11.8	14.5	13.4	14.0
12	12.9	13.9	15.0	13.8	11.9
18	14.1	13.1	12.7	12.9	12.9
21	11.4	12.5	12.3	10.5	10.8
22	15.5	15.2	15.3	16.2	16.8
31	12.8	14.7	14.4	16.1	16.3
33	13.4	13.5	13.3	15.6	12.2
41	16.2	17.0	13.5	13.4	15.0
Mean	13.6	13.8	13.6	14.0	13.9
SD	1.6	1.6	1.4	1.8	2.1

HRmax

MICT	Week 0	Week 3	Week 6	Week 9	Week 12
4	157	161	169	169	170
7	136	132	130	130	136
8	168	169	167	174	174
15	174	171	169	171	167
17	142	130	146	146	144
20	169	164	171	172	163
23	152	135	138	140	140
24	178	167	169	181	183
28	167	169	158	172	173
30	144	146	146	139	137
39	143	152	145	163	150
43	150	161	160	163	163
Mean	157	155	156	160	158
SD	14	15	14	17	16

HIIT	Week 0	Week 3	Week 6	Week 9	Week 12
26	144	145	147	150	149
34	150	157	154	158	144
35	154	160	153	175	158
36	157	154	153	152	152
38	178	180	176	170	185
45	158	163	161	164	169
47	174	168	170	176	171
48	183	188	188	186	180
49	164	173	154	150	151
Mean	162	165	162	165	162
SD	13	13	13	13	15

CON	Week 0	Week 3	Week 6	Week 9	Week 12
3	149	140	128	140	133
10	148	112	133	132	132
12	158	169	160	173	174
18	160	160	150	151	154
21	169	151	155	153	147
22	180	160	147	157	157
31	188	180	174	180	174
33	160	150	160	158	160
41	167	172	170	174	183
Mean	164	155	153	158	157
SD	13	20	15	16	18

SVmax

MICT	Week 0	Week 3	Week 6	Week 9	Week 12
4	146	171	149	156	182
7	90	118	111	102	90
8	63	74	79	76	76
15	113	123	135	150	153
17	73	87	80	73	74
20	93	104	101	96	100
23	71	81	82	89	80
24	80	87	88	82	83
28	84	86	98	94	98
30	132	133	149	155	157
39	85	94	90	90	107
43	74	67	73	75	76
Mean	92	102	103	103	106
SD	26	30	27	32	37
HIIT	Week 0	Week 3	Week 6	Week 9	Week 12
26	83	90	89	88	95
34	90	94	102	89	104
35	88	90	99	87	89
36	126	129	133	132	132
38	56	59	68	71	66
45	117	123	126	120	115
47	120	137	127	123	128
48	60	65	68	75	73
49	134	127	131	161	160
Mean	97	102	105	105	107
SD	28	29	26	30	30
CON	Week 0	Week 3	Week 6	Week 9	Week 12
3	100	100	107	91	98
10	59	79	68	72	76
12	119	114	101	108	108
18	63	66	71	69	62
21	86	80	87	92	98
22	56	74	69	64	64
31	96	101	103	86	94
33	130	138	130	126	144
41	59	61	77	75	66
Mean	85	90	90	87	90
SD	28	25	21	20	27

Anthropometric data throughout the intervention period

Body mass (kg)

MICT DSP ID	W0	W3	W6	W9	W12
4	116.5	116.6	116.2	115.3	115.0
7	95.0	96.2	95.7	94.1	91.9
8	60.0	59.2	58.8	58.2	57.2
15	115.0	111.0	111.0	110.0	108.5
17	92.0	91.8	91.5	92.3	91.4
20	90.0	90.5	89.3	86.7	85.0
23	75.7	75.4	74.8	75.4	73.4
24	116.0	115.0	115.0	111.0	110.0
28	94.7	92.0	93.3	95.0	92.9
30	94.1	93.2	91.5	91.9	93.0
32	116.7	117.8	116.7	118.0	116.9
39	72.5	75.0	74.1	73.3	73.0
43	59.0	57.4	56.9	57.4	57.4
Mean	92.1	91.6	91.1	90.7	89.7
SD	20.6	20.4	20.5	20.2	20.1

CON DSP ID	W0	W3	W6	W9	W12
3	94.5	94.0	93.0	94.1	93.2
10	73.0	73.0	72.3	72.0	73.5
12	108.8	108.0	111.0	110.0	109.9
18	65.0	59.3	58.9	58.8	59.0
21	76.0	79.4	80.0	75.8	76.5
22	86.0	87.8	88.4	88.5	88.0
31	92.5	96.3	96.1	94.9	96.7
33	99.0	100.2	99.4	101.2	100.4
41	79.1	80.3	80.0	79.0	80.6
Mean	86.0	86.5	86.6	86.0	86.4
SD	14.0	15.1	15.6	16.0	15.6

LVHIIT DSP ID	W0	W3	W6	W9	W12
26	66.5	66.1	66.7	66.7	65.7
34	99.0	96.7	95.0	95.0	94.0
35	79.0	79.0	78.7	77.6	78.0
36	96.7	94.0	94.0	94.0	93.8
38	74.5	73.0	73.2	74.0	73.0
45	100.4	99.6	100.0	101.0	98.9
47	96.4	101.0	100.6	100.0	100.0
48	80.6	83.0	82.6	82.0	82.0
49	94.0	91.4	90.6	90.3	93.0
Mean	87.5	87.1	86.8	86.7	86.5
SD	12.4	12.4	12.1	12.2	12.2

BMI (kg.m2)

MICT DSP ID	W0	W3	W6	W9	W12
4	34.8	34.8	34.7	34.4	34.3
7	30.0	30.4	30.2	29.7	29.0
8	20.8	20.5	20.3	20.1	19.8
15	38.0	36.7	36.7	36.3	35.8
17	33.8	33.7	33.6	33.9	33.6
20	31.5	31.7	31.3	30.4	29.8
23	28.7	28.6	28.3	28.6	27.8
24	38.3	38.0	38.0	36.7	36.3
28	31.3	30.4	30.8	31.4	30.7
30	26.6	26.4	25.9	26.0	26.3
32	37.2	37.6	37.2	37.7	37.3
39	25.1	26.0	25.6	25.4	25.3
43	23.6	23.0	22.8	23.0	23.0
Mean	30.7	30.6	30.4	30.3	29.9
SD	5.6	5.6	5.6	5.5	5.4

CON DSP ID	W0	W3	W6	W9	W12
3	31.2	31.0	30.7	30.7	30.4
10	28.2	28.2	28.2	28.1	28.7
12	32.8	32.6	33.5	33.2	33.2
18	26.0	23.8	23.0	23.0	23.6
21	30.4	31.8	32.0	30.4	30.6
22	35.8	37.5	37.8	37.8	36.6
31	26.7	27.8	27.8	27.4	28.0
33	28.0	28.3	28.1	29.3	28.4
41	35.2	35.7	35.6	35.1	35.8
Mean	30.5	30.8	30.7	30.6	30.6
SD	3.6	4.3	4.5	4.4	4.1

LVHIIT DSP ID	W0	W3	W6	W9	W12
26	26.0	26.1	26.4	26.4	25.7
34	28.0	27.4	26.9	26.9	26.6
35	24.9	24.9	24.8	24.5	24.6
36	31.6	30.7	30.7	30.0	29.9
38	27.4	26.8	26.9	27.2	26.8
45	28.4	28.2	28.3	28.6	28.0
47	29.1	30.5	30.0	30.2	30.2
48	35.8	36.9	36.7	36.4	36.4
49	28.1	27.3	27.1	27.0	27.8
Mean	28.8	28.8	28.6	28.6	28.4
SD	3.2	3.6	3.5	3.5	3.5

Glycaemic profiles pre- and post- the intervention period

Week 0

MICT DSP ID	HbA1c (%)	FG (mmol.L
4	6.0	7.0
7	6.6	8.8
8	6.2	6.7
15	7.6	8.5
17	7.0	8.4
20	7.1	8.4
23	7.5	8.8
24	6.5	6.9
28	6.7	8.1
30	6.5	7.4
32	6.9	X
39	7.4	4.8
Mean	6.8	7.6
SD	0.5	1.2

Week 12

MICT DSP ID	HbA1c (%)	FG (mmol.L
4	5.8	7.4
7	6.4	6.6
8	6.1	5.7
15	6.7	7.6
17	7.3	8.1
20	6.7	7.5
23	7.3	10.1
24	6.3	5.6
28	6.9	7.7
30	6.0	6.7
32	7.4	X
39	6.7	6.1
Mean	6.6	7.19
SD	0.5	1.28

Week 0

LVHIIT DSP ID	HbA1c (%)	FG (mmol.L
26	7.9	10.9
34	7.2	13.5
35	7.5	X
36	7.3	7.7
47	7.4	7.6
48	6.3	4.5
49	7.7	11.6
Mean	7.3	9.30
SD	0.5	3.29

Week 12

LVHIIT DSP ID	HbA1c (%)	FG (mmol.L
26	6.2	7.5
34	5.3	8.1
35	6.7	X
36	6.9	7.7
47	7.6	9.6
48	6.0	7.1
49	7.5	9.0
Mean	6.6	8.2
SD	0.8	0.95

Week 0

CON DSP ID	HbA1c (%)	FG (mmol.L
3	7.1	12.8
10	5.5	4.8
18	7.3	9.8
21	6.4	6.1
22	6.7	6.1
31	8.6	12.0
41	6.3	3.9
Mean	6.8	7.9
SD	1.0	3.6

Week 12

CON DSP ID	HbA1c (%)	FG (mmol.L
3	7.8	9.1
10	5.9	5.9
18	7.1	7.8
21	6.5	7.1
22	6.5	6.6
31	8.6	9.3
41	6.3	3.4
Mean	7.0	7.0
SD	1.0	2.0

Blood pressure responses throughout the intervention period

MICT rest SBP (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
4	152	148	148	138	142
7	140	145	145	140	136
8	112	92	118	100	110
15	138	153	144	130	124
17	122	110	122	128	104
20	124	131	126	122	136
23	100	102	100	100	107
24	114	114	110	117	116
28	118	134	134	130	126
30	122	122	125	124	118
39	110	117	118	126	124
43	102	122	104	118	112
MEAN	121	124	125	123	121
SD	16	19	16	13	12

LVHIIT rest SBP (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
26	138	116	129	122	118
34	112	126	124	122	115
35	102	106	121	126	110
36	124	135	130	125	122
38	130	122	135	122	142
45	124	116	121	126	124
47	143	146	147	117	115
48	118	130	134	134	141
49	124	115	118	103	124
Mean	124	124	129	122	123
SD	13	12	9	8	11

CON rest SBP (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
3	146	138	124	134	126
10	128	106	127	122	140
12	132	134	132	136	136
18	118	118	112	110	102
21	114	138	116	140	142
22	143	120	140	112	118
31	129	126	145	130	136
33	140	133	130	115	124
41	118	142	110	117	118
Mean	130	128	126	124	127
SD	12	12	12	11	13

MICT DBP rest (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
4	80	78	84	78	80
7	90	73	81	76	76
8	70	56	54	52	60
15	88	92	78	80	72
17	70	60	70	68	60
20	70	68	76	77	72
23	70	60	58	58	60
24	66	74	85	69	75
28	78	74	80	74	74
30	88	76	80	78	78
39	62	86	78	70	74
43	70	64	62	68	62
MEAN	75	72	74	71	70
SD	9	11	10	9	8

LVHIIT rest DBP (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
26	70	56	60	78	68
34	64	76	86	76	70
35	62	62	68	70	70
36	78	68	80	72	67
38	75	78	70	67	70
45	70	72	70	74	82
47	80	95	96	71	79
48	78	74	85	85	78
49	74	67	71	67	70
Mean	72	72	76	73	73
SD	6	11	11	6	5

CON DBP rest (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
26	76	70	68	82	62
34	60	60	67	66	68
35	74	72	80	78	80
36	70	68	68	60	70
38	76	76	70	79	81
45	63	52	70	52	56
47	77	67	74	77	78
48	80	84	82	76	70
49	78	75	66	67	78
Mean	73	69	72	71	71
SD	7	9	6	10	9

MICT MAP rest (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
4	104	101	105	98	100
7	107	97	102	97	96
8	84	68	75	68	77
15	105	112	100	97	89
17	87	77	87	88	75
20	88	89	93	92	93
23	80	74	72	72	76
24	82	87	93	85	89
28	91	94	98	92	91
30	99	91	95	93	91
39	78	96	91	88	91
43	81	83	76	85	79
MEAN	90	89	91	88	87
SD	11	12	11	10	9

LVHIIT rest MAP (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
26	92	76	83	93	85
34	80	93	99	91	85
35	75	77	85	88	83
36	93	90	97	89	85
38	93	93	91	85	94
45	88	87	87	91	96
47	101	112	113	86	91
48	91	92	101	101	99
49	91	83	87	79	88
Mean	89	89	94	89	89
SD	8	11	10	6	6

CON rest MAP (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
26	99	92	86	99	83
34	82	75	87	84	92
35	93	92	97	97	98
36	86	85	83	77	81
38	89	96	85	99	101
45	89	74	93	72	76
47	94	86	97	94	97
48	100	100	98	89	88
49	91	97	81	84	91
Mean	92	89	90	88	90
SD	6	9	7	10	8

MICT max SBP (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
4	219	210	173	204	207
7	149	197	170	193	173
15	172	195	160	165	189
20	158	156	162	153	175
23	152	193	124	136	169
28	158	166	171	203	220
30	154	150	144	158	151
39	147	181	165	179	166
MEAN	164	181	159	174	181
SD	24	22	17	25	23

LVHIIT max SBP (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
26	168	182	191	167	181
34	143	206	161	180	153
35	168	158	180	198	175
36	175	203	187	170	191
38	165	183	216	195	180
45	183	228	197	211	180
47	188	193	184	199	212
48	142	184	211	160	168
Mean	167	192	191	185	180
SD	17	21	18	18	17

CON max SBP (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
3	170	198	155	179	190
10	152	151	155	176	177
12	143	160	180	191	194
18	147	162	143	157	150
21	185	185	190	179	198
22	220	173	205	153	198
31	164	223	182	170	196
33	209	204	217	204	183
41	181	168	192	154	142
Mean	175	180	180	174	181
SD	27	24	25	17	21

MICT DBP max	Week 0	Week 3	Week 6	Week 9	Week 12
4	119	109	112	119	114
7	82	96	88	109	78
15	118	112	118	103	109
20	90	81	73	87	93
23	80	94	68	71	100
28	84	95	102	100	108
30	93	87	84	98	93
39	65	114	91	98	87
MEAN	91	99	92	98	98
SD	19	12	18	14	12

LVHIIT max DBP	Week 0	Week 3	Week 6	Week 9	Week 12
26	84	105	109	99	91
34	74	118	87	104	90
35	78	100	115	110	98
36	85	108	94	102	109
38	80	82	110	102	109
45	94	116	107	108	93
47	96	98	110	104	110
48	90	103	110	88	97
Mean	85	104	105	102	100
SD	8	11	10	7	8

CON DBP max	Week 0	Week 3	Week 6	Week 9	Week 12
3	100	104	88	99	102
10	94	83	84	96	80
12	104	103	110	117	119
18	78	77	80	97	80
21	90	86	109	109	109
22	118	97	109	83	98
31	83	103	100	105	101
33	100	118	109	102	94
41	95	88	88	97	90
Mean	96	95	97	101	97
SD	12	13	12	9	13

MICT MAP max (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
4	152	142	132	147	145
7	104	129	115	137	109
15	136	139	132	123	135
20	112	106	102	109	120
23	104	127	86	92	123
28	108	118	125	134	145
30	113	108	104	118	112
39	92	136	115	125	113
MEAN	115	126	114	123	125
SD	19	14	16	17	15

LVHIIT max MAP (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
26	112	130	136	121	121
34	97	147	111	129	111
35	108	119	136	139	123
36	115	139	125	124	136
38	108	115	145	133	132
45	123	153	137	142	122
47	126	129	134	135	144
48	107	130	143	112	120
Mean	112	133	134	129	126
SD	10	13	11	10	10

CON max MAP (mmHg)	Week 0	Week 3	Week 6	Week 9	Week 12
3	123	135	110	125	131
10	113	105	107	122	112
12	117	122	133	141	144
18	101	105	101	117	103
21	121	119	136	132	138
22	152	122	141	106	131
31	110	143	127	126	132
33	136	146	145	136	123
41	123	114	122	116	107
Mean	122	123	125	125	125
SD	15	15	16	11	14

Appendix 7.5. Experiment 2 raw data.

The baseline characteristics of the participants and peak physiological responses at each time point can be found in Appendix 8.4. The participant ID numbers of those who took part in Experiment 2 are listed in the table below.

Participant ID numbers		
MICT	LVHIIT	CON
4	26	3
7	34	10
8	35	12
15	36	18
20	38	21
23	45	22
24	47	31
28	48	33
30	49	41
39		

VO_2 kinetics responses during 'unprimed' moderate-intensity exercise at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
4	0.87	1.29	9.00	38.77	2.17	13.42
7	0.64	0.64	7.30	36.11	1.28	10.58
8	0.97	0.52	5.00	30.41	1.49	13.66
15	1.11	1.11	6.08	51.86	2.22	10.07
20	1.32	0.70	15.41	56.00	2.03	9.57
23	0.70	0.46	11.79	51.09	1.16	9.63
24	1.03	0.56	11.54	58.12	1.59	8.80
28	1.01	0.79	0.00	62.08	1.80	12.86
30	0.81	0.95	18.80	31.99	1.76	10.66
39	0.74	0.29	25.36	31.00	1.02	7.82
Mean	0.92	0.73	11.03	44.74	1.65	10.71
SD	0.21	0.31	7.35	12.31	0.42	1.99

LVHIIT DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
26	0.73	0.92	9.39	33.74	1.65	11.25
34	0.46	1.14	10.00	49.81	1.61	14.38
35	0.69	0.87	0.00	40.06	1.57	11.06
36	1.20	0.78	28.00	35.65	1.98	9.13
38	0.80	0.24	6.57	52.43	1.04	8.17
45	0.86	1.02	11.97	32.17	1.88	9.81
47	0.64	1.54	4.90	39.93	2.17	14.37
48	0.78	0.48	18.00	50.50	1.26	7.62
49	0.78	1.30	5.84	47.00	2.08	11.64
Mean	0.77	0.92	10.52	42.37	1.69	10.83
SD	0.20	0.40	8.25	7.74	0.38	2.43

CON DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
3	0.66	0.75	3.87	49.99	1.41	13.70
10	0.59	0.33	11.85	53.94	0.92	9.82
12	1.00	0.54	13.28	45.00	1.54	9.10
18	0.64	0.41	10.40	35.88	1.05	9.08
21	0.78	0.44	7.76	35.13	1.22	10.63
22	0.70	0.47	13.70	41.31	1.17	11.28
31	1.08	0.74	6.65	39.68	1.82	9.65
33	0.85	1.06	11.11	35.00	1.91	11.00
41	0.87	0.38	22.00	50.09	1.25	7.12
Mean	0.80	0.57	11.18	42.89	1.37	10.15
SD	0.17	0.24	5.18	7.19	0.34	1.82

VO_2 kinetics responses during 'unprimed' moderate-intensity exercise at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
4	0.95	1.04	8.73	29.68	1.99	10.83
7	0.71	0.70	13.00	37.69	1.41	11.61
8	1.09	0.26	23.55	30.00	1.35	6.82
15	1.28	0.88	21.00	28.22	2.16	8.02
20	1.31	0.49	11.15	38.00	1.80	6.66
23	0.70	0.47	17.00	26.07	1.18	9.89
24	1.17	0.46	9.45	38.67	1.63	7.13
28	0.93	0.71	12.89	38.00	1.64	11.51
30	0.89	0.90	22.85	27.30	1.79	10.07
39	0.79	0.29	11.71	32.72	1.08	7.77
Mean	0.98	0.62	15.13	32.63	1.60	9.03
SD	0.22	0.27	5.57	5.01	0.35	1.96

LVHIIT DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
26	0.85	0.72	10.00	33.20	1.57	8.80
34	0.77	0.85	11.31	38.92	1.62	10.68
35	0.79	0.86	24.00	28.62	1.65	10.84
36	1.06	0.75	9.88	34.00	1.81	8.81
38	0.78	0.20	23.00	29.91	0.98	6.96
45	0.97	0.88	21.52	27.00	1.85	8.46
47	0.90	1.15	14.13	31.99	2.04	10.72
48	0.90	0.43	19.64	29.77	1.33	6.71
49	0.94	0.99	26.94	33.99	1.93	8.85
Mean	0.88	0.76	17.82	31.93	1.64	8.98
SD	0.10	0.29	6.57	3.59	0.33	1.54

CON DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
3	0.74	0.64	7.00	46.48	1.38	11.65
10	0.58	0.32	18.01	39.02	0.89	9.29
12	0.79	0.64	5.27	44.48	1.43	10.69
18	0.60	0.50	7.13	35.42	1.10	11.05
21	0.98	0.40	15.00	43.99	1.37	9.57
22	0.69	0.44	9.51	37.00	1.13	10.43
31	0.84	0.89	3.00	46.00	1.73	11.65
33	0.78	0.99	17.18	30.67	1.77	10.27
41	0.83	0.52	19.00	46.10	1.35	9.61
Mean	0.76	0.59	11.23	41.02	1.35	10.47
SD	0.12	0.22	6.09	5.70	0.28	0.88

VO_2 kinetics responses during 'unprimed' moderate-intensity exercise at week 6.

MICT DSP ID	A1	TD1	Tau	End Vo2	Vo2 Gain
4	0.95	19.88	16.72	2.01	9.88
7	0.67	16.30	27.89	1.42	11.02
8	0.45	2.37	34.55	1.35	11.95
15	0.81	21.00	29.90	2.21	7.37
20	0.63	15.71	55.02	1.91	8.55
23	0.62	9.98	22.85	1.17	12.96
24	0.55	17.05	25.00	1.52	8.61
28	0.60	20.00	26.90	1.47	9.75
30	0.95	17.93	29.00	1.79	10.65
39	0.29	28.80	17.59	0.99	7.85
Mean	0.65	16.90	28.54	1.58	9.86
SD	0.21	6.98	10.79	0.39	1.81

LVHIIT DSP ID	A1	TD1	Tau	End Vo2	Vo2 Gain
26	0.87	8.41	29.64	1.57	10.66
34	0.87	33.00	34.05	1.79	10.91
35	0.84	12.45	25.00	1.55	10.59
36	0.70	22.00	24.40	1.66	8.29
38	0.25	28.81	35.00	0.93	8.61
45	0.98	19.73	23.87	1.78	9.47
47	1.15	14.31	26.26	1.98	10.71
48	0.60	17.60	25.00	1.49	9.51
49	1.11	17.10	31.52	1.96	9.88
Mean	0.82	19.27	28.31	1.63	9.85
SD	0.27	7.78	4.34	0.32	0.95

CON DSP ID	A1	TD1	Tau	End Vo2	Vo2 Gain
3	0.67	7.48	48.57	1.32	12.14
10	0.34	8.60	45.98	0.94	10.00
12	0.54	11.31	45.65	1.48	9.03
18	0.50	8.20	39.99	1.04	10.88
21	0.43	12.00	34.25	1.20	10.37
22	0.45	14.00	40.00	1.12	10.84
31	0.82	13.88	38.87	1.75	10.77
33	1.03	20.00	27.79	1.86	10.67
41	0.52	9.79	47.00	1.34	9.61
Mean	0.59	11.70	40.90	1.34	10.48
SD	0.21	4.15	7.05	0.31	1.13

VO_2 kinetics responses during 'unprimed' moderate-intensity exercise at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
4	0.944	1.026	14.999	24.307	1.970	10.643
7	0.772	0.598	17.341	23.801	1.370	9.908
8	0.995	0.327	15.000	27.991	1.322	8.605
15	1.330	0.996	18.344	24.000	2.326	9.055
20	1.327	0.635	10.879	33.098	1.962	8.624
23	0.700	0.493	13.482	20.835	1.193	10.274
24	0.845	0.650	19.000	30.347	1.495	10.149
28	0.812	0.684	18.820	24.999	1.496	11.094
30	0.946	0.805	12.950	26.000	1.751	9.025
39	0.861	0.259	28.877	25.000	1.120	7.015
Mean	0.953	0.647	16.969	26.038	1.600	9.439
SD	0.216	0.252	4.995	3.553	0.390	1.209

LVHIIT DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
26	0.656	0.814	16.000	20.897	1.470	9.929
34	0.921	0.688	27.843	30.000	1.609	8.639
35	0.690	0.884	16.000	24.800	1.574	11.186
36	0.961	0.845	19.000	22.600	1.806	9.942
38	0.700	0.241	19.000	28.603	0.941	8.299
45	0.786	0.988	15.565	25.000	1.774	9.522
47	0.758	1.182	16.971	21.988	1.940	11.055
48	1.062	0.405	17.600	31.989	1.467	6.388
49	0.910	1.103	14.336	28.599	2.013	9.864
Mean	0.827	0.794	18.035	26.053	1.622	9.425
SD	0.141	0.309	3.991	3.897	0.321	1.483

CON DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
3	0.747	0.561	27.001	43.962	1.308	10.233
10	0.635	0.329	17.000	39.385	0.965	9.689
12	0.919	0.557	17.000	38.230	1.476	9.346
18	0.579	0.437	24.000	39.777	1.016	9.584
21	0.758	0.404	16.000	27.028	1.173	10.000
22	0.682	0.430	10.335	59.134	1.113	10.267
31	1.013	0.778	23.000	45.265	1.792	10.188
33	0.894	0.965	16.729	29.000	1.859	10.006
41	0.839	0.495	19.000	42.060	1.333	9.160
Mean	0.79	0.55	18.90	40.43	1.337	9.831
SD	0.143	0.200	5.119	8.110	0.320	0.404

VO_2 kinetics responses during 'unprimed' moderate-intensity exercise at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
4	1.029	0.939	15.551	27.014	1.968	9.745
7	0.827	0.562	12.000	34.406	1.389	9.306
8	0.930	0.405	12.920	25.992	1.335	10.658
15	1.020	1.134	14.956	25.313	2.154	10.305
20	1.239	0.717	10.529	30.000	1.956	9.743
23	0.654	0.444	17.000	20.030	1.097	9.241
24	0.833	0.639	15.320	25.992	1.472	9.984
28	0.841	0.674	18.000	23.478	1.514	10.920
30	0.810	0.913	18.000	23.523	1.723	10.230
39	0.835	0.249	16.452	28.000	1.084	6.755
Mean	0.902	0.667	15.073	26.375	1.569	9.689
SD	0.161	0.271	2.534	3.928	0.370	1.163

LVHIIT DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
26	0.872	0.754	13.086	25.000	1.626	9.195
34	0.758	0.873	21.800	29.986	1.631	10.967
35	0.701	0.791	13.757	27.000	1.492	10.013
36	0.800	0.941	14.029	22.319	1.741	11.074
38	0.545	0.402	7.171	28.999	0.947	13.854
45	0.638	1.128	8.689	24.999	1.766	10.871
47	0.858	1.029	11.600	23.993	1.887	9.623
48	0.627	0.671	6.854	29.999	1.298	10.584
49	0.941	0.990	26.940	33.999	1.931	8.854
Mean	0.749	0.842	13.769	27.366	1.591	10.559
SD	0.131	0.219	6.712	3.685	0.310	1.472

CON DSP ID	Baseline	A1	TD1	Tau	End Vo2	Vo2 Gain
3	0.738	0.561	27.000	40.051	1.299	10.235
10	0.639	0.367	9.000	47.969	1.006	10.807
12	0.879	0.560	13.000	50.106	1.439	9.389
18	0.516	0.481	10.000	39.420	0.997	10.547
21	0.742	0.404	34.900	36.000	1.142	9.688
22	0.701	0.472	19.609	44.357	1.193	11.355
31	0.941	0.862	12.000	52.849	1.803	11.278
33	0.859	1.018	11.967	32.169	1.877	10.555
41	0.780	0.483	18.004	50.505	1.263	8.943
Mean	0.757	0.579	14.749	45.563	1.335	10.311
SD	0.129	0.217	5.681	7.011	0.318	0.829

Muscle deoxygenation kinetics responses during ‘unprimed’ moderate-intensity exercise at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
4	-46.00	130.24	15.35	14.23	29.58	84.24
7	-70.00	86.29	18.03	7.41	25.43	16.29
8	-20.40	26.86	7.66	29.03	36.69	6.46
15	-18.50	99.36	10.24	14.06	24.30	80.86
20	23.00	57.29	15.98	16.00	31.98	80.29
23	-97.00	15.00	6.80	42.00	48.80	-82.00
24	39.00	124.21	12.05	29.51	41.56	163.21
28	-67.00	89.85	13.20	11.80	25.00	22.85
30	-127.00	74.33	18.11	10.97	29.07	-52.67
39	-2.00	86.87	19.29	11.02	30.30	84.87
Mean	-38.59	79.03	13.67	18.60	32.27	40.44
SD	52.67	37.45	4.43	11.10	7.91	72.95

LVHIIT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
26	-35.00	24.62	15.14	12.20	27.34	-10.38
34	-49.00	293.44	11.96	8.97	20.92	244.44
35	-108.00	138.00	13.02	12.78	25.79	30.00
36	-2.88	157.46	10.60	16.55	27.16	154.58
38	-32.99	13.51	15.59	15.97	31.56	-19.48
45	-18.00	151.75	18.21	6.38	24.59	133.75
47	-30.00	272.78	13.32	8.37	21.69	242.78
49	-55.00	72.41	14.65	7.79	22.43	17.41
Mean	-41.36	140.50	14.06	11.13	25.19	99.14
SD	31.51	103.86	2.36	3.83	3.54	109.25

CON DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
3	-44.93	68.5	10.37	12.03	22.40	23.57
10	9.30	3.90	12.26	10.89	23.15	13.20
12	-120.00	123.44	16.80	8.02	24.82	3.44
18	-58.90	78.90	12.31	16.17	28.48	20.00
21	-31.40	11.99	17.57	8.13	25.70	-19.41
22	-37.30	10.51	16.14	20.07	36.20	-26.79
31	-5.00	115.18	15.52	17.77	33.29	110.18
33	-30.00	164.78	18.05	7.69	25.74	134.78
Mean	-39.04	72.67	15.52	12.67	28.20	33.63
SD	42.01	64.78	2.37	5.22	4.82	63.34

Muscle deoxygenation kinetics responses during 'unprimed' moderate-intensity exercise at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
4	-40.00	101.90	19.34	13.92	33.27	61.90
7	-98.00	102.11	16.33	9.78	26.11	4.11
8	-35.56	9.08	17.01	13.60	30.61	-26.48
15	-25.57	123.60	8.00	17.35	25.35	98.03
20	-15.00	98.87	19.66	30.43	50.09	83.87
23	-160.00	30.06	28.42	65.02	93.44	-129.94
24	-190.00	156.72	11.40	13.49	24.89	-33.28
28	-37.00	174.12	15.64	11.31	26.95	137.12
30	-97.00	173.86	16.40	13.06	29.46	76.86
39	-5.00	60.00	24.57	23.96	48.53	55.00
Mean	-70.31	103.03	17.68	21.19	38.87	32.72
SD	63.60	57.15	5.88	16.64	21.26	79.03

LVHIIT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
26	-11.00	57.33	13.38	9.14	22.52	46.33
34	18.00	140.10	20.60	17.87	38.47	158.10
35	-45.03	248.71	7.78	19.43	27.20	203.68
36	-30.00	263.35	12.51	13.69	26.20	233.35
38	-21.00	27.20	17.12	19.21	36.33	6.20
45	-71.00	98.89	19.70	3.91	23.61	27.89
47	-104.00	304.92	12.65	7.95	20.60	200.92
49	-55.01	117.99	15.18	11.98	27.16	62.98
Mean	-39.88	157.31	14.87	12.90	27.76	117.43
SD	37.75	102.52	4.22	5.71	6.40	90.96

CON DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
3	-21	85.82	12.39	9.605	22.00	64.82
10	1.30	23.69	15.03	19.40	34.42	24.99
12	-45.00	109.49	16.70	7.96	24.66	64.49
18	-60.00	78.34	13.65	11.74	25.39	18.34
21	-79.69	16.32	11.70	7.50	19.20	-63.36
22	-78.00	12.00	14.00	22.00	36.00	-66.00
31	-26.00	140.90	13.78	8.01	21.79	114.90
33	-65.00	116.00	18.73	5.96	24.70	51.00
Mean	-50.34	70.96	14.80	11.80	26.59	20.62
SD	29.50	53.47	2.30	6.37	6.28	66.23

Muscle deoxygenation kinetics responses during 'unprimed' moderate-intensity exercise at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
4	-106.00	140.51	17.68	9.88	27.56	246.51
7	-100.00	84.13	19.59	6.05	25.64	184.13
8	-45.00	23.35	14.92	5.69	20.61	68.35
15	-86.00	69.39	12.00	14.77	26.76	155.39
20	-76.00	84.01	15.89	33.12	49.00	160.01
23	-29.00	14.78	32.39	27.93	60.32	43.78
24	-165.00	150.32	9.12	13.63	22.75	315.32
28	-158.00	194.35	6.66	12.42	19.08	352.35
30	-186.00	118.55	16.21	7.18	23.39	304.55
39	-23.00	67.63	21.10	26.61	47.72	90.63
Mean	-97.40	94.70	16.56	15.73	32.28	192.10
SD	57.46	56.54	7.14	9.93	14.46	108.79

LVHIIT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
26	-43.00	62.46	11.62	8.74	20.36	19.46
34	-27.00	289.81	15.06	8.38	23.44	262.81
35	-70.00	240.54	10.36	15.09	25.46	170.54
36	-69.15	140.62	13.35	10.12	23.47	71.47
38	-15.00	34.88	17.78	26.61	44.40	19.89
45	-7.00	111.75	17.06	7.79	24.85	104.75
47	-114.00	266.18	11.60	8.00	19.60	152.18
49	-117.80	59.98	14.00	6.00	20.00	-57.82
Mean	-57.87	150.78	13.85	11.34	25.20	92.91
SD	42.45	101.28	2.66	6.73	8.08	101.74

CON DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
3	-25	59.26	9.94	13.9	23.84	84.26
10	-78.00	32.32	7.97	42.72	50.69	110.32
12	-73.00	132.79	16.48	10.26	26.73	205.79
18	-104.00	60.97	8.00	20.00	28.00	164.97
21	-70.00	11.09	17.53	6.91	24.44	81.09
22	-50.00	10.46	18.69	17.88	36.57	60.46
31	-29.97	-117.60	14.50	23.91	38.41	-87.63
33	-13.00	127.77	14.96	4.83	19.80	140.77
Mean	-55.37	39.63	13.51	17.55	31.06	95.00
SD	31.15	79.04	4.29	12.08	10.15	88.12

Muscle deoxygenation kinetics responses during 'unprimed' moderate-intensity exercise at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
4	-91.00	121.58	18.67	6.19	24.86	30.58
7	-59.00	88.23	18.44	12.71	31.14	29.23
8	-42.00	19.24	5.84	19.10	24.93	-22.76
15	-74.00	43.26	14.08	7.99	22.07	-30.74
20	-15.00	51.13	35.53	52.78	88.31	36.13
23	-260.00	112.98	37.40	25.99	63.39	-147.02
24	-116.00	102.62	11.57	10.09	21.65	-13.38
28	-10.00	175.28	11.36	8.23	19.59	165.28
30	-148.00	160.46	13.10	10.58	23.68	12.46
39	18.60	54.00	18.17	10.98	29.15	72.60
Mean	-79.64	92.88	18.42	16.46	34.88	13.24
SD	81.11	51.47	10.30	14.07	22.64	79.82

LVHIIT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
26	-29.00	56.45	14.58	6.31	20.90	27.45
34	-28.00	317.77	14.97	11.02	25.99	289.77
35	-136.10	216.90	3.42	7.22	10.64	80.81
36	-77.00	153.22	12.90	8.55	21.45	76.22
38	5.60	38.15	16.75	25.21	41.95	43.75
45	-83.00	117.72	19.26	7.55	26.81	34.72
47	-22.00	281.00	10.40	8.00	18.40	259.00
49	-56.01	101.05	11.03	14.04	25.06	45.04
Mean	-53.19	160.28	12.91	10.99	23.90	107.10
SD	44.70	102.57	4.81	6.26	8.95	105.24

CON DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
3	197	38.42	13	20.97	33.97	235.42
10	9.13	7.30	13.44	20.00	33.44	16.43
12	-88.00	115.30	18.08	8.18	26.26	27.30
18	-57.00	74.48	10.45	19.29	29.74	17.48
21	-110.00	26.70	14.97	13.87	28.84	-83.30
22	-66.88	10.92	16.00	34.74	50.74	-55.97
31	-42.00	142.93	15.57	11.35	26.92	100.93
33	-18.00	129.21	17.01	5.95	22.96	111.21
Mean	-21.97	68.16	14.82	16.79	31.61	46.19
SD	96.13	54.99	2.44	9.15	8.55	101.63

Muscle deoxygenation kinetics responses during 'unprimed' moderate-intensity exercise at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
4	-62.00	80.48	20.02	10.19	30.21	18.48
7	-105.00	47.39	26.37	11.16	37.53	152.39
8	-81.12	23.61	18.00	15.62	33.62	104.73
15	-48.43	96.84	15.00	17.84	32.84	48.41
20	-29.90	60.62	14.59	18.39	32.98	30.72
23	-215.00	73.50	29.47	28.18	57.65	288.50
24	-54.00	116.89	11.62	11.96	23.58	62.89
28	-48.00	112.75	13.25	6.39	19.64	64.75
30	-111.00	126.85	17.27	8.80	26.07	15.85
39	-17.00	51.83	17.79	16.79	34.59	34.83
Mean	-77.14	79.08	18.34	14.53	32.87	82.16
SD	56.99	33.93	5.67	6.28	10.30	83.78

LVHIIT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
26	-62.00	49.04	13.43	5.47	18.90	-12.96
34	-72.00	273.75	14.47	5.14	19.61	201.75
35	-150.93	344.57	10.37	12.53	22.90	193.63
36	-12.00	193.60	14.01	13.39	27.40	181.60
38	-38.00	22.75	20.11	24.33	44.44	-15.25
45	-123.00	101.06	18.20	6.00	24.20	-21.94
47	-71.63	276.89	11.60	8.00	19.60	205.26
49	-116.79	91.52	13.40	9.99	23.39	-25.27
Mean	-80.79	169.15	14.45	10.61	25.06	88.35
SD	46.41	119.79	3.23	6.38	8.34	114.88

CON DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
3	-40	56	12	30	42.00	96.00
10	-44.00	20.66	33.11	17.21	50.31	64.66
12	-126.00	113.30	16.65	9.10	25.75	239.29
18	-83.26	94.41	11.11	16.79	27.90	177.67
21	-100.00	48.54	13.80	11.41	25.21	148.54
22	-38.24	12.90	19.00	14.02	33.02	51.13
31	-29.02	133.28	15.00	14.60	29.60	162.30
33	-18.00	151.75	18.21	6.38	24.59	169.75
Mean	-59.81	78.85	17.36	14.94	32.30	138.67
SD	38.45	51.94	6.95	7.13	9.25	63.50

Heart rate kinetics responses during ‘unprimed’ moderate-intensity exercise at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	86	21	0	50	107
7	86	20	0	46	106
8	111	20	0	64	131
15	111	35	0	70	146
20	110	30	5	78	140
23	85	22	0	70	107
24	128	20	2	78	148
28	109	27	7	100	136
30	87	27	4	58	114
39	113	15	9	88	128
Mean	103	23	3	70	126
SD	15	6	3	17	17

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	80	34	3	34	114
34	112	38	0	107	150
35	94	39	0	70	134
36	97	25	6	82	122
38	107	24	4	121	131
45	92	24	2	33	116
47	107	32	4	93	138
48	108	35	0	96	143
49	107	24	0	63	131
Mean	100	30	2	78	131
SD	10	7	2	31	12

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	101	21	0	106	122
10	91	18	0	88	109
12	100	19	0	48	119
18	110	22	10	38	132
21	102	20	3	34	122
22	91	28	2	54	119
31	86	42	9	28	128
33	85	24	2	34	110
41	115	22	0	68	137
Mean	98	24	3	55	122
SD	10	7	4	27	9

Heart rate kinetics responses during 'unprimed' moderate-intensity exercise at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	80	26	2	32	106
7	93	17	2	50	110
8	100	19	8	30	119
15	99	32	6	51	131
20	100	27	0	68	128
23	83	17	7	38	100
24	112	23	1	42	135
28	96	23	9	55	119
30	95	25	6	44	120
39	116	11	0	62	127
Mean	98	22	4	47	120
SD	11	6	3	12	11

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	81	29	0	33	110
34	92	31	7	108	122
35	101	35	0	70	136
36	97	21	0	54	118
38	104	19	3	84	123
45	94	24	6	32	118
47	91	29	1	67	120
48	118	28	7	59	146
49	100	28	0	114	127
Mean	97	27	3	69	124
SD	10	5	3	29	11

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	100	17	6	88	117
10	85	19	0	46	103
12	98	21	0	57	119
18	109	30	9	43	140
21	95	21	0	48	116
22	89	28	0	65	117
31	102	27	5	36	129
33	87	24	2	36	111
41	115	27	0	67	142
Mean	98	24	2	54	121
SD	10	5	3	17	13

Heart rate kinetics responses during 'unprimed' moderate-intensity exercise at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	80	22	3	25	102
7	84	18	4	46	102
8	103	17	6	39	120
15	99	29	9	48	128
20	100	29	0	58	129
23	84	15	0	33	99
24	127	18	2	62	145
28	100	16	2	39	116
30	92	21	11	37	113
39	100	12	4	52	112
Mean	97	20	4	44	116
SD	14	6	4	11	14

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	83	30	1	26	113
34	93	17	7	45	110
35	87	35	1	39	122
36	99	16	2	36	114
38	89	25	0	84	115
45	92	25	0	40	117
47	84	30	0	54	113
48	109	28	6	59	137
49	99	31	0	86	130
Mean	93	26	2	52	119
SD	8	6	3	21	9

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	99	23	0	155	122
10	85	21	4	78	106
12	98	19	2	47	117
18	108	27	0	47	135
21	97	20	3	48	117
22	94	28	2	56	122
31	105	28	4	39	133
33	78	26	1	28	104
41	112	31	4	101	143
Mean	97	25	2	67	122
SD	11	4	2	40	13

Heart rate kinetics responses during 'unprimed' moderate-intensity exercise at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	77	21	7	21	98
7	79	17	14	38	96
8	99	18	3	34	117
15	98	26	2	48	124
20	104	21	0	65	126
23	90	14	2	40	103
24	119	20	0	81	139
28	92	18	0	39	110
30	89	24	3	39	113
39	117	8	3	65	125
Mean	96	19	3	47	115
SD	14	5	4	18	14

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	82	31	0	27	113
34	95	18	15	60	113
35	91	32	3	43	123
36	92	20	0	38	112
38	91	17	3	41	108
45	91	28	3	42	119
47	84	31	0	44	114
48	107	26	0	70	133
49	109	21	1	60	130
Mean	94	25	3	47	118
SD	9	6	5	13	8

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	96	25	2	128	121
10	82	22	4	49	104
12	103	22	0	48	125
18	108	25	10	43	133
21	87	23	3	33	111
22	86	31	3	55	117
31	110	28	6	42	138
33	92	27	1	43	119
41	117	31	3	89	148
Mean	98	26	4	59	124
SD	12	3	3	30	14

Heart rate kinetics responses during 'unprimed' moderate-intensity exercise at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	90	16	10	29	106
7	78	12	9	40	91
8	103	11	10	25	114
15	94	26	0	40	119
20	92	27	3	40	119
23	86	14	0	34	101
24	119	19	6	58	137
28	94	17	6	34	111
30	84	24	2	30	107
39	113	9	2	51	122
Mean	95	17	5	38	113
SD	13	6	4	10	13

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	82	27	0	34	108
34	94	20	8	58	114
35	90	31	0	42	121
36	94	16	0	45	110
38	94	23	1	57	117
45	92	26	2	34	117
47	96	31	4	56	127
48	109	26	3	72	135
49	96	23	1	54	119
Mean	94	25	2	50	119
SD	7	5	3	12	8

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	96	18	0	88	113
10	86	17	2	50	103
12	102	22	1	78	124
18	105	30	0	54	135
21	83	19	1	66	102
22	78	28	0	64	106
31	93	25	9	46	118
33	92	24	2	33	116
41	110	32	5	87	142
Mean	94	24	2	63	118
SD	10	5	3	19	14

Δ[HHb+Mb]/ΔVO_2 ratios responses during 'unprimed' moderate-intensity exercise throughout the intervention period.

MICT DSP ID	week 0	week 3	week 6	week 9	week 12
4	1.09	1.04	0.99	1.03	1.01
7	1.15	1.12	1.09	1.03	1.02
8	1.08	1.19	1.00	1.05	1.04
15	1.06	1.06	1.14	1.07	0.99
20	1.26	0.87	0.90	0.95	1.01
23	1.09	0.97	0.90	0.99	0.91
24	1.14	0.89	1.09	0.94	1.12
28	1.27	1.10	1.14	1.14	1.11
30	1.27	1.10	1.12	1.09	1.05
39	1.10	1.01	1.10	1.10	0.97
MEAN	1.15	1.04	1.05	1.04	1.02
SD	0.08	0.10	0.09	0.06	0.06

LVHIIT DSP ID	week 0	week 3	week 6	week 9	week 12
26	1.13	1.13	1.09	1.06	1.12
34	1.27	1.01	1.15	1.05	1.03
35	1.16	1.13	1.03	1.09	1.03
36	1.23	1.03	1.00	1.04	1.02
38	1.35	1.05	1.04	0.90	0.94
45	1.14	0.98	1.05	1.03	1.08
47	1.19	1.03	1.10	1.06	1.01
49	1.16	1.11	1.04	1.04	0.95
MEAN	1.20	1.06	1.06	1.03	1.02
SD	0.08	0.06	0.05	0.06	0.06

CON DSP ID	week 0	week 3	week 6	week 9	week 12
3	1.18	1.13	1.23	1.11	1.17
10	1.19	1.13	0.99	1.16	1.04
12	1.14	1.01	1.17	1.16	1.17
18	1.04	1.09	1.12	1.08	0.95
21	1.09	1.23	1.26	1.19	1.29
22	1.11	1.47	1.13	1.26	1.13
31	1.11	1.21	1.02	1.16	1.18
33	1.09	1.12	1.21	1.16	1.25
MEAN	1.12	1.17	1.14	1.16	1.15
SD	0.05	0.14	0.10	0.05	0.11

VO_2 kinetics responses during 'primed' moderate-intensity exercise at week 0.

MICT DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
4	1.05	1.15	5.48	30.00	2.20	11.93
7	0.67	0.80	16.00	27.64	1.46	13.19
8	1.04	0.48	7.00	25.75	1.52	12.56
15	1.24	1.01	13.62	29.99	2.25	9.14
20	1.36	0.73	9.65	37.98	2.09	9.90
23	0.72	0.46	14.90	41.72	1.17	9.56
24	1.07	0.50	16.57	34.86	1.57	7.82
28	1.07	0.77	25.98	30.08	1.84	12.48
30	0.87	0.89	13.54	28.09	1.76	9.94
39	0.72	0.34	13.65	27.00	1.06	9.23
Mean	0.98	0.71	13.64	31.31	1.69	10.57
SD	0.23	0.26	5.72	5.20	0.41	1.81

LVHIIT DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
26	0.71	0.93	10.32	27.27	1.64	11.34
34	0.88	0.73	7.46	42.00	1.61	9.17
35	0.70	0.96	23.37	23.35	1.66	12.19
36	1.34	0.57	14.33	31.99	1.91	6.75
38	0.84	0.30	16.53	26.09	1.14	10.36
45	1.09	0.81	19.17	28.23	1.91	7.84
47	1.03	1.19	20.73	21.58	2.22	11.11
48	0.81	0.49	18.83	37.06	1.30	7.79
49	1.00	1.22	5.00	37.99	2.23	10.94
Mean	0.93	0.80	15.08	30.62	1.74	9.72
SD	0.20	0.31	6.29	7.06	0.37	1.90

CON DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
3	0.89	0.48	33.00	35.83	1.37	8.82
10	0.59	0.34	12.66	30.00	0.93	10.00
12	0.94	0.57	8.74	37.04	1.51	9.50
18	0.64	0.46	11.89	27.99	1.10	10.02
21	0.97	0.46	10.76	28.14	1.43	10.96
22	0.71	0.46	20.01	31.95	1.17	10.90
31	1.21	0.69	21.00	22.20	1.90	9.04
33	0.89	1.00	14.08	27.99	1.89	10.39
41	0.78	0.46	19.32	36.03	1.24	8.48
Mean	0.85	0.55	16.83	30.80	1.39	9.79
SD	0.19	0.20	7.47	4.88	0.33	0.89

VO_2 kinetics responses during 'primed' moderate-intensity exercise at week 3.

MICT DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
4	1.32	0.69	12.47	21.91	2.01	7.11
7	0.91	0.56	28.67	26.22	1.47	9.25
8	0.95	0.40	13.90	24.17	1.35	10.63
15	1.22	0.93	19.69	25.99	2.14	8.41
20	1.46	0.61	15.31	34.41	2.07	8.30
23	0.59	0.57	15.26	27.99	1.17	11.96
24	0.99	0.70	9.58	29.32	1.69	10.88
28	0.93	0.65	19.34	25.00	1.58	10.52
30	1.00	0.77	17.98	27.75	1.77	8.64
39	0.82	0.30	26.31	27.00	1.12	8.06
Mean	1.02	0.62	17.85	26.97	1.64	9.38
SD	0.25	0.18	5.97	3.36	0.37	1.54

LVHIIT DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
26	0.77	0.84	8.32	30.00	1.61	10.28
34	1.04	0.77	18.86	29.99	1.81	9.66
35	0.72	0.93	12.68	24.17	1.65	11.75
36	1.06	0.84	12.00	28.54	1.90	9.91
38	0.82	0.19	18.91	25.27	1.01	6.41
45	0.85	1.00	12.42	25.00	1.85	9.64
47	0.90	1.20	16.59	24.28	2.10	11.20
48	0.81	0.53	16.75	24.54	1.34	8.42
49	0.97	1.03	14.10	32.17	2.00	9.19
Mean	0.88	0.81	14.51	27.11	1.70	9.61
SD	0.12	0.30	3.54	3.07	0.34	1.56

CON DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
3	0.97	0.48	22.74	29.80	1.46	8.83
10	0.53	0.38	8.00	31.99	0.91	11.15
12	0.94	0.54	19.49	21.48	1.48	9.01
18	0.55	0.49	14.66	26.14	1.04	10.72
21	0.78	0.38	13.61	28.04	1.16	9.11
22	0.73	0.42	16.25	29.99	1.14	9.97
31	1.04	0.81	17.13	28.44	1.85	10.55
33	0.81	1.01	13.28	27.86	1.81	10.43
41	0.92	0.43	20.94	36.84	1.35	7.98
Mean	0.81	0.55	16.23	28.95	1.36	9.75
SD	0.18	0.22	4.50	4.17	0.33	1.06

VO_2 kinetics responses during 'primed' moderate-intensity exercise at week 6.

MICT DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
4	1.00	1.06	14.95	22.48	2.06	11.01
7	0.64	0.75	11.94	25.97	1.39	12.48
8	1.03	0.36	21.39	23.44	1.39	9.44
15	1.13	0.97	11.40	26.34	2.10	8.84
20	1.16	0.73	14.36	30.12	1.89	9.87
23	0.65	0.50	12.26	23.99	1.15	10.33
24	0.86	0.60	17.02	23.54	1.46	9.44
28	0.78	0.69	18.11	23.29	1.47	11.22
30	0.97	0.84	15.80	27.37	1.81	9.43
39	0.70	0.30	8.32	23.99	1.00	8.17
Mean	0.89	0.68	14.55	25.05	1.57	10.02
SD	0.19	0.25	3.77	2.37	0.38	1.27

LVHIIT DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
26	0.71	0.89	13.49	23.84	1.60	10.89
34	0.99	1.00	18.85	34.36	1.99	12.59
35	0.72	0.85	14.10	27.28	1.57	10.76
36	0.94	0.69	9.61	25.82	1.63	8.15
38	0.71	0.25	26.22	27.14	0.96	8.77
45	0.86	0.95	22.56	15.46	1.81	9.16
47	0.85	1.12	16.60	21.39	1.97	10.48
48	0.91	0.57	19.54	21.89	1.48	9.00
49	0.93	1.15	15.80	20.00	2.07	10.25
Mean	0.85	0.83	17.42	24.13	1.68	10.00
SD	0.11	0.29	5.01	5.38	0.34	1.37

CON DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
3	0.96	0.38	22.64	37.23	1.34	6.94
10	0.60	0.34	27.47	42.04	0.94	9.96
12	0.98	0.57	20.73	26.29	1.55	9.59
18	0.70	0.36	24.99	30.63	1.06	7.97
21	0.76	0.50	21.15	27.99	1.25	11.92
22	0.67	0.43	17.80	28.00	1.10	10.28
31	0.96	0.81	17.06	33.99	1.77	10.58
33	0.90	1.04	12.64	28.49	1.94	10.79
41	1.01	0.40	22.93	24.78	1.41	7.40
Mean	0.84	0.54	20.82	31.05	1.37	9.49
SD	0.16	0.24	4.47	5.64	0.33	1.69

VO_2 kinetics responses during 'primed' moderate-intensity exercise at week 9.

MICT DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
4	1.02	0.95	18.42	20.63	1.97	9.82
7	0.84	0.48	18.20	23.99	1.33	8.00
8	0.85	0.49	15.03	24.00	1.33	12.78
15	1.23	1.15	10.00	20.89	2.38	10.45
20	1.29	0.68	16.34	24.38	1.97	9.24
23	0.82	0.49	17.48	23.00	1.31	10.29
24	0.84	0.61	18.85	26.91	1.45	9.49
28	0.82	0.53	19.52	21.00	1.35	8.66
30	0.94	0.84	18.10	22.19	1.78	9.45
39	0.87	0.26	23.29	23.71	1.13	7.00
Mean	0.95	0.65	17.52	23.07	1.60	9.52
SD	0.18	0.26	3.41	1.95	0.40	1.55

LVHIIT DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
26	0.77	0.69	16.00	20.04	1.46	8.41
34	0.87	0.77	22.36	28.15	1.64	9.67
35	0.84	0.80	17.75	25.00	1.64	10.18
36	1.03	0.81	10.40	22.15	1.84	9.51
38	0.74	0.21	17.58	22.31	0.96	7.28
45	0.84	0.93	15.32	20.00	1.77	8.91
47	0.96	1.03	14.93	20.33	1.99	9.62
48	0.88	0.56	14.60	31.99	1.44	8.85
49	1.08	0.93	14.72	25.04	2.01	8.30
Mean	0.89	0.75	15.96	23.89	1.64	8.97
SD	0.11	0.24	3.21	4.10	0.33	0.89

CON DSP ID	VO2 Baseline	A1	TD1	Tau	VO2End	VO2 Gain
3	0.64	0.64	5.84	35.00	1.27	11.61
10	0.72	0.29	24.72	30.96	1.01	8.55
12	0.98	0.52	13.82	27.56	1.50	8.79
18	0.60	0.44	16.16	30.38	1.04	9.72
21	0.81	0.41	21.14	29.71	1.22	9.82
22	0.69	0.46	13.62	45.51	1.14	10.88
31	1.01	0.81	18.66	31.50	1.82	10.58
33	0.88	1.04	12.07	25.96	1.92	10.82
41	0.88	0.47	15.50	30.34	1.36	8.78
Mean	0.80	0.56	15.73	31.88	1.36	9.95
SD	0.15	0.23	5.46	5.70	0.32	1.09

VO_2 kinetics responses during 'primed' moderate-intensity exercise at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	VO2End	VO2 Gain
4	1.14	0.76	15.20	21.99	1.90	7.84
7	0.82	0.64	18.80	23.99	1.45	10.58
8	0.97	0.44	9.20	21.99	1.42	11.68
15	1.04	1.16	12.49	21.99	2.20	10.54
20	1.31	0.73	15.70	31.99	2.04	9.92
23	0.66	0.48	9.71	25.99	1.14	9.90
24	0.88	0.65	18.22	26.67	1.53	10.18
28	1.07	0.38	20.06	23.99	1.45	6.14
30	0.95	0.85	21.71	20.34	1.80	9.49
39	0.83	0.34	13.91	24.40	1.18	9.25
Mean	0.97	0.64	15.50	24.34	1.61	9.55
SD	0.19	0.25	4.25	3.32	0.36	1.56

LVHIIT DSP ID	Baseline	A1	TD1	Tau	VO2End	VO2 Gain
26	0.71	0.96	16.38	20.29	1.67	11.71
34	0.87	0.81	18.46	28.83	1.68	10.16
35	0.73	0.81	19.06	24.17	1.54	10.21
36	1.06	0.81	16.65	22.15	1.87	9.49
38	0.69	0.29	29.76	20.44	0.98	10.08
45	0.84	0.92	13.51	20.98	1.76	8.86
47	0.94	1.03	11.48	23.99	1.97	9.60
48	0.82	0.56	11.57	24.00	1.38	8.85
49	0.94	1.15	16.15	26.25	2.09	10.26
Mean	0.84	0.81	17.00	23.46	1.66	9.91
SD	0.12	0.26	5.51	2.85	0.33	0.87

CON DSP ID	Baseline	A1	TD1	Tau	VO2End	VO2 Gain
3	0.77	0.60	19.59	34.27	1.37	10.93
10	0.71	0.34	20.00	39.21	1.05	10.10
12	0.94	0.56	18.46	26.44	1.50	9.39
18	0.59	0.43	14.45	31.31	1.02	9.48
21	0.76	0.42	21.26	28.23	1.17	10.02
22	0.78	0.42	13.46	42.64	1.20	9.94
31	1.04	0.80	15.64	30.66	1.84	10.50
33	0.98	0.93	15.75	28.03	1.91	9.60
41	0.81	0.46	22.58	22.40	1.27	8.48
Mean	0.82	0.55	17.91	31.47	1.37	9.83
SD	0.14	0.20	3.20	6.35	0.32	0.71

Muscle deoxygenation kinetics responses during 'primed' moderate-intensity exercise at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
4	-40.00	132.53	15.21	12.07	27.28	92.53
7	-102.00	93.43	17.10	12.07	29.17	-8.57
8	-16.36	28.46	7.86	31.21	39.08	12.10
15	131.40	175.60	10.41	19.00	29.41	307.00
20	63.40	87.68	11.60	17.98	29.58	151.08
23	-108.00	5.46	5.61	8.11	13.72	-102.54
24	5.20	167.59	9.04	22.70	31.74	172.79
28	-39.00	132.55	9.28	19.95	29.22	93.56
30	-66.00	27.18	18.84	40.25	59.10	-38.82
39	-19.00	68.05	14.85	17.92	32.77	49.05
Mean	-19.04	91.85	11.98	20.13	32.11	72.82
SD	72.92	59.92	4.32	9.54	11.40	118.26

LVHIIT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
26	14.30	25.10	15.94	12.54	28.48	39.40
34	21.00	398.94	1.52	23.39	24.91	419.95
35	68.50	273.22	9.35	14.20	23.54	341.72
36	94.03	190.17	9.19	24.96	34.15	284.20
38	-17.00	24.23	21.18	39.19	60.38	7.23
45	-99.00	25.00	20.74	16.36	37.10	-74.00
47	67.00	330.88	11.69	14.02	25.71	397.88
48	-26.00	11.16	13.86	13.27	27.13	-14.84
49	-49.00	101.48	12.11	12.68	24.79	52.48
Mean	8.20	153.35	12.84	18.96	31.80	161.56
SD	62.48	150.02	6.11	8.89	11.65	196.01

CON DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
3	-7.90	76.74	9.24	14.02	23.26	68.84
10	-93.00	3.90	12.27	10.89	23.16	-89.10
12	-59.00	137.53	15.12	13.04	28.16	78.53
18	-8.00	103.85	10.76	19.91	30.67	95.85
21	-12.00	17.35	15.10	12.88	27.98	5.35
22	-34.00	7.66	33.52	8.43	41.95	-26.34
31	54.00	126.58	17.14	14.10	31.23	180.58
33	-47.00	144.39	18.72	14.16	32.88	97.39
Mean	-25.86	77.25	16.48	13.43	29.91	51.39
SD	43.64	59.87	7.58	3.28	6.01	84.28

Muscle deoxygenation kinetics responses during 'primed' moderate-intensity exercise at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
4	1.13	90.77	14.01	10.00	24.01	91.90
7	-99.40	104.03	18.07	11.81	29.89	4.63
8	-41.00	30.19	15.32	18.60	33.92	-10.81
15	-55.00	119.94	10.77	16.67	27.44	64.94
20	-63.00	102.47	16.13	28.01	44.14	39.47
23	-132.50	26.99	5.72	42.30	48.01	-105.51
24	-235.00	177.28	11.99	18.09	30.07	-57.72
28	0.00	162.18	11.67	9.94	21.61	162.18
30	-123.00	174.22	19.48	10.12	29.59	51.22
39	9.50	70.94	18.78	22.04	40.82	80.44
Mean	-73.83	105.90	14.19	18.76	32.95	32.08
SD	76.05	54.32	4.27	10.18	8.71	77.41

LVHIIT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
26	-1.00	56.69	11.27	11.49	22.76	55.69
34	78.00	283.36	7.94	18.48	26.43	361.36
35	-16.90	268.87	9.82	12.03	21.85	251.97
36	-12.00	307.52	9.39	21.12	30.51	295.52
38	-9.40	36.95	11.78	25.44	37.22	27.55
45	29.00	110.80	17.61	8.04	25.65	139.80
47	-69.98	314.38	12.31	7.98	20.29	244.40
48	-39.00	12.88	10.76	14.31	25.07	-26.11
49	-81.70	157.88	15.20	12.00	27.20	76.18
Mean	-13.66	172.15	11.79	14.54	26.33	158.49
SD	48.55	123.09	2.99	5.97	5.10	134.61

CON DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
3	45.68	114.75	8.60	13.99	22.59	160.43
10	1.30	23.69	15.03	19.39	34.42	24.99
12	-68.00	149.10	13.88	16.20	30.09	81.10
18	-36.50	68.88	11.59	13.91	25.50	32.38
21	-8.60	27.13	9.55	11.55	21.09	18.53
22	-26.21	4.01	9.82	11.71	21.53	-22.20
31	41.50	192.11	11.59	11.98	23.57	233.61
33	-49.00	131.32	17.46	9.98	27.44	82.32
Mean	-12.48	88.87	12.19	13.59	25.78	76.39
SD	40.85	68.05	3.04	3.03	4.65	84.08

Muscle deoxygenation kinetics responses during ‘primed’ moderate-intensity exercise at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
4	-165.00	130.85	17.96	11.79	29.75	295.85
7	-108.00	112.03	18.91	10.00	28.91	220.03
8	13.00	37.68	8.66	10.01	18.67	24.68
15	-77.00	72.47	9.51	16.34	25.84	149.48
20	-4.60	102.88	14.75	40.20	54.95	107.48
23	-66.00	26.29	16.53	25.30	41.82	92.29
24	-52.00	160.86	11.41	13.11	24.52	212.86
28	48.50	116.07	10.76	9.68	20.45	67.57
30	-50.00	125.47	13.50	10.13	23.63	175.47
39	-46.00	96.73	14.11	18.12	32.23	142.73
Mean	-50.71	98.13	13.61	16.47	30.08	148.84
SD	60.85	41.86	3.52	9.70	10.93	80.59

LVHIIT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
26	6.80	55.98	10.31	13.95	24.26	62.78
34	-67.99	345.33	12.07	17.88	29.95	277.34
35	-83.50	248.08	9.94	10.15	20.10	164.58
36	-21.00	210.82	7.28	9.71	16.99	189.82
38	-5.82	40.68	13.93	27.99	41.92	34.86
45	-63.00	121.92	17.67	7.95	25.62	58.92
47	-123.71	263.56	12.83	9.93	22.76	139.85
48	-29.00	8.91	18.57	19.39	37.96	-20.09
49	-106.11	74.49	14.64	5.96	20.60	-31.62
Mean	-54.81	152.20	13.03	13.66	26.68	97.38
SD	45.34	118.06	3.65	6.98	8.42	102.64

CON DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
3	27.60	96.05	11.99	17.80	29.79	123.65
10	-78.00	32.32	7.97	42.74	50.71	-45.68
12	-43.00	154.26	13.97	15.34	29.31	111.26
18	-72.00	68.97	12.02	17.69	29.71	-3.03
21	-4.60	21.04	17.27	21.82	39.09	16.44
22	-18.44	4.26	10.17	11.19	21.36	-14.18
31	-16.00	116.37	11.70	16.85	28.55	100.37
33	-52.99	124.61	15.20	9.94	25.14	71.61
Mean	-32.18	77.23	12.54	19.17	31.71	45.06
SD	35.90	54.29	2.91	10.25	9.18	64.59

Muscle deoxygenation kinetics responses during ‘primed’ moderate-intensity exercise at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
4	-137.50	131.26	17.59	8.76	26.35	-6.24
7	-68.00	78.19	19.67	12.80	32.47	10.19
8	-36.00	25.33	14.98	16.77	31.75	-10.67
15	-36.00	19.57	14.22	19.12	33.34	-16.43
20	22.94	58.28	28.00	16.06	44.06	81.22
23	-155.00	91.49	2.60	29.99	32.59	-63.51
24	-126.01	100.34	13.61	9.86	23.47	-25.67
28	20.00	127.56	14.34	9.75	24.09	147.56
30	-140.32	181.73	13.23	14.14	27.37	41.41
39	0.10	44.69	14.03	15.92	29.95	44.79
Mean	-65.58	85.84	15.23	15.32	30.54	20.26
SD	69.63	51.43	6.31	6.18	5.96	60.74

LVHIIT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
26	15.00	78.57	6.42	10.96	17.38	93.57
34	1.00	432.69	12.80	12.02	24.82	433.69
35	3.30	205.93	10.57	9.71	20.27	209.23
36	7.98	268.91	6.80	16.00	22.80	276.89
38	26.30	40.69	15.36	20.34	35.70	66.99
45	-54.00	122.45	16.60	8.30	24.89	68.45
47	-100.91	317.14	12.81	8.01	20.82	216.23
48	-60.00	12.21	11.67	12.61	24.29	-47.79
49	-18.53	92.22	12.81	10.02	22.84	73.69
Mean	-19.98	174.53	11.76	12.00	23.76	154.55
SD	42.49	141.35	3.43	3.97	5.11	144.03

CON DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
3	22.30	56.93	11.12	16.17	27.29	79.23
10	9.13	7.30	13.44	20.00	33.44	16.43
12	-71.00	148.94	14.74	13.55	28.29	77.94
18	32.00	70.36	11.86	9.18	21.04	102.36
21	-29.50	36.11	7.77	15.07	22.83	6.61
22	-37.00	7.17	19.19	27.33	46.53	-29.83
31	44.00	176.38	12.59	14.74	27.33	220.38
33	-28.00	103.51	17.50	9.82	27.32	75.51
Mean	-7.26	75.84	13.53	15.73	29.26	68.58
SD	39.97	62.79	3.63	5.82	7.90	76.23

Muscle deoxygenation kinetics responses during 'primed' moderate-intensity exercise at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
4	-66.00	104.04	20.28	13.76	34.04	170.04
7	-66.00	81.12	18.16	12.99	31.16	147.12
8	-100.00	42.45	7.93	39.77	47.69	142.45
15	-15.00	92.91	14.08	13.60	27.68	77.91
20	58.00	96.39	14.00	16.88	30.89	154.39
23	-221.00	90.21	21.17	31.81	52.98	311.21
24	-96.00	171.96	8.97	15.50	24.47	267.96
28	-31.10	75.92	12.00	9.49	21.49	107.02
30	-69.00	131.65	12.22	12.01	24.23	200.65
39	-31.00	60.50	19.85	13.91	33.76	91.50
Mean	-63.71	94.71	14.87	17.97	32.84	167.02
SD	71.85	36.34	4.76	9.77	10.19	74.92

LVHIIT DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
26	-17.00	62.63	12.87	9.53	22.40	45.63
34	-44.00	344.08	13.01	13.05	26.06	300.08
35	-170.99	241.63	9.40	12.26	21.66	70.64
36	-15.00	213.87	10.15	15.34	25.48	198.87
38	-40.00	26.67	21.17	35.27	56.45	66.00
45	-91.00	64.42	16.59	7.68	24.27	155.00
47	-69.28	301.46	9.20	10.00	19.20	232.18
48	-32.99	8.48	13.47	3.91	17.39	40.00
49	-81.89	126.49	11.60	21.99	33.59	44.60
Mean	-62.46	154.41	13.05	14.34	27.39	128.11
SD	48.80	124.33	3.83	9.35	11.85	96.72

CON DSP ID	Baseline	A1	TD1	Tau	τ' [HHb + Mb]	END A
3	-9.00	28.81	21.78	20.43	42.21	37.00
10	-44.00	20.66	33.18	17.21	50.39	64.00
12	-30.00	156.68	9.67	15.44	25.11	126.68
18	-31.00	96.66	11.70	16.46	28.16	127.00
21	-81.00	37.81	12.29	24.99	37.28	118.00
22	-22.44	14.52	8.00	19.28	27.28	36.00
31	-21.00	133.66	14.35	12.49	26.84	154.00
33	-56.00	107.94	18.92	9.43	28.35	163.00
Mean	-36.80	74.59	16.24	16.97	33.20	103.21
SD	22.94	55.80	8.24	4.80	9.13	50.61

Heart rate kinetics responses during 'primed' moderate-intensity exercise at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	98	22	7	66	120
7	97	17	0	62	114
8	112	16	0	48	128
15	128	28	0	71	157
17	123	13	24	113	136
20	128	24	11	76	152
23	99	19	5	90	118
24	137	18	0	76	155
28	122	26	0	102	148
30	107	24	6	55	131
39	119	13	0	74	132
Mean	116	20	5	76	135
SD	14	5	7	19	15

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	93	29	0	31	122
34	110	29	0	94	139
35	116	30	2	65	146
36	110	26	0	74	136
38	124	13	3	64	137
45	112	20	7	38	132
47	115	37	7	88	152
48	118	34	6	83	152
49	117	22	2	56	139
Mean	113	27	3	66	139
SD	9	7	3	22	10

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	112	18	12	62	130
10	102	20	0	62	122
12	116	19	0	38	135
18	114	26	8	41	140
21	108	22	7	40	130
22	98	30	4	63	128
31	129	26	7	59	155
33	106	22	7	45	128
41	109	26	0	74	135
Mean	110	23	5	54	134
SD	9	4	4	13	9

Heart rate kinetics responses during 'primed' moderate-intensity exercise at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	92	21	0	28	112
7	89	16	14	45	104
8	104	20	5	46	124
15	114	29	0	54	143
17	113	10	0	74	123
20	113	21	8	46	134
23	89	18	0	45	107
24	120	23	0	58	142
28	110	16	6	44	126
30	98	27	4	51	125
39	125	11	0	115	135
Mean	106	19	3	55	125
SD	13	6	5	23	13

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	94	28	0	33	122
34	110	30	10	86	140
35	109	27	5	50	135
36	105	21	0	46	126
38	110	19	0	66	129
45	107	23	1	54	130
47	100	27	4	62	128
48	127	28	2	60	155
49	106	25	0	48	131
Mean	108	25	2	56	133
SD	9	4	3	15	10

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	113	16	10	106	128
10	90	24	0	58	113
12	113	21	0	44	133
18	109	31	5	38	140
21	104	22	5	56	126
22	102	25	3	58	127
31	119	28	6	46	147
33	98	28	3	45	126
41	116	26	0	79	142
Mean	107	24	4	59	131
SD	9	5	3	21	10

Heart rate kinetics responses during 'primed' moderate-intensity exercise at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	83	22	3	20	104
7	87	20	4	50	107
8	107	21	6	58	128
15	115	27	0	57	142
17	119	6	0	76	125
20	105	23	6	46	128
23	86	15	0	37	102
24	134	17	4	70	150
28	105	16	3	49	121
30	104	25	9	53	129
39	108	10	0	64	117
Mean	105	18	3	53	123
SD	15	6	3	15	15

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	86	35	0	35	121
34	101	28	0	76	129
35	97	34	1	38	130
36	101	18	0	42	119
38	104	23	15	65	127
45	98	22	2	34	120
47	95	27	4	44	123
48	112	25	4	60	136
49	115	24	4	44	139
Mean	101	26	3	49	127
SD	9	5	5	15	7

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	108	16	3	116	124
10	92	21	0	60	113
12	108	20	0	60	128
18	114	28	6	55	142
21	110	18	17	49	128
22	105	29	4	60	134
31	119	28	5	46	147
33	106	24	7	50	130
41	120	31	0	74	151
Mean	109	24	5	63	133
SD	8	5	5	21	12

Heart rate kinetics responses during ‘primed’ moderate-intensity exercise at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	80	20	5	18	101
7	85	14	18	27	99
8	107	21	6	66	128
15	98	26	2	44	124
17	117	6	0	75	124
20	113	21	6	42	134
23	101	15	5	58	116
24	131	18	4	70	149
28	100	16	3	44	116
30	99	23	10	40	122
39	119	9	2	66	128
Mean	105	17	6	50	122
SD	15	6	5	18	14

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	86	34	2	30	120
34	109	24	5	52	133
35	101	29	6	38	130
36	101	22	0	40	123
38	105	18	5	66	123
45	100	27	1	30	127
47	95	31	4	44	126
48	114	23	12	59	137
49	120	19	7	58	139
Mean	104	25	5	46	129
SD	10	5	3	13	7

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	103	18	3	108	121
10	88	25	3	59	113
12	113	17	1	38	130
18	115	26	5	52	141
21	103	21	4	43	124
22	96	31	1	56	127
31	124	29	3	51	153
33	117	24	11	39	141
41	135	29	6	84	164
Mean	110	24	4	59	135
SD	14	5	3	23	16

Heart rate kinetics responses during 'primed' moderate-intensity exercise at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	101	17	8	26	117
7	84	13	0	60	97
8	105	13	5	42	118
15	107	23	8	34	130
17	114	7	0	92	121
20	111	21	7	38	132
23	96	14	3	47	110
24	134	17	16	70	150
28	99	18	3	26	116
30	95	22	5	38	116
39	118	6	2	19	124
Mean	106	15	5	45	121
SD	13	5	5	22	14

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	92	24	2	30	115
34	101	23	9	54	124
35	95	32	0	38	126
36	101	15	8	38	116
38	104	20	4	45	124
45	100	27	2	33	127
47	96	31	4	54	127
48	115	23	7	38	137
49	110	22	4	76	132
Mean	101	24	4	45	125
SD	7	5	3	14	7

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	106	16	0	97	121
10	85	19	0	68	104
12	126	16	0	70	142
18	112	31	5	53	143
21	87	20	0	43	107
22	92	29	0	68	121
31	112	29	6	35	141
33	112	20	7	38	132
41	119	33	6	82	152
Mean	106	24	3	62	129
SD	15	7	3	21	17

Δ[HHb+Mb]/ΔVO_2 ratios responses during 'primed' moderate-intensity exercise throughout the intervention period.

MICT DSP ID	week 0	week 3	week 6	week 9	week 12
4	1.04	0.96	0.99	1.02	0.98
7	0.93	1.12	1.04	1.01	1.05
8	0.83	1.09	0.82	1.06	0.88
15	1.04	1.00	0.97	1.05	0.99
20	1.12	0.94	0.77	1.10	1.06
23	1.11	0.94	0.97	0.95	0.85
24	1.07	0.98	1.03	1.10	1.04
28	1.15	1.05	1.07	0.97	0.97
30	1.15	1.07	1.06	1.08	1.02
39	1.14	0.99	0.95	0.98	0.99
MEAN	1.06	1.01	0.97	1.03	0.98
SD	0.10	0.06	0.10	0.05	0.07

LVHIIT DSP ID	week 0	week 3	week 6	week 9	week 12
26	1.02	0.99	1.03	1.06	1.07
34	1.01	0.95	1.13	1.10	1.02
35	1.07	1.08	0.93	1.06	1.00
36	1.10	1.01	1.07	1.02	1.21
38	0.94	0.95	0.97	1.06	1.04
45	0.97	1.04	1.07	1.00	0.98
47	1.10	1.06	1.10	1.04	1.05
49	1.10	1.12	1.06	1.08	1.02
MEAN	1.04	1.02	1.04	1.05	1.05
SD	0.06	0.06	0.07	0.03	0.07

CON DSP ID	week 0	week 3	week 6	week 9	week 12
3	1.09	1.09	1.05	1.04	1.09
10	1.08	1.16	1.07	1.01	0.80
12	1.06	1.07	1.07	1.05	1.09
18	1.00	1.05	0.89	1.08	1.01
21	1.02	1.08	1.14	1.09	0.72
22	0.90	1.09	1.01	0.92	1.11
31	0.94	1.08	0.92	1.03	1.08
33	0.99	1.02	1.06	1.04	1.04
MEAN	1.01	1.08	1.03	1.03	0.99
SD	0.06	0.04	0.08	0.05	0.15

Appendix 7.6. Experiment 3 raw data

The baseline characteristics of the participants and peak physiological responses at each time point can be found in Appendix 8.

4. The individual VO_2, [HHb+Mb] and HR responses during the 'primed' moderate-intensity exercise bouts can be found in Appendix 8.5. The participant ID numbers of those who took part in Experiment 3 are listed in the table below.

Participant ID numbers		
MICT	LVHIIT	CON
4	26	3
7	34	10
8	35	12
15	36	18
17	45	21
20	47	22
23	48	31
24	49	33
28		41
30		
39		

VO_2 kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
4	2.27	0.73	15.90	59.74	0.12	151.60	100.88	3.03
7	1.31	0.51	10.16	47.93	0.32	132.54	110.50	1.99
8	1.53	0.46	17.92	45.60	0.17	151.20	59.75	2.04
15	1.55	0.65	17.10	55.40	0.31	147.63	79.64	2.37
17	2.32	0.46	17.00	57.75	0.21	121.70	20.00	2.97
20	2.02	0.56	1.42	53.64	0.10	181.60	107.50	2.57
23	1.20	0.46	15.40	53.50	0.10	160.55	75.00	1.59
24	1.59	0.45	18.88	34.10	0.18	106.38	66.59	2.19
28	1.95	0.37	18.94	28.40	0.17	132.20	52.99	2.43
30	1.58	0.65	14.10	51.60	0.24	159.00	96.44	2.34
39	0.97	0.23	16.46	41.39	0.11	76.85	14.00	1.39
Mean	1.66	0.50	14.84	48.10	0.18	138.30	71.21	2.26
SD	0.43	0.14	5.09	9.95	0.08	28.93	32.93	0.51

LVHIIT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
26	1.67	0.42	12.88	35.93	0.16	108.80	61.50	2.11
34	1.57	0.49	10.68	42.30	0.14	117.60	64.85	2.19
35	1.65	0.48	8.70	26.16	0.10	81.20	65.00	2.14
36	2.13	0.42	11.15	24.49	0.23	129.77	74.77	2.67
45	1.88	0.82	16.96	47.73	0.29	141.33	87.93	2.91
47	2.22	0.77	8.02	60.69	0.26	144.30	131.70	3.22
48	0.13	0.30	18.00	53.74	0.16	120.94	114.00	1.64
49	2.10	0.73	7.03	52.77	0.28	119.78	117.60	2.98
Mean	1.67	0.55	11.68	42.98	0.20	120.47	89.67	2.48
SD	0.67	0.19	4.04	13.22	0.07	19.92	27.73	0.54

CON DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
3	1.25	0.53	23.10	40.13	0.16	110.30	87.90	1.75
10	0.97	0.30	10.91	46.10	0.07	96.75	50.55	1.26
12	1.53	0.71	8.10	57.46	0.12	143.49	122.85	2.25
18	1.34	0.30	10.78	46.47	0.17	168.78	70.33	1.83
21	1.21	0.36	1.17	47.31	0.17	114.20	78.55	1.59
22	1.14	0.40	10.10	44.00	0.09	130.34	79.21	1.59
31	1.94	0.63	4.00	39.94	0.16	102.89	65.20	2.72
33	1.87	0.88	18.85	37.85	0.23	135.58	0.20	2.91
41	1.25	0.30	23.71	47.85	0.12	103.02	60.00	1.66
Mean	1.39	0.49	12.30	45.23	0.14	122.82	68.31	1.95
SD	0.33	0.21	7.98	5.84	0.05	23.61	32.82	0.56

VO_2 kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
4	2.01	0.73	17.77	45.71	0.09	185.02	12.01	2.82
7	1.40	0.51	15.14	36.68	0.14	155.00	43.23	2.07
8	1.42	0.28	19.83	32.86	0.06	162.93	14.00	1.79
15	2.34	0.53	38.87	33.50	0.14	127.90	46.29	2.98
17	1.18	0.20	17.99	23.04	0.08	81.18	14.21	1.46
20	1.91	0.42	18.47	38.12	0.05	165.87	16.83	2.35
23	1.17	0.34	14.06	26.10	0.02	117.60	31.64	1.50
24	1.69	0.40	13.67	18.58	0.10	98.91	45.56	2.13
28	1.71	0.55	18.64	20.11	0.15	160.49	18.18	2.46
30	1.77	0.65	18.26	31.95	0.18	148.90	52.10	2.69
39	1.08	0.32	16.06	26.63	0.06	83.57	21.00	1.43
Mean	1.61	0.45	18.98	30.30	0.10	135.21	28.64	2.15
SD	0.40	0.16	6.89	8.27	0.05	35.60	15.41	0.56

LVHIIT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
26	1.65	0.34	22.00	22.61	0.09	144.99	46.64	2.07
34	1.87	0.45	23.72	26.24	0.11	96.44	31.87	2.36
35	1.68	0.42	22.72	26.43	0.10	100.76	14.59	2.13
36	1.83	0.53	13.79	34.37	0.13	144.52	24.63	2.50
45	1.81	0.75	19.32	29.30	0.17	167.80	20.35	2.88
47	1.92	0.77	13.00	31.00	0.26	158.00	73.50	2.96
48	1.35	0.32	20.85	31.16	0.07	153.21	21.00	1.73
49	1.92	0.59	17.18	14.57	0.19	71.27	42.60	2.69
Mean	1.75	0.52	19.07	26.96	0.14	129.62	34.40	2.41
SD	0.19	0.17	4.05	6.18	0.06	35.08	19.34	0.43

CON DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
3	1.42	0.57	15.15	36.16	0.17	127.78	43.15	2.14
10	0.92	0.20	20.34	34.65	0.09	79.14	16.88	1.19
12	1.47	0.65	7.53	49.87	0.17	128.18	43.92	2.31
18	1.05	0.18	20.53	31.30	0.07	88.73	57.97	1.24
21	1.10	0.34	10.80	41.53	0.12	158.77	66.70	1.53
22	1.14	0.42	9.60	47.91	0.10	120.88	93.15	1.69
31	1.79	0.63	9.42	45.97	0.14	170.69	49.70	2.52
33	1.78	0.84	12.36	28.02	0.31	135.96	15.10	2.90
41	1.35	0.28	7.91	50.13	0.08	114.00	63.40	1.43
Mean	1.34	0.46	12.63	40.62	0.14	124.90	50.00	1.88
SD	0.31	0.23	4.99	8.36	0.08	29.42	24.45	0.61

VO_2 kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
4	2.06	0.98	15.59	37.87	0.08	233.41	13.77	3.02
7	1.36	0.55	22.50	31.91	0.10	198.59	28.55	2.01
8	1.40	0.38	19.24	20.52	0.11	162.25	81.28	1.87
15	2.19	0.65	24.01	28.22	0.04	120.76	42.87	2.82
17	1.15	0.22	20.17	22.14	0.03	134.39	18.41	1.39
20	1.88	0.38	11.90	34.23	0.12	120.21	41.30	2.39
23	1.15	0.44	9.82	32.03	0.04	164.00	32.82	1.61
24	1.50	0.44	18.99	28.45	0.10	115.99	49.78	2.05
28	1.41	0.77	14.06	33.90	0.14	102.00	50.24	2.29
30	1.83	0.77	18.33	34.26	0.18	181.39	26.83	2.62
39	0.94	0.30	19.25	26.75	0.07	97.75	19.75	1.29
Mean	1.53	0.53	17.62	30.03	0.09	148.25	36.87	2.13
SD	0.40	0.23	4.35	5.37	0.05	43.35	19.31	0.57

LVHIIT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
26	1.62	0.44	11.64	24.42	0.12	144.07	66.76	2.17
34	1.92	0.63	28.36	34.36	0.11	154.25	17.78	2.63
35	1.60	0.45	12.47	24.40	0.07	77.10	34.02	2.07
36	1.62	0.47	18.90	30.80	0.19	111.00	50.10	2.33
45	1.73	0.86	19.56	32.31	0.14	180.67	21.00	2.79
47	1.98	0.63	14.03	40.54	0.23	120.09	67.71	2.85
48	1.49	0.38	13.59	30.40	0.07	187.53	16.41	1.90
49	2.10	0.52	29.85	47.38	0.32	158.20	42.80	3.00
Mean	1.76	0.55	18.55	33.08	0.15	141.61	39.57	2.47
SD	0.22	0.16	7.12	7.79	0.09	37.10	20.84	0.40

CON DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
3	1.34	0.46	15.56	35.85	0.15	84.00	73.40	1.82
10	0.94	0.26	24.00	40.00	0.06	70.58	73.00	1.18
12	1.49	0.67	17.09	41.94	0.15	149.47	27.80	2.30
18	1.04	0.24	8.40	36.14	0.11	114.20	88.70	1.27
21	1.24	0.36	7.32	39.95	0.15	158.56	33.85	1.72
22	1.12	0.38	7.80	41.91	0.12	137.14	41.68	1.62
31	1.72	0.67	8.80	41.95	0.11	158.40	57.80	2.47
33	1.89	0.86	18.89	34.03	0.29	140.84	49.29	3.03
41	1.45	0.30	11.93	38.10	0.09	103.06	49.62	1.73
Mean	1.36	0.47	13.31	38.87	0.14	124.03	55.02	1.91
SD	0.31	0.22	5.89	2.98	0.06	32.54	20.10	0.59

VO_2 kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
4	1.98	0.88	19.19	38.03	0.06	233.06	13.63	2.89
7	1.32	0.59	22.07	32.12	0.10	200.85	33.00	2.25
8	1.31	0.44	15.69	18.50	0.06	138.25	55.06	1.79
15	2.42	0.75	21.40	28.27	0.12	127.83	43.10	3.21
17	1.25	0.28	17.68	22.64	0.04	99.69	39.24	1.54
20	1.98	0.40	17.86	28.33	0.11	114.78	66.17	2.40
23	1.26	0.39	12.61	34.68	0.06	112.29	48.34	1.71
24	1.46	0.41	17.00	34.84	0.22	111.25	75.00	2.07
28	1.47	0.73	18.98	32.24	0.14	143.13	38.87	2.31
30	1.74	0.63	24.81	34.26	0.21	153.17	57.12	2.60
39	1.10	0.38	25.46	26.37	0.08	105.80	30.89	1.53
Mean	1.57	0.53	19.34	30.03	0.11	140.01	45.49	2.21
SD	0.41	0.19	3.85	5.86	0.06	42.10	17.34	0.55

LVHIIT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
26	1.46	0.41	19.80	19.00	0.07	122.20	74.10	1.96
34	1.62	0.55	23.66	30.49	0.14	106.51	59.80	2.34
35	1.63	0.42	15.38	10.71	0.11	64.82	14.71	2.15
36	1.83	0.65	11.68	22.40	0.21	165.92	36.23	2.66
45	1.77	0.83	19.49	32.15	0.14	224.17	21.00	2.77
47	1.96	0.55	16.47	8.25	0.26	119.05	50.10	2.82
48	1.49	0.36	13.60	30.19	0.07	186.50	17.84	1.94
49	2.09	0.65	14.50	40.57	0.16	119.49	70.00	2.78
Mean	1.73	0.55	16.82	24.22	0.14	138.58	42.97	2.43
SD	0.22	0.16	3.91	11.17	0.07	50.50	23.88	0.38

CON DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
3	1.26	0.51	22.20	38.11	0.18	100.20	71.60	1.75
10	1.00	0.30	22.22	38.38	0.08	87.22	37.44	1.31
12	1.42	0.76	13.03	41.96	0.15	137.15	75.53	2.30
18	1.03	0.28	16.92	51.96	0.13	143.24	72.00	1.37
21	1.17	0.32	20.91	31.69	0.10	144.84	29.87	1.58
22	1.13	0.28	19.95	37.67	0.13	120.02	117.00	1.55
31	1.81	0.61	10.52	43.85	0.20	114.80	64.20	2.62
33	1.89	0.86	10.00	34.10	0.29	139.12	49.12	3.03
41	1.33	0.32	15.44	44.14	0.08	92.35	41.00	1.72
Mean	1.34	0.47	16.80	40.21	0.15	119.88	61.97	1.92
SD	0.32	0.23	4.84	6.06	0.07	22.57	26.57	0.60

VO_2 kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A
4	1.91	0.75	17.46	30.38	0.09	124.43	50.51	2.75
7	1.43	1.44	20.00	28.10	0.09	127.69	35.40	2.00
8	1.39	0.44	19.13	26.44	0.10	128.59	61.93	1.90
15	2.20	0.75	19.19	16.48	0.12	115.30	34.59	3.06
17	1.25	0.28	18.29	26.67	0.06	119.82	44.34	1.55
20	1.97	0.45	18.86	26.26	0.08	101.53	81.25	2.50
23	1.13	0.40	9.84	34.14	0.07	116.06	22.13	1.59
24	1.49	0.44	15.84	34.25	0.09	109.09	29.08	2.05
28	1.46	0.67	18.31	25.70	0.14	102.90	36.84	2.29
30	1.82	0.59	25.12	25.14	0.19	154.33	58.29	2.62
39	1.19	0.34	14.88	26.57	0.10	115.04	39.73	1.63
Mean	1.57	0.59	17.90	27.28	0.10	119.53	44.92	2.18
SD	0.35	0.32	3.74	4.82	0.04	14.64	16.97	0.51

LVHIIT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
26	1.67	0.48	14.06	31.95	0.04	168.00	18.62	2.25
34	1.65	0.59	22.52	36.15	0.10	99.75	35.16	2.31
35	1.45	0.53	32.47	18.45	0.10	103.70	15.51	2.00
36	1.77	0.53	13.00	30.00	0.16	120.79	55.50	2.43
45	1.77	0.82	19.48	32.21	0.08	130.34	11.47	2.76
47	1.91	0.55	11.64	22.52	0.23	79.63	38.52	2.72
48	1.34	0.39	21.13	22.51	0.07	132.70	51.89	1.78
49	2.05	0.61	13.59	32.10	0.20	106.50	36.56	2.87
Mean	1.70	0.56	18.49	28.24	0.12	117.68	32.90	2.39
SD	0.23	0.13	6.97	6.23	0.07	26.77	16.42	0.38

CON DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
3	1.34	0.49	20.00	39.99	0.16	111.10	67.37	1.89
10	1.01	0.26	13.10	40.15	0.10	87.36	40.46	1.29
12	1.49	0.73	12.36	45.75	0.10	111.00	70.91	2.22
18	1.00	0.23	14.50	35.15	0.12	66.68	69.86	1.32
21	1.82	0.61	12.90	37.97	0.14	121.34	86.67	2.47
22	1.23	0.34	12.51	46.03	0.12	116.33	79.16	1.68
31	1.82	0.59	10.64	38.00	0.11	121.02	43.84	2.47
33	1.88	0.82	16.96	47.73	0.29	141.33	87.93	2.91
41	0.13	0.30	18.00	53.74	0.16	120.94	114.00	1.64
Mean	1.30	0.49	14.55	42.72	0.14	110.79	73.36	1.99
SD	0.56	0.22	3.09	5.95	0.06	21.73	22.59	0.56

VO_2 mean response times during 'unprimed' heavy-intensity exercise initiated from an elevated.

MRT (S)					
MICT DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
4	76	62	50	53	57
7	122	74	61	72	70
8	51	42	41	40	42
15	87	76	54	56	50
17	90	70	60	60	56
20	77	53	59	46	50
23	63	44	36	47	51
24	76	64	63	62	63
28	68	53	51	52	46
30	102	81	95	86	91
39	69	55	58	53	70
Mean	80	61	57	57	59
SD	19	13	15	13	14

MRT (S)					
LVHIIT DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
26	65	52	51	46	56
34	98	76	53	60	62
35	56	48	45	48	50
36	58	62	61	56	69
45	59	41	46	46	47
47	95	78	78	61	54
48	82	65	55	55	59
49	72	58	64	67	54
Mean	73	60	57	55	56
SD	17	13	11	8	7

MRT (S)					
CON DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
3	76	53	47	44	56
10	53	46	50	56	50
12	68	72	72	66	64
18	70	73	59	72	74
21	48	47	47	50	54
22	75	74	74	76	78
31	75	78	73	75	52
33	72	78	72	75	73
41	64	63	54	58	56
Mean	67	65	61	64	62
SD	10	13	12	12	11

Muscle deoxygenation kinetics responses during ‘unprimed’ heavy-intensity exercise initiated from an elevated baseline at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
4	111	107	3	41	9	141	49	116	43
7	17	109	14	11	11	130	22	120	24
8	-2	8	1	44	11	204	51	19	45
15	171	37	7	12	6	149	15	43	20
20	29	16	9	16	3	245	17	19	25
24	156	56	3	20	8	138	38	64	23
28	3	42	19	24	24	171	73	66	43
30	-50	46	1	61	10	118	78	57	63
39	75	73	13	48	0	104	60	74	60
Mean	57	55	8	31	9	156	45	64	39
SD	76	36	6	18	7	45	24	36	16

LVHIIT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
34	300	82	6	20	20	123	24	102	26
35	142	83	5	24	8	106	25	91	29
36	227	32	5	9	3	33	5	35	13
45	109	137	9	25	22	163	37	159	34
47	24	44	31	53	15	159	78	59	84
48	-3	14	11	40	4	180	21	18	51
49	61	69	11	40	12	147	16	81	51
Mean	123	66	11	30	12	130	29	78	41
SD	110	41	9	15	7	50	23	47	23

CON DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
3	-33	30	7	16	6	132	11	36	23
12	18	104	12	18	5	130	24	109	30
21	-48	16	12	16	7	173	17	23	28
22	-30	4	13	25	10	141	59	15	38
33	109	134	9	26	25	154	34	159	34
41	-106	10	10	5	8	154	47	18	15
Mean	-15	50	10	18	10	147	32	60	28
SD	73	58	3	5	8	18	19	63	6

Muscle deoxygenation kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
4	42	107	6	44	14	140	34	121	50
7	-22	118	14	10	16	135	21	134	24
8	-302	62	1	37	24	101	68	86	38
15	57	37	15	23	8	154	15	45	38
20	103	28	9	21	7	173	17	35	30
24	-72	42	8	29	4	139	52	46	36
28	115	69	6	17	15	114	18	84	24
30	60	85	9	23	38	123	50	123	32
39	63	62	11	24	13	124	40	75	35
Mean	5	68	9	25	15	133	35	83	34
SD	129	31	4	10	10	22	19	37	8

LVHIIT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
34	74	40	33	32	12	101	23	53	65
35	196	43	11	12	6	50	19	49	24
36	281	112	4	30	5	195	8	118	34
45	9	137	10	18	13	115	19	150	28
47	175	134	10	33	25	246	35	159	43
48	-40	14	8	12	18	111	101	31	20
49	112	69	10	40	5	120	17	74	50
Mean	115	79	12	25	12	134	32	91	38
SD	112	49	9	11	8	65	32	51	16

CON DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
3	53	37	2	49	3	121	60	40	51
12	109	77	4	22	1	211	21	79	27
21	-64	7	3	13	6	168	30	13	17
22	-83	8	10	10	11	197	60	18	20
33	52	98	9	16	12	109	33	109	26
41	-35	5	4	10	1	67	60	6	15
Mean	14	45	6	22	7	161	41	44	26
SD	83	41	4	16	5	45	18	41	14

Muscle deoxygenation kinetics responses during ‘unprimed’ heavy-intensity exercise initiated from an elevated baseline at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
4	26	115	11	18	53	91	97	168	29
7	-9	119	16	18	4	138	23	124	34
8	0	28	6	24	14	108	100	42	30
15	-37	31	17	32	9	182	48	40	49
20	-12	54	9	34	6	144	17	59	43
24	14	61	3	32	13	144	41	75	35
28	50	76	4	26	13	195	45	89	30
30	-56	84	8	65	15	156	55	99	73
39	93	104	11	34	10	132	49	114	45
Mean	8	75	9	32	15	143	53	90	41
SD	45	34	5	14	15	32	29	42	14

LVHIIT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
34	316	61	9	44	11	91	34	73	53
35	240	136	5	24	8	89	23	145	29
36	88	142	2	42	28	134	100	171	44
45	78	119	10	14	17	120	18	136	24
47	158	95	11	24	23	144	31	118	36
48	-68	6	8	11	12	103	52	19	18
49	-57	71	10	79	98	93	70	169	88
Mean	108	90	8	34	28	111	47	119	42
SD	143	48	3	23	32	22	29	55	24

CON DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
3	6	31	4	16	4	106	15	35	20
12	101	61	12	10	4	199	21	65	22
21	-82	20	13	16	8	157	19	29	29
22	-71	4	50	23	4	161	40	8	74
33	43	157	1	34	27	120	50	184	35
41	-56	8	4	18	5	170	33	13	23
Mean	-1	55	16	20	9	149	29	56	34
SD	77	61	20	9	10	37	15	70	22

Muscle deoxygenation kinetics responses during ‘unprimed’ heavy-intensity exercise initiated from an elevated baseline at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
4	48	139	11	36	34	156	54	173	47
7	-2	77	17	24	3	118	44	81	41
8	-3	9	3	24	14	149	100	22	27
15	-39	15	16	20	3	123	56	17	36
20	126	88	9	30	12	161	17	100	39
24	-23	63	9	20	2	27	28	65	29
28	130	144	4	18	14	128	33	158	22
30	21	97	4	40	11	211	29	108	44
39	68	74	15	40	2	109	43	76	55
Mean	36	78	10	28	11	131	45	89	38
SD	61	47	6	9	10	50	24	53	10

LVHIIT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
34	354	52	6	34	11	110	32	63	39
35	111	168	1	28	8	98	23	177	29
36	208	85	5	22	8	182	23	94	27
45	16	140	8	16	68	94	101	208	25
47	229	188	2	34	43	118	84	231	36
48	-35	14	1	18	9	180	21	23	20
49	-5	79	10	34	15	108	88	94	44
Mean	125	104	5	27	23	127	53	127	32
SD	144	64	3	8	23	38	36	79	9

CON DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
3	239	16	4	17	5	74	37	22	21
12	21	119	15	14	5	122	38	124	29
21	-94	24	16	14	9	185	26	32	30
22	-50	7	19	38	20	126	72	27	57
33	46	112	9	14	34	96	55	146	23
41	-170	3	4	11	1	67	60	4	15
Mean	32	56	12	20	15	121	45	59	29
SD	128	55	6	10	12	42	18	60	14

Muscle deoxygenation kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
4	62	109	13	44	26	163	78	135	57
7	-50	52	12	44	9	113	42	61	56
8	-45	30	9	30	7	134	100	37	39
15	57	54	13	34	17	120	76	71	46
20	62	37	3	32	2	132	17	39	35
24	97	69	3	32	10	187	32	79	35
28	40	71	11	25	10	139	56	80	36
30	40	69	7	38	29	152	71	98	45
39	41	95	10	50	1	130	32	96	59
Mean	34	65	9	36	13	141	56	78	45
SD	49	26	4	8	10	23	27	31	10

LVHIIT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
34	252	70	10	24	4	98	7	74	34
35	86	97	7	24	13	60	15	111	31
36	211	94	3	40	13	149	38	107	43
45	-111	101	10	14	29	113	58	130	24
47	191	105	2	30	9	170	122	115	32
48	-13	12	8	63	9	120	89	21	72
49	-15	78	2	46	6	111	42	85	48
Mean	86	80	6	34	12	117	53	92	41
SD	137	32	4	16	8	35	41	36	16

CON DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
3	-30	16	6	16	4	49	27	20	22
12	-10	24	7	8	4	132	25	27	16
21	-63	15	14	12	65	175	26	80	27
22	-37	6	13	14	22	185	88	28	27
33	26	31	40	26	16	146	23	47	66
41	-35	15	10	43	3	168	60	18	54
Mean	-23	18	16	15	22	137	38	37	35
SD	33	10	14	7	25	54	28	24	20

Muscle deoxygenation mean response times during 'unprimed' heavy-intensity exercise initiated from an elevated baseline

	MRT (s)				
MICT DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
4	44	60	74	68	78
7	14	36	20	24	73
8	91	91	90	77	40
15	16	32	46	26	58
20	28	46	46	46	38
24	21	28	50	22	46
28	70	30	42	26	48
30	128	84	98	52	90
39	64	44	54	42	52
Mean	53	50	58	43	58
SD	39	23	25	20	18

	MRT (s)				
LVHIIT DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
34	26	52	58	52	26
35	26	14	24	28	28
36	8	32	72	26	54
45	54	20	22	66	64
47	26	42	36	56	34
48	66	100	82	56	142
49	46	46	124	60	52
Mean	36	44	60	49	57
SD	20	29	37	16	40

	MRT (s)				
CON DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
3	30	52	18	18	18
12	22	20	16	16	4
21	65	34	34	22	80
22	146	132	69	122	154
33	38	20	50	56	56
41	43	4	40	38	64
Mean	57	44	38	45	63
SD	46	46	20	40	53

Heart rate kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	111	32	3	119	143
7	109	20	3	119	129
8	125	38	0	104	163
15	47	28	1	119	75
17	124	18	0	116	142
20	137	36	0	103	173
23	110	36	4	119	146
24	150	21	5	119	171
28	139	17	0	58	156
30	118	25	0	150	143
39	130	27	0	86	157
Mean	118	27	1	110	145
SD	27	8	2	23	27

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	116	31	0	96	147
34	126	31	0	72	157
35	142	17	0	71	159
36	123	34	0	124	157
45	122	32	0	107	154
47	143	37	3	80	180
48	144	37	3	156	181
49	132	23	3	79	155
Mean	131	30	1	98	161
SD	11	7	2	30	12

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	125	18	2	94	143
10	115	34	0	94	149
12	130	26	0	85	156
18	138	20	7	84	158
21	124	29	0	77	152
22	121	38	0	78	159
31	136	41	0	105	178
33	111	45	0	108	156
41	139	27	11	129	166
Mean	127	31	2	95	157
SD	10	9	4	17	10

Heart rate kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	106	33	0	98	139
7	97	26	0	112	123
8	124	27	4	83	150
15	135	26	0	90	161
17	119	14	0	89	133
20	130	24	0	104	154
23	102	35	0	59	137
24	137	30	0	114	167
28	122	25	4	71	146
30	120	20	4	85	140
39	130	15	0	88	145
Mean	120	25	1	90	145
SD	13	7	2	17	13

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	115	30	0	89	145
34	124	32	2	95	156
35	136	21	1	92	157
36	121	29	0	117	151
45	119	32	6	80	151
47	120	29	3	100	149
48	154	23	7	116	177
49	128	23	0	90	150
Mean	127	27	2	97	154
SD	13	4	3	13	10

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	121	39	7	200	160
10	108	23	0	49	131
12	119	38	0	78	157
18	140	20	23	64	160
21	117	33	5	67	150
22	117	36	0	78	153
31	135	36	0	80	171
33	111	45	0	113	157
41	146	24	21	128	170
Mean	124	33	6	95	157
SD	13	8	9	46	12

Heart rate kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	103	30	0	67	133
7	103	22	4	131	125
8	125	32	0	75	157
15	133	20	0	69	153
17	124	12	0	108	136
20	136	10	13	49	145
23	100	19	0	52	119
24	154	19	0	131	173
28	116	23	0	48	139
30	118	21	0	79	139
39	113	13	0	70	126
Mean	120	20	2	80	140
SD	16	7	4	30	16

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	115	28	0	92	143
34	109	34	4	105	143
35	129	20	0	78	149
36	116	23	0	75	139
45	112	36	0	64	148
47	115	27	0	90	141
48	136	28	3	83	164
49	129	26	4	98	155
Mean	120	28	1	86	148
SD	10	5	2	13	8

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	120	36	2	178	156
10	108	23	0	56	131
12	123	36	6	92	159
18	136	21	1	67	157
21	118	27	5	87	145
22	118	43	2	89	161
31	136	35	1	80	171
33	103	54	0	118	156
41	135	35	5	65	170
Mean	122	34	2	92	156
SD	12	10	2	37	12

Heart rate kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	98	27	3	54	125
7	95	26	0	106	121
8	119	40	0	76	159
15	126	20	1	67	146
17	120	13	16	108	133
20	130	19	0	95	149
23	109	19	0	71	128
24	142	27	2	141	169
28	109	28	0	66	137
30	114	18	0	83	132
39	128	13	0	96	141
Mean	117	23	2	88	140
SD	14	8	5	25	15

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	117	26	3	92	143
34	115	34	5	119	149
35	127	19	7	67	146
36	116	28	0	104	144
45	119	31	0	61	150
47	117	28	2	75	144
48	136	27	6	111	162
49	131	24	6	11	155
Mean	122	27	4	80	149
SD	8	4	3	35	7

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	120	27	2	126	147
10	110	26	4	54	136
12	125	39	0	117	164
18	131	23	19	36	154
21	114	35	5	85	149
22	117	42	3	97	160
31	15	36	2	80	50
33	130	39	0	105	169
41	161	19	18	65	180
Mean	114	32	6	85	145
SD	40	8	7	30	38

Heart rate kinetics responses during 'unprimed' heavy-intensity exercise initiated from an elevated baseline at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	110	26	0	67	136
7	92	26	0	121	118
8	116	31	0	57	147
15	126	20	0	69	146
17	118	12	3	95	130
20	123	20	3	56	143
23	106	18	4	54	124
24	139	28	1	118	167
28	114	23	0	52	137
30	112	16	9	58	128
39	126	13	10	100	139
Mean	117	21	3	77	138
SD	12	6	4	26	13

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	110.904	22.421	0.000	91.449	133.325
34	107	31	0	119	138
35	1223	22	0	87	1245
36	112	22	0	95	134
45	119	31	0	61	150
47	127	29	2	88	156
48	135	26	9	92	161
49	121	26	9	92	146
Mean	257	26	3	91	283
SD	390	4	4	16	389

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	116	29	5	140	145
10	106	25	32	81	131
12	131	37	6	79	168
18	138	21	16	75	159
21	100	52	7	114	152
22	112	44	0	103	156
31	117	44	2	87	161
33	122	32	0	101	154
41	146	31	18	122	177
Mean	121	35	10	100	156
SD	15	10	10	22	13

VO_2 kinetics responses during 'unprimed' moderate-intensity exercise at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	End Vo2
4	0.89	1.30	2.08	41.21	2.19
7	0.61	0.64	7.30	36.11	1.25
8	0.99	0.54	0.00	46.81	1.52
15	1.00	1.19	2.79	44.99	2.19
20	1.32	0.70	15.41	56.00	2.03
23	0.70	0.46	11.52	52.43	1.16
24	1.03	0.56	11.54	58.12	1.59
28	1.00	0.91	14.19	55.78	1.91
30	0.82	0.97	13.75	48.58	1.79
39	0.74	0.24	29.90	41.87	0.98
Mean	0.91	0.75	10.85	48.19	1.66
SD	0.21	0.33	8.67	7.32	0.43

LVHIIT DSP ID	Baseline	A1	TD1	Tau	End Vo2
26	0.73	0.92	9.39	33.74	1.65
34	0.46	1.14	10.00	50.06	1.60
35	0.70	0.92	9.24	39.92	1.62
36	1.40	0.65	22.96	60.00	2.05
45	0.86	1.02	11.97	32.17	1.88
47	0.87	1.30	8.16	39.99	2.18
48	0.78	0.48	18.00	50.50	1.26
49	0.97	1.11	5.73	43.31	2.08
Mean	0.85	0.94	11.93	43.71	1.79
SD	0.27	0.27	5.71	9.36	0.31

CON DSP ID	Baseline	A1	TD1	Tau	End Vo2
3	0.66	0.71	14.34	44.99	1.37
10	0.73	0.25	22.79	58.98	0.98
12	1.00	0.52	15.40	47.92	1.52
18	0.75	0.36	15.04	46.29	1.11
21	0.88	0.33	13.85	40.00	1.21
22	0.74	0.40	20.19	45.00	1.15
31	1.08	0.74	6.65	39.68	1.82
33	0.74	1.13	10.22	30.00	1.87
41	0.87	0.38	22.00	50.09	1.25
Mean	0.83	0.54	15.61	44.77	1.36
SD	0.14	0.28	5.34	7.98	0.31

VO_2 kinetics responses during 'unprimed' moderate-intensity exercise at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	End Vo2
4	0.95	1.04	8.66	31.13	1.99
7	0.80	0.61	14.13	41.68	1.41
8	1.08	0.33	17.00	31.99	1.40
15	1.15	1.02	15.00	33.55	2.18
20	1.31	0.49	11.15	38.00	1.80
23	0.70	0.47	16.22	25.39	1.17
24	0.90	0.79	9.49	32.00	1.69
28	0.95	0.73	14.99	38.00	1.68
30	0.89	0.90	22.85	27.30	1.79
39	0.87	0.23	12.39	26.57	1.10
Mean	0.96	0.66	14.19	32.56	1.62
SD	0.18	0.28	4.13	5.38	0.35

LVHIIT DSP ID	Baseline	A1	TD1	Tau	End Vo2
26	0.90	0.67	11.65	31.00	1.58
34	0.77	0.85	11.31	38.92	1.62
35	0.76	0.91	11.32	36.00	1.67
36	1.06	0.75	9.88	34.00	1.81
45	0.97	0.88	21.52	27.00	1.85
47	0.89	1.14	14.94	31.55	2.03
48	0.90	0.43	19.64	29.77	1.33
49	0.87	1.04	19.72	34.26	1.91
Mean	0.89	0.83	15.00	32.81	1.72
SD	0.10	0.22	4.64	3.76	0.22

CON DSP ID	Baseline	A1	TD1	Tau	End Vo2
3	0.73	0.64	6.70	41.26	1.38
10	0.58	0.32	18.01	39.02	0.89
12	0.97	0.49	19.27	45.48	1.46
18	0.60	0.40	17.89	22.60	1.01
21	0.98	0.40	15.00	43.99	1.37
22	0.68	0.43	13.82	36.10	1.11
31	1.00	0.82	11.00	50.67	1.82
33	0.78	0.99	18.15	29.64	1.76
41	0.83	0.52	19.00	46.10	1.35
Mean	0.79	0.56	15.43	39.43	1.35
SD	0.16	0.22	4.27	8.82	0.31

VO_2 kinetics responses during 'unprimed' moderate-intensity exercise at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau	End Vo2
4	1.10	0.94	22.56	15.74	2.04
7	0.73	0.64	11.16	32.56	1.37
8	0.90	0.46	3.97	29.04	1.36
15	1.00	1.20	11.20	27.99	2.20
20	1.28	0.62	16.23	43.43	1.90
23	0.54	0.62	9.98	22.85	1.17
24	0.96	0.54	17.51	26.00	1.50
28	0.86	0.55	21.87	26.00	1.41
30	0.84	0.95	17.93	29.00	1.79
39	0.68	0.29	19.89	25.00	0.96
Mean	0.89	0.68	15.23	27.76	1.57
SD	0.21	0.27	5.96	7.10	0.40

LVHIIT DSP ID	Baseline	A1	TD1	Tau	End Vo2
26	1.08	0.52	30.97	31.43	1.60
34	0.93	0.87	33.00	34.05	1.79
35	1.00	0.58	23.67	31.76	1.59
36	0.95	0.70	22.00	24.40	1.66
45	0.80	0.98	19.73	23.87	1.78
47	0.83	1.15	14.31	26.26	1.98
48	0.89	0.60	17.60	25.00	1.49
49	0.85	1.11	17.10	31.52	1.96
Mean	0.92	0.81	22.30	28.54	1.73
SD	0.09	0.24	6.67	4.05	0.18

CON DSP ID	Baseline	A1	TD1	Tau	End Vo2
3	0.65	0.67	7.48	48.57	1.32
10	0.60	0.32	20.00	34.25	0.92
12	0.96	0.55	9.71	50.66	1.50
18	0.55	0.50	8.20	39.99	1.04
21	0.76	0.50	12.00	34.78	1.26
22	0.67	0.45	20.00	33.93	1.12
31	0.93	0.77	12.18	40.00	1.71
33	0.83	1.03	20.00	27.79	1.86
41	0.83	0.49	18.00	34.57	1.32
Mean	0.75	0.59	14.17	38.28	1.34
SD	0.15	0.21	5.31	7.38	0.31

VO_2 kinetics responses during 'unprimed' moderate-intensity exercise at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	End Vo2
4	0.96	0.99	19.33	20.88	1.96
7	0.77	0.60	19.00	21.99	1.37
8	0.99	0.32	23.10	25.00	1.31
15	1.39	0.99	28.82	22.06	2.38
20	1.32	0.63	9.60	30.84	1.95
23	0.84	0.41	17.58	22.25	1.25
24	0.85	0.65	19.28	29.99	1.50
28	0.81	0.65	11.65	26.96	1.46
30	0.95	0.81	12.95	26.00	1.75
39	0.80	0.31	19.62	24.79	1.11
Mean	0.97	0.64	18.09	25.08	1.60
SD	0.22	0.24	5.64	3.43	0.39

LVHIIT DSP ID	Baseline	A1	TD1	Tau	End Vo2
26	0.64	0.80	12.47	26.22	1.44
34	0.92	0.69	27.84	30.00	1.61
35	0.77	0.85	16.15	21.54	1.62
36	0.96	0.84	16.00	25.42	1.80
45	0.79	0.99	15.57	25.00	1.77
47	0.76	1.18	16.97	21.99	1.94
48	1.06	0.41	17.60	31.99	1.47
49	0.91	1.10	14.34	28.60	2.01
Mean	0.85	0.86	17.12	26.34	1.71
SD	0.13	0.25	4.62	3.68	0.21

CON DSP ID	Baseline	A1	TD1	Tau	End Vo2
3	0.75	0.56	27.00	43.96	1.31
10	0.64	0.33	17.00	39.39	0.96
12	0.93	0.53	21.75	30.89	1.46
18	0.58	0.44	24.00	39.78	1.02
21	0.76	0.40	16.00	27.03	1.16
22	0.68	0.43	10.33	59.13	1.11
31	1.01	0.78	23.00	45.26	1.79
33	0.89	0.96	16.73	29.00	1.86
41	0.84	0.49	19.00	42.06	1.33
Mean	0.79	0.55	19.42	39.61	1.33
SD	0.14	0.20	5.05	9.91	0.32

VO_2 kinetics responses during 'unprimed' moderate-intensity exercise at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	End Vo2
4	1.00	0.91	14.93	29.76	1.91
7	0.82	0.64	12.38	35.00	1.46
8	0.93	0.41	12.92	25.99	1.34
15	1.10	1.12	17.73	23.64	2.22
20	1.24	0.72	10.53	30.00	1.96
23	0.77	0.36	17.03	24.79	1.13
24	0.89	0.63	16.26	30.00	1.53
28	0.84	0.63	18.78	25.00	1.47
30	0.82	0.96	18.00	19.09	1.77
39	0.56	0.61	0.25	35.69	1.18
Mean	0.90	0.70	13.88	27.90	1.59
SD	0.19	0.24	5.50	5.17	0.36

LVHIIT DSP ID	Baseline	A1	TD1	Tau	End Vo2
26	0.87	0.75	9.98	30.87	1.63
34	0.76	0.87	21.80	29.99	1.63
35	0.70	0.79	25.19	22.53	1.49
36	1.17	0.56	17.01	27.82	1.72
45	0.64	1.13	8.69	25.00	1.77
47	0.86	1.03	11.60	23.99	1.89
48	0.63	0.67	6.85	30.00	1.30
49	0.94	0.99	26.94	34.00	1.93
Mean	0.82	0.85	16.01	28.02	1.67
SD	0.18	0.19	7.85	3.91	0.21

CON DSP ID	Baseline	A1	TD1	Tau	End Vo2
3	0.74	0.58	13.50	44.99	1.31
10	0.64	0.37	9.00	47.97	1.01
12	0.88	0.56	13.00	50.11	1.44
18	0.51	0.47	6.68	44.94	0.98
21	0.73	0.39	22.88	34.66	1.12
22	0.70	0.47	19.61	44.36	1.17
31	0.94	0.86	14.21	50.00	1.80
33	0.86	1.02	11.97	32.17	1.88
41	0.78	0.48	18.00	50.50	1.26
Mean	0.75	0.58	14.32	44.41	1.33
SD	0.13	0.22	5.12	6.70	0.32

Muscle deoxygenation kinetics responses during ‘unprimed’ moderate-intensity exercise at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	τ'[HHb+Mb]	End A
4	-32.00	129.84	15.81	12.00	27.81	97.84
7	-56.90	81.78	15.67	7.45	23.12	24.88
8	-27.83	22.68	10.40	21.05	31.45	-5.15
15	-8.99	127.71	1.72	12.62	14.34	118.72
20	23.00	57.29	15.98	16.00	31.98	80.29
23	-132.00	4.99	6.81	8.00	14.81	-127.01
24	39.00	124.21	12.05	29.51	41.56	163.21
28	-90.00	109.10	1.17	14.42	15.59	19.10
30	-103.98	37.36	2.02	21.09	23.11	-66.62
39	-1.00	67.43	19.96	9.02	28.98	66.43
Mean	-39.07	76.24	10.16	15.12	25.28	37.17
SD	56.02	45.74	6.88	7.01	8.82	87.51

LVHIIT DSP ID	Baseline	A1	TD1	Tau	τ'[HHb+Mb]	End A
26	-35.00	24.62	15.14	12.20	27.34	-10.38
34	21.00	204.74	17.70	6.50	24.20	225.74
35	-150.00	274.47	11.73	13.32	25.05	124.47
36	2.00	212.50	9.84	22.74	32.58	214.50
45	-29.99	152.02	18.22	6.50	24.72	122.03
47	-4.00	267.88	13.42	8.51	21.93	263.88
49	-32.00	79.74	14.55	8.08	22.63	47.74
Mean	-32.57	173.71	14.37	11.12	25.49	141.14
SD	55.80	94.00	3.03	5.77	3.58	99.94

CON DSP ID	Baseline	A1	TD1	Tau	τ'[HHb+Mb]	End A
3	-89.22	66.23	1.45	8.2	9.65	-22.99
10	-15.40	3.47	14.65	6.00	20.65	-11.93
12	-95.00	126.96	15.59	7.90	23.49	31.96
18	-35.00	89.97	11.23	20.77	32.00	54.97
21	-56.99	19.58	16.72	11.06	27.78	-37.41
22	-36.90	8.29	18.94	14.61	33.55	-28.61
31	-5.00	115.18	15.52	17.77	33.29	110.18
33	-29.00	156.50	18.23	7.85	26.08	127.50
Mean	-39.04	74.28	15.84	12.28	28.12	35.24
SD	29.70	63.00	2.55	5.59	5.05	65.96

Muscle deoxygenation kinetics responses during 'unprimed' moderate-intensity exercise at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
4	-40.00	89.82	9.80	14.00	23.80	49.82
7	-115.00	109.58	13.92	9.58	23.50	-5.42
8	14.31	10.38	11.07	10.64	21.71	24.69
15	-55.00	112.20	11.74	14.27	26.01	57.20
20	-15.00	98.87	19.66	30.43	50.09	83.87
23	-182.10	20.52	30.98	35.04	66.02	-161.58
24	-224.90	153.78	11.68	15.65	27.33	-71.12
28	-66.00	182.89	15.54	10.71	26.25	116.89
30	-97.00	173.86	16.40	13.06	29.46	76.86
39	3.00	60.51	21.70	16.10	37.80	63.51
Mean	-77.77	101.24	16.25	16.95	33.20	23.47
SD	78.40	59.12	6.45	8.66	14.32	83.46

LVHIIT DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
26	9.00	60.52	11.85	11.98	23.83	69.52
34	18.00	140.10	20.60	17.87	38.47	158.10
35	-79.00	246.79	12.15	19.86	32.01	167.79
36	-30.00	263.35	12.51	13.69	26.20	233.35
45	-71.00	98.89	19.70	3.91	23.61	27.89
47	-147.23	313.30	12.70	6.26	18.96	166.07
49	-58.00	120.67	14.92	11.10	26.02	62.67
Mean	-51.18	177.66	14.92	12.10	27.01	126.48
SD	56.71	95.83	3.72	5.75	6.38	73.86

CON DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
3	-21	81.61	12.21	11.27	23.48	60.61
10	1.30	23.69	15.03	19.40	34.42	24.99
12	4.00	109.60	14.06	9.70	23.76	113.60
18	-60.00	74.65	9.61	15.41	25.02	14.65
21	-79.69	16.32	11.70	7.50	19.20	-63.36
22	-88.10	8.01	12.85	7.58	20.43	-80.09
31	-32.00	173.93	13.73	8.00	21.73	141.93
33	-67.10	130.23	18.54	7.50	26.04	63.13
Mean	-45.94	76.63	13.64	10.73	24.37	30.69
SD	37.60	64.00	2.79	4.77	5.06	83.38

Muscle deoxygenation kinetics responses during 'unprimed' moderate-intensity exercise at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
4	-105.99	116.23	1.60	9.72	11.32	10.24
7	-100.00	102.16	19.61	5.88	25.49	2.16
8	-34.00	22.63	13.92	6.11	20.03	-11.37
15	-91.00	31.34	12.32	12.41	24.73	-59.66
20	-74.00	75.32	17.30	36.44	53.74	1.32
23	-29.00	14.78	32.39	27.93	60.32	-14.22
24	-163.00	170.99	7.38	15.62	23.00	7.99
28	-61.00	119.58	14.48	9.98	24.46	58.58
30	-186.00	118.55	16.21	7.18	23.39	-67.45
39	15.00	66.98	18.99	13.95	32.94	81.98
Mean	-82.90	83.86	15.42	14.52	29.94	0.96
SD	60.90	50.65	8.10	10.05	15.32	45.65

LVHIIT DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
26	-62.99	51.40	11.35	10.37	21.72	-11.59
34	-27.00	289.81	15.06	8.38	23.44	262.81
35	-5.00	244.00	11.00	15.87	26.87	239.00
36	-69.15	140.62	13.35	10.12	23.47	71.47
45	-7.00	111.75	17.06	7.79	24.85	104.75
47	-114.00	266.18	11.60	8.00	19.60	152.18
49	-117.80	59.98	14.00	6.00	20.00	-57.82
Mean	-57.56	166.25	13.35	9.50	22.85	108.68
SD	46.96	99.51	2.23	3.17	2.61	119.87

CON DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
3	-25	59.26	9.94	13.9	23.84	34.26
10	-78.00	32.32	7.97	42.72	50.69	-45.68
12	-49.00	154.18	12.92	13.95	26.87	105.18
18	-104.00	60.97	8.00	20.00	28.00	-43.03
21	-84.50	11.86	14.97	11.16	26.13	-72.64
22	-50.00	10.46	18.69	17.88	36.57	-39.54
31	-30.99	107.88	13.76	17.00	30.76	76.89
33	-13.00	127.77	14.96	4.83	19.80	114.78
Mean	-54.31	70.59	12.65	17.68	30.33	16.28
SD	31.84	53.98	3.77	11.14	9.58	75.57

Muscle deoxygenation kinetics responses during 'unprimed' moderate-intensity exercise at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
4	-76.00	120.79	15.59	9.41	25.00	44.79
7	-70.99	84.53	18.56	11.55	30.11	13.54
8	-44.00	14.25	9.60	32.10	41.70	-29.75
15	-64.00	20.27	10.70	10.97	21.67	-43.73
20	30.99	54.16	23.55	43.35	66.90	85.15
23	-392.00	177.27	22.75	60.00	82.75	-214.73
24	-129.16	110.17	12.72	10.01	22.73	-18.99
28	-10.40	172.68	12.58	8.10	20.68	162.28
30	-148.00	160.46	13.10	10.58	23.68	12.46
39	9.00	50.13	17.75	7.79	25.54	59.13
Mean	-89.46	96.47	15.69	20.39	36.08	7.02
SD	120.29	61.33	4.85	18.36	21.62	99.00

LVHIIT DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
26	-21.00	72.78	13.00	7.40	20.40	51.78
34	-28.00	317.77	14.97	11.02	25.99	289.77
35	-99.00	174.30	12.89	8.67	21.56	75.30
36	-77.00	249.26	9.64	19.37	29.01	172.26
45	-83.00	117.72	19.26	7.55	26.81	34.72
47	-22.00	281.00	10.40	8.00	18.40	259.00
49	-56.01	101.05	11.03	14.04	25.06	45.04
Mean	-55.14	187.70	13.03	10.87	23.89	132.55
SD	32.09	95.92	3.29	4.44	3.84	107.48

CON DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
3	197	38.42	13	20.97	33.97	235.42
10	9.13	7.30	13.44	20.00	33.44	16.43
12	-90.99	126.61	19.59	8.03	27.62	35.62
18	-57.00	74.48	10.45	19.29	29.74	17.48
21	-110.00	26.70	14.97	13.87	28.84	-83.30
22	-66.88	10.92	16.00	34.74	50.74	-55.97
31	-42.00	142.93	15.57	11.35	26.92	100.93
33	-18.00	129.21	17.01	5.95	22.96	111.21
Mean	-22.34	69.57	15.00	16.77	31.78	47.23
SD	96.43	56.50	2.77	9.17	8.44	101.45

Muscle deoxygenation kinetics responses during ‘unprimed’ moderate-intensity exercise at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
4	-48.00	88.16	21.50	20.54	42.04	40.16
7	-104.00	56.42	25.70	22.64	48.34	-47.58
8	-81.12	23.61	18.00	15.62	33.62	-57.50
15	-49.00	96.89	13.93	18.04	31.97	47.89
20	-31.00	67.60	16.48	21.60	38.08	36.60
23	-206.00	70.36	13.65	18.45	32.10	-135.64
24	-54.00	128.00	11.31	14.03	25.34	74.00
28	-48.00	89.60	13.28	9.29	22.57	41.60
30	-8.90	129.83	18.06	7.80	25.86	120.93
39	-44.42	74.60	16.32	14.87	31.19	30.18
Mean	-67.44	82.51	16.82	16.29	33.11	15.06
SD	55.06	31.94	4.29	4.98	7.94	74.30

LVHIIT DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
26	74.00	56.91	11.93	5.69	17.62	130.91
34	-72.00	273.75	14.47	5.14	19.61	201.75
35	-221.00	264.70	6.80	15.72	22.52	43.70
36	-24.00	197.10	12.70	15.83	28.53	173.10
45	-123.00	101.06	18.20	6.00	24.20	-21.94
47	-71.63	276.89	11.60	8.00	19.60	205.26
49	-116.79	91.52	13.40	9.99	23.39	-25.27
Mean	-79.20	180.28	12.73	9.48	22.21	101.07
SD	91.35	95.62	3.43	4.60	3.65	101.21

CON DSP ID	Baseline	A1	TD1	Tau	'[HHb+Mb	End A
3	-56	53.4	22.3	71.45	93.75	-2.60
10	-44.00	20.66	33.11	17.21	50.31	-23.34
12	-126.00	113.30	16.65	9.10	25.75	-12.70
18	-92.10	94.78	14.42	13.34	27.76	2.68
21	-89.30	38.81	13.90	9.91	23.81	-50.49
22	-38.24	12.90	19.00	14.02	33.02	-25.34
31	-30.00	112.63	15.23	14.84	30.07	82.63
33	-18.00	151.75	18.21	6.38	24.59	133.75
Mean	-61.70	74.78	19.10	19.53	38.63	13.07
SD	37.09	50.36	6.29	21.27	23.85	62.41

Δ[HHb+Mb]/ΔVO_2 ratios responses during 'unprimed' moderate-intensity exercise throughout the intervention period.

MICT DSP ID	0	3	6	9	12
4	1.04	1.04	0.96	1.02	1.04
7	1.15	1.13	1.05	1.01	1.00
8	1.11	1.15	1.08	1.07	1.06
15	1.18	1.05	1.12	1.05	1.08
20	1.25	0.95	1.08	1.10	0.98
23	1.12	1.13	0.97	0.95	1.10
24	1.08	1.12	1.14	1.19	1.11
28	1.37	1.14	1.10	0.98	1.04
30	1.19	1.15	1.13	1.10	0.99
39	1.37	1.12	1.05	1.07	1.05
Mean	1.19	1.10	1.07	1.05	1.04
SD	0.11	0.06	0.06	0.07	0.05

LVHIIT DSP ID	0	3	6	9	12
26	1.12	1.11	0.90	1.07	1.04
34	1.22	1.06	1.18	1.05	1.00
35	1.09	1.19	1.07	1.03	0.99
36	1.30	1.06	1.09	1.03	0.98
45	1.08	0.99	1.09	1.02	1.03
47	1.15	1.15	1.10	1.09	1.10
49	1.25	1.09	1.05	1.05	0.93
Mean	1.17	1.09	1.07	1.05	1.01
SD	0.08	0.06	0.09	0.02	0.05

CON DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
3	1.22	1.16	1.30	1.19	1.08
10	1.19	1.12	0.95	1.17	1.24
12	1.17	1.15	1.14	1.11	1.09
18	1.09	0.99	1.09	1.06	1.12
21	1.04	1.23	1.16	1.23	1.01
22	0.96	1.48	1.09	1.26	1.11
31	1.03	1.26	1.05	1.14	1.16
33	1.03	1.16	1.13	1.11	1.20
Mean	1.09	1.19	1.11	1.16	1.13
SD	0.09	0.14	0.10	0.07	0.07

HR kinetics responses during 'unprimed' moderate-intensity exercise at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	86	25	0	50	111
7	86	22	0	40	108
8	105	20	0	68	125
15	111	35	0	70	146
20	110	30	5	78	140
23	85	22	0	70	107
24	128	20	2	78	148
28	109	27	7	100	136
30	86	32	0	48	118
39	115	15	0	88	130
Mean	102	25	1	69	127
SD	15	6	2	19	15

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	80	34	3	34	114
34	108	17	13	84	125
35	105	36	1	77	141
36	100	24	0	97	124
45	92	24	2	33	116
47	107	32	4	93	138
48	108	35	0	96	143
49	107	24	0	63	131
Mean	101	28	3	72	129
SD	10	7	4	26	11

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	105	21	0	128	126
10	91	23	0	70	114
12	110	19	0	52	129
18	110	22	10	38	132
21	102	20	3	34	122
22	91	28	2	54	119
31	108	27	4	40	135
33	86	25	1	37	111
41	115	22	0	68	137
Mean	102	23	2	58	125
SD	10	3	3	29	9

HR kinetics responses during 'unprimed' moderate-intensity exercise at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	80	26	2	32	106
7	83	15	11	49	98
8	101	21	0	60	122
15	104	30	0	62	134
20	104	26	0	70	130
23	83	17	7	38	100
24	112	23	1	42	135
28	97	24	0	57	121
30	95	25	6	44	120
39	119	11	1	94	130
Mean	98	22	3	55	120
SD	13	6	4	18	14

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	81	29	0	33	110
34	95	30	0	133	125
35	102	33	0	61	135
36	97	25	0	58	122
45	94	24	6	32	118
47	91	29	1	67	120
48	118	28	7	59	146
49	100	28	0	114	127
Mean	97	28	2	69	125
SD	11	3	3	36	11

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	104	17	2	108	121
10	88	21	0	63	109
12	99	21	0	54	120
18	109	30	9	43	140
21	95	21	0	48	116
22	89	28	0	65	117
31	107	28	4	33	135
33	85	26	0	37	111
41	115	27	0	67	142
Mean	99	24	2	58	123
SD	11	5	3	23	12

HR kinetics responses during 'unprimed' moderate-intensity exercise at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	80	22	3	25	102
7	83	20	7	41	103
8	104	20	1	55	124
15	101	31	0	56	132
20	113	25	0	162	138
23	84	15	0	33	99
24	133	22	2	132	155
28	100	16	2	39	116
30	92	21	11	37	113
39	102	11	0	48	113
Mean	99	20	3	63	119
SD	16	6	4	46	18

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	83	30	1	26	113
34	93	17	7	45	110
35	87	35	1	39	122
36	99	16	2	36	114
45	92	25	0	40	117
47	84	30	0	54	113
48	109	28	6	59	137
49	99	31	0	86	130
Mean	93	26	2	48	120
SD	9	7	3	18	9

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	102	19	3	124	121
10	88	19	0	58	107
12	98	19	2	47	117
18	101	21	0	60	122
21	98	19	4	59	117
22	90	28	0	67	118
31	105	28	4	39	133
33	78	26	1	28	104
41	112	31	4	101	143
Mean	97	23	2	65	120
SD	10	5	2	30	12

HR kinetics responses during 'unprimed' moderate-intensity exercise at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	78	19	8	20	97
7	79	17	15	37	96
8	101	19	1	50	120
15	98	26	2	48	124
20	107	19	0	60	126
23	90	14	2	40	103
24	119	20	0	81	139
28	90	19	1	36	109
30	89	24	3	39	113
39	120	8	9	75	128
Mean	97	18	4	49	115
SD	15	5	5	19	14

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	82	31	0	27	113
34	95	18	15	60	113
35	96	30	4	46	126
36	92	20	0	38	112
45	91	28	3	42	119
47	84	31	0	44	114
48	107	26	0	70	133
49	109	21	1	60	130
Mean	95	25	3	48	120
SD	10	5	5	14	8

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	94	27	1	101	121
10	82	25	0	46	107
12	102	24	0	47	126
18	108	25	10	43	133
21	92	19	4	36	111
22	86	31	3	55	117
31	114	25	14	38	139
33	92	27	1	43	119
41	117	31	3	89	148
Mean	99	26	4	55	124
SD	12	4	5	23	13

HR kinetics responses during 'unprimed' moderate-intensity exercise at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	92	18	4	32	110
7	82	12	31	34	94
8	103	11	10	25	114
15	94	26	0	40	119
20	92	27	3	40	119
23	89	16	0	38	105
24	118	21	0	92	139
28	96	15	0	48	111
30	88	23	0	43	111
39	112	11	2	58	123
Mean	97	18	5	45	115
SD	11	6	10	19	12

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	82	27	0	34	108
34	94	20	8	58	114
35	88	35	0	42	123
36	94	16	0	45	110
45	92	26	2	34	117
47	96	31	4	56	127
48	109	26	3	72	135
49	96	23	1	54	119
Mean	94	25	2	49	119
SD	8	6	3	13	9

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	99	16	5	75	115
10	85	18	0	43	103
12	100	25	0	53	125
18	105	30	0	54	135
21	83	19	1	66	102
22	78	28	0	64	106
31	93	25	9	46	118
33	92	24	2	33	116
41	110	32	5	87	142
Mean	94	24	2	58	118
SD	11	5	3	17	14

VO_2 kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
4	2.19	0.75	19.08	36.05	0.12	119.98	23.42	0.87
7	1.49	0.53	18.66	22.54	0.04	108.26	24.30	0.57
8	1.52	0.45	20.39	28.46	0.06	160.42	23.10	0.51
15	2.29	0.53	15.67	40.89	0.33	106.10	35.00	0.87
17	1.46	0.36	8.03	18.60	0.17	93.80	66.14	0.53
20	2.12	0.48	19.48	36.31	0.13	129.89	26.39	0.60
23	1.20	0.38	21.64	23.59	0.06	112.58	14.87	0.44
24	1.59	0.40	22.30	21.05	0.08	106.28	18.39	0.47
28	1.93	0.40	22.26	22.90	0.18	90.54	77.00	0.58
30	1.86	0.53	18.70	28.40	0.21	132.20	56.41	0.74
39	1.08	0.24	13.45	24.60	0.13	94.10	32.50	0.37
Mean	1.70	0.46	18.15	27.58	0.14	114.01	36.14	0.60
SD	0.40	0.13	4.30	7.22	0.08	20.70	20.81	0.17

LVHIIT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
26	1.66	0.40	21.54	12.06	0.12	90.64	20.91	0.51
34	1.65	0.45	21.50	24.39	0.04	92.28	19.25	0.49
35	1.72	0.42	14.90	22.18	0.12	68.17	28.87	0.53
36	1.96	0.63	9.13	34.13	0.10	108.66	24.68	0.73
45	1.92	0.86	17.41	34.10	0.16	113.13	27.10	1.02
47	2.31	0.67	22.05	32.24	0.11	228.69	23.98	0.78
48	1.29	0.32	16.93	29.53	0.05	109.40	15.62	0.37
49	2.21	0.55	15.04	26.26	0.16	103.50	23.14	0.71
Mean	1.84	0.54	17.31	26.86	0.11	114.31	22.94	0.64
SD	0.33	0.18	4.41	7.45	0.04	48.45	4.28	0.21

CON DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
3	1.46	0.39	17.43	26.21	0.14	102.10	60.50	0.53
10	0.96	0.28	11.76	28.13	0.04	74.90	22.36	0.32
12	1.48	0.75	22.05	38.10	0.19	134.70	51.44	0.93
18	1.11	0.32	11.39	35.94	0.11	187.13	49.60	0.43
21	1.22	0.36	13.31	28.23	0.12	106.64	52.37	0.48
22	1.17	0.38	16.24	32.58	0.11	126.38	107.98	0.49
31	2.08	0.55	10.40	32.16	0.14	173.93	65.43	0.69
33	1.89	0.94	14.47	36.02	0.15	142.00	65.66	1.09
41	1.27	0.20	13.18	17.46	0.15	98.28	35.46	0.36
Mean	1.40	0.46	14.47	30.54	0.13	127.34	56.76	0.59
SD	0.37	0.24	3.64	6.37	0.04	36.53	23.79	0.26

VO_2 kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
4	1.99	0.73	19.10	35.85	0.10	120.00	22.70	0.83
7	1.47	0.48	19.00	27.87	0.15	117.49	33.84	0.62
8	1.38	0.38	18.65	26.40	0.05	142.10	21.36	0.43
15	2.15	0.73	8.56	36.03	0.05	97.29	11.15	0.78
17	1.16	0.15	11.70	35.11	0.15	81.70	15.00	0.30
20	2.07	0.42	17.28	28.49	0.09	110.78	19.25	0.51
23	1.20	0.30	16.87	30.25	0.05	96.14	17.29	0.35
24	1.72	0.27	12.30	20.27	0.13	63.31	23.53	0.40
28	1.57	0.73	19.20	26.33	0.19	108.40	56.87	0.92
30	1.81	0.63	23.35	25.54	0.20	123.75	23.50	0.84
39	1.10	0.25	28.01	12.19	0.12	72.72	25.34	0.38
Mean	1.60	0.46	17.64	27.67	0.12	103.06	24.53	0.58
SD	0.37	0.21	5.43	7.08	0.05	23.61	12.24	0.23

LVHIIT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
26	1.63	0.40	18.51	20.30	0.10	96.25	22.69	0.50
34	1.90	0.43	21.37	24.41	0.11	67.43	20.70	0.53
35	1.85	0.28	21.67	24.49	0.07	67.69	18.18	0.35
36	1.91	0.46	15.36	22.93	0.23	127.77	25.05	0.68
45	1.87	0.78	7.12	43.48	0.16	151.20	174.00	0.94
47	2.14	0.61	18.48	31.99	0.13	115.24	24.10	0.74
48	1.31	0.35	16.19	33.12	0.03	140.00	31.29	0.38
49	1.96	0.57	13.30	26.25	0.10	69.69	16.00	0.67
Mean	1.82	0.48	16.50	28.37	0.12	104.41	41.50	0.60
SD	0.25	0.16	4.75	7.50	0.06	34.03	53.74	0.20

CON DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
3	1.39	0.61	15.26	42.00	0.11	120.46	33.20	0.71
10	0.94	0.26	11.23	30.47	0.09	60.94	22.10	0.35
12	1.49	0.65	10.99	40.10	0.28	99.71	146.61	0.93
18	1.01	0.30	9.90	30.38	0.08	104.22	59.71	0.38
21	1.17	0.36	10.55	36.26	0.08	132.47	57.20	0.44
22	1.18	0.36	11.72	34.41	0.13	107.63	79.71	0.49
31	1.89	0.49	17.02	34.36	0.09	108.22	33.16	0.58
33	1.82	0.84	17.43	36.02	0.25	127.49	33.20	1.09
41	1.38	0.28	23.92	32.22	0.08	99.59	37.91	0.36
Mean	1.36	0.46	14.22	35.14	0.13	106.75	55.87	0.59
SD	0.33	0.20	4.62	4.00	0.08	20.88	38.45	0.27

VO_2 kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
4	2.07	0.85	17.79	28.28	0.13	137.07	23.18	0.97
7	1.35	0.50	24.36	20.67	0.10	108.65	21.76	0.60
8	1.37	0.42	11.52	26.32	0.10	111.33	40.16	0.51
15	2.22	0.71	14.54	36.50	0.08	136.48	7.86	0.79
17	1.19	0.20	14.70	36.52	0.05	72.13	8.30	0.25
20	1.87	0.42	8.33	24.26	0.06	115.00	13.04	0.47
23	1.15	0.40	20.72	20.74	0.06	115.27	13.61	0.46
24	1.48	0.44	20.96	28.39	0.12	99.02	35.57	0.55
28	1.45	0.73	17.13	31.00	0.16	105.60	82.30	0.89
30	1.84	0.48	22.50	21.30	0.23	109.70	23.18	0.71
39	1.03	0.38	23.15	26.20	0.10	89.61	32.41	0.47
Mean	1.55	0.50	17.79	27.29	0.11	109.08	27.40	0.61
SD	0.39	0.19	5.12	5.66	0.05	18.63	21.16	0.21

LVHIIT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
26	1.65	0.42	18.45	18.42	0.10	127.27	21.00	0.52
34	2.03	0.47	23.45	14.94	0.16	111.91	16.24	0.63
35	1.59	0.47	17.36	28.28	0.06	85.09	23.13	0.53
36	1.66	0.61	18.06	32.15	0.09	183.24	25.33	0.70
45	1.76	0.94	19.11	35.94	0.11	110.92	29.43	1.05
47	2.05	0.59	18.70	32.63	0.18	170.37	20.11	0.77
48	1.49	0.38	16.93	28.46	0.06	192.43	11.70	0.44
49	1.99	0.68	21.37	26.76	0.13	115.71	100.00	0.80
Mean	1.78	0.57	19.18	27.20	0.11	137.12	30.87	0.68
SD	0.22	0.18	2.19	7.18	0.04	39.42	28.45	0.20

CON DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
3	1.26	0.53	14.58	23.84	0.13	60.61	58.38	0.66
10	0.96	0.30	19.75	26.42	0.03	87.13	5.00	0.33
12	1.54	0.71	9.32	47.06	0.25	132.63	72.73	0.96
18	1.08	0.26	22.72	18.63	0.06	120.39	10.02	0.32
21	1.27	0.34	18.11	34.52	0.08	129.92	32.57	0.42
22	1.11	0.44	14.10	34.26	0.09	137.73	66.78	0.52
31	1.79	0.67	13.96	30.26	0.10	126.19	79.66	0.77
33	1.93	0.81	10.85	33.94	0.29	98.70	50.70	1.09
41	1.45	0.22	15.73	28.33	0.05	93.40	29.00	0.27
Mean	1.38	0.47	15.46	30.81	0.12	109.63	44.98	0.59
SD	0.33	0.21	4.21	8.08	0.09	26.01	27.13	0.30

VO_2 kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
4	1.97	0.83	17.47	28.29	0.10	127.23	23.38	0.92
7	1.35	0.49	21.62	30.36	0.15	106.71	57.71	0.64
8	1.34	0.42	12.80	28.29	0.06	126.95	63.68	0.47
15	2.22	0.98	6.01	35.86	0.07	96.78	34.20	1.05
17	1.18	0.30	6.20	36.10	0.05	120.81	48.96	0.35
20	1.98	0.49	17.72	32.10	0.03	120.00	57.50	0.52
23	1.15	0.55	6.70	28.18	0.09	122.88	55.52	0.64
24	1.48	0.40	25.73	14.63	0.15	96.79	39.41	0.55
28	1.34	0.69	18.97	26.29	0.12	145.62	19.02	0.81
30	1.75	0.71	23.24	36.03	0.16	140.20	77.40	0.87
39	1.13	0.32	16.32	22.50	0.13	89.40	39.85	0.45
Mean	1.53	0.56	15.71	28.97	0.10	117.58	46.97	0.66
SD	0.38	0.22	6.96	6.45	0.04	18.17	17.66	0.22

LVHIIT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
26	1.47	0.47	18.64	26.47	0.05	128.10	22.17	0.52
34	1.68	0.59	16.83	28.21	0.16	113.30	32.60	0.75
35	1.59	0.53	15.67	24.35	0.08	69.88	15.51	0.61
36	1.94	0.59	21.57	32.21	0.09	151.44	24.42	0.68
45	1.76	0.86	25.04	18.43	0.11	110.85	19.49	0.97
47	1.99	0.73	17.20	40.10	0.13	141.65	36.75	0.86
48	1.40	0.42	16.88	28.65	0.03	192.70	13.50	0.45
49	2.00	0.69	20.03	22.10	0.23	106.60	30.63	0.91
Mean	1.73	0.61	18.98	27.56	0.11	126.81	24.38	0.72
SD	0.23	0.14	3.11	6.60	0.06	36.36	8.33	0.19

CON DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
3	1.26	0.47	18.10	24.38	0.11	88.86	38.83	0.58
10	1.01	0.30	21.51	24.17	0.16	98.10	15.12	0.46
12	1.54	0.65	11.49	41.88	0.16	101.71	61.59	0.81
18	1.07	0.26	17.68	36.25	0.06	108.64	55.37	0.32
21	1.22	0.40	11.58	30.28	0.11	130.59	38.19	0.51
22	1.15	0.28	18.11	28.23	0.08	129.43	13.37	0.36
31	1.82	0.63	9.83	32.20	0.10	139.88	33.44	0.73
33	1.93	0.79	15.02	28.13	0.29	98.72	38.06	1.07
41	1.36	0.32	21.03	29.30	0.05	99.44	27.17	0.37
Mean	1.37	0.45	16.04	30.54	0.12	110.60	35.68	0.58
SD	0.33	0.19	4.28	5.65	0.07	17.99	16.12	0.25

VO_2 kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A
4	1.90	0.75	17.40	28.57	0.06	112.24	25.45	0.81
7	1.39	0.51	9.22	28.30	0.14	111.30	49.62	0.65
8	1.43	0.47	12.76	28.33	0.06	126.13	62.61	0.53
15	2.19	0.84	16.91	34.06	0.19	115.61	31.37	1.03
17	1.18	0.30	6.20	36.10	0.05	120.81	48.96	0.35
20	2.05	0.40	18.86	31.95	0.11	132.00	70.70	0.51
23	1.42	0.38	6.74	34.29	0.05	79.01	75.32	0.43
24	1.52	0.44	14.56	28.35	0.16	104.13	45.23	0.59
28	1.46	0.69	19.06	26.54	0.14	145.11	14.00	0.83
30	1.81	0.61	15.73	26.50	0.20	108.54	56.92	0.81
39	1.20	0.36	15.43	32.30	0.08	128.21	37.20	0.44
Mean	1.60	0.52	13.90	30.48	0.11	116.65	47.03	0.63
SD	0.34	0.18	4.61	3.37	0.06	17.25	19.01	0.21

LVHIIT DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
26	1.63	0.55	18.51	26.25	0.08	144.35	21.11	0.63
34	1.71	0.51	16.25	24.41	0.09	101.49	23.00	0.60
35	1.49	0.53	12.16	24.76	0.10	86.14	13.84	0.63
36	1.80	0.61	6.90	18.64	0.11	121.49	26.70	0.72
45	1.76	0.86	11.02	32.16	0.11	110.61	19.40	0.97
47	1.95	0.69	7.85	39.77	0.13	105.98	41.00	0.82
48	1.37	0.40	17.85	33.00	0.04	141.86	21.90	0.44
49	2.12	0.69	8.23	39.98	0.17	115.15	28.54	0.86
Mean	1.73	0.61	12.35	29.87	0.10	115.88	24.44	0.71
SD	0.24	0.14	4.66	7.66	0.04	19.77	8.05	0.17

CON DSP ID	Baseline	A1	TD1	Tau1	Amp2	TD2	Tau2	END A
3	1.35	0.53	18.60	30.22	0.16	127.65	40.69	0.69
10	1.06	0.30	15.81	30.38	0.11	94.10	57.95	0.40
12	1.49	0.69	13.82	36.14	0.17	101.34	60.77	0.86
18	1.02	0.32	17.12	32.30	0.03	96.33	54.71	0.35
21	1.22	0.32	17.92	31.95	0.08	136.80	38.30	0.40
22	1.19	0.38	8.77	36.24	0.10	99.17	31.91	0.48
31	1.87	0.65	12.78	24.34	0.07	106.11	53.86	0.72
33	1.92	0.86	17.41	34.10	0.16	113.13	27.10	1.02
41	1.29	0.36	15.10	40.13	0.06	114.10	30.82	0.42
Mean	1.38	0.49	15.26	32.87	0.10	109.86	44.01	0.59
SD	0.33	0.20	3.10	4.52	0.05	14.59	12.93	0.24

VO_2 mean response times during 'primed' heavy-intensity exercise initiated from an elevated baseline

MRT (s)					
MICT DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
4	52	68	48	44	42
7	60	62	52	54	54
8	65	44	42	42	42
15	80	34	49	44	47
17	54	41	43	35	57
20	72	72	44	36	51
23	63	47	40	55	36
24	61	26	44	70	54
28	83	55	65	54	64
30	82	70	92	67	65
39	36	23	26	34	42
Mean	64	49	50	49	50
SD	14	18	17	13	10

MRT (s)					
LVHIIT DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
26	70	54	70	47	46
34	55	38	26	43	50
35	38	48	78	46	38
36	57	112	41	49	39
45	61	54	64	64	46
47	42	69	64	80	69
48	60	47	49	48	43
49	38	36	48	60	58
Mean	53	57	55	55	49
SD	12	24	17	13	10

MRT (s)					
CON DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
3	52	33	30	36	58
10	30	38	32	35	51
12	78	82	80	82	72
18	54	23	46	38	30
21	52	72	72	71	56
22	83	69	70	80	68
31	102	67	68	68	28
33	77	70	70	70	72
41	96	60	30	31	42
Mean	69	57	55	57	53
SD	24	21	21	21	17

Muscle deoxygenation kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
4	183	76	4	30	10	144	24	87	34
7	-28	106	11	14	6	147	34	113	25
8	-18	14	11	31	0	248	199	14	41
15	255	22	9	8	6	126	15	29	17
20	189	18	15	20	4	234	21	22	35
24	180	30	6	16	2	99	17	33	22
28	92	29	16	13	4	102	11	34	29
30	-42	17	17	12	33	105	89	50	30
39	69	49	8	36	8	108	19	58	44
Mean	98	40	11	20	8	146	48	49	31
SD	110	32	5	10	10	57	62	32	9

LVHIIT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
34	446	33	7	16	3	57	9	36	23
35	412	55	8	14	6	51	7	62	23
36	9	72	16	32	29	122	44	101	48
45	-76	30	24	17	10	156	19	41	41
47	430	32	15	10	4	157	20	37	25
48	-36	16	1	12	0	152	63	17	14
49	67	31	14	22	8	72	25	39	36
Mean	179	39	12	18	9	110	27	47	30
SD	238	19	7	7	10	48	20	27	12

CON DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
3	67	24	2	30	2	57	21	27	32
12	73	94	10	26	12	129	21	107	36
21	15	18	9	24	11	105	49	28	33
22	-32	10	8	24	9	147	48	18	32
33	106	121	13	24	8	99	9	130	37
41	55	8	3	16	7	148	59	15	19
Mean	46	53	8	26	8	108	30	54	32
SD	54	51	4	3	4	34	18	52	2

Muscle deoxygenation kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
4	114	86	4	300	10	162	21	97	304
7	-6	130	15	18	6	144	21	137	33
8	-8	14	9	28	0	204	150	14	37
15	75	44	11	24	8	135	25	52	36
20	57	47	7	14	3	195	21	50	21
24	-49	47	8	24	8	114	23	56	32
28	210	99	7	12	10	141	21	110	19
30	69	103	3	42	18	126	89	122	44
39	75	57	8	30	20	150	50	78	38
Mean	60	70	8	24	9	151	47	79	63
SD	76	37	4	92	7	30	45	40	91

LVHIIT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
34	83	101	17	28	30	102	23	132	45
35	267	69	8	14	8	51	7	78	23
36	309	85	7	43	0	147	7	86	50
45	143	126	12	24	11	156	20	137	36
47	259	110	12	11	22	18	19	133	23
48	-18	8	5	11	25	95	17	34	16
49	189	40	5	14	1	96	25	41	19
Mean	176	77	9	21	14	95	17	91	30
SD	116	41	4	12	12	49	7	44	14

CON DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
3	166	30	9	30	4	81	21	35	39
12	89	70	10	18	2	136	22	73	28
21	18	17	7	14	13	132	56	30	21
22	-36	11	12	17	4	183	47	15	29
33	48	85	12	12	6	162	15	91	24
41	-3	7	8	14	1	52	13	8	22
Mean	57	43	10	18	6	139	32	42	27
SD	76	33	2	7	4	38	18	32	7

Muscle deoxygenation kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
4	-17	130	11	24	26	144	54	157	36
7	-10	128	11	18	2	147	62	131	30
8	50	26	1	26	7	136	55	34	27
15	6	46	15	40	6	94	43	52	55
20	101	50	5	27	6	141	23	56	32
24	122	53	5	26	4	108	23	58	31
28	160	76	6	20	9	156	25	86	26
30	82	64	16	30	21	156	39	86	46
39	87	73	11	30	9	81	50	82	41
Mean	65	72	9	27	8	127	41	82	36
SD	62	36	5	6	8	28	15	39	10

LVHIIT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
34	310	51	11	16	10	102	9	62	28
35	169	141	3	18	9	51	6	150	22
36	219	91	4	26	8	177	15	100	30
45	52	103	12	12	18	150	15	122	24
47	151	96	14	30	23	150	62	119	44
48	-23	4	32	18	4	140	54	9	50
49	-18	58	12	26	23	106	49	81	38
Mean	123	78	13	21	14	125	30	92	34
SD	125	44	9	6	7	42	24	46	11

CON DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
3	113	16	6	30	4	30	12	20	36
12	114	90	13	20	16	90	19	107	33
21	12	26	11	20	6	139	45	33	32
22	-20	6	2	20	1	137	8	8	22
33	78	150	4	24	19	114	19	170	28
41	11	8	9	7	3	67	15	10	16
Mean	59	58	7	23	9	102	21	58	28
SD	61	61	5	4	8	45	14	69	6

Muscle deoxygenation kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
4	16	125	12	14	44	84	66	170	26
7	-7	77	16	34	2	297	6	80	50
8	-45	26	6	36	5	148	55	32	42
15	-13	10	16	21	3	169	36	13	36
20	132	120	4	40	3	132	12	123	44
24	-19	69	9	22	3	128	29	72	31
28	150	123	6	24	16	129	93	139	30
30	28	93	13	40	20	144	54	113	52
39	43	68	3	22	3	103	21	71	25
Mean	32	79	9	30	7	156	41	90	37
SD	67	41	5	9	14	61	28	51	10

LVHIIT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
34	463	49	11	57	8	139	32	57	68
35	232	175	6	22	8	98	18	184	28
36	340	76	6	19	6	160	60	82	25
45	72	173	10	22	28	171	33	201	32
47	213	182	3	38	9	155	27	191	41
48	-41	4	12	12	4	156	90	9	24
49	87	50	10	38	3	60	5	53	47
Mean	195	101	8	30	10	134	38	111	38
SD	172	74	3	15	8	40	28	79	16

CON DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
3	50	22	6	16	5	47	15	27	22
12	75	99	12	14	4	123	39	103	26
21	-24	31	5	9	2	114	11	33	13
22	-39	9	13	32	12	132	77	21	45
33	84	111	8	20	29	154	56	140	27
41	11	8	9	7	3	67	15	10	16
Mean	29	54	9	18	11	114	40	56	25
SD	57	47	4	9	11	40	28	53	12

Muscle deoxygenation kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
4	70	95	12	26	30	112	74	126	38
7	8	56	14	32	10	138	18	67	46
8	-51	36	6	36	5	148	55	42	41
15	89	54	13	34	8	120	97	61	47
20	167	50	1	28	5	124	30	55	29
24	86	75	5	26	5	139	37	80	31
28	52	53	6	24	16	156	93	69	30
30	71	81	5	51	14	198	46	95	56
39	47	81	12	22	35	136	70	116	34
Mean	60	65	8	32	12	145	58	79	39
SD	60	19	5	9	11	25	28	28	9

LVHIIT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
34	294	77	11	18	4	114	44	82	29
35	100	115	5	20	11	60	22	127	25
36	220	97	5	26	3	122	42	101	31
45	-18	109	10	18	18	138	32	127	28
47	223	126	2	36	9	125	48	136	38
48	-45	9	12	18	4	148	60	13	30
49	70	41	9	30	9	92	73	50	39
Mean	121	82	8	24	9	114	46	91	31
SD	129	43	4	7	5	30	17	46	5

MICT DSP ID	Baseline	A1	TD1	Tau	Amp2	TD2	Tau2	END A	τ' [HHb + Mb]
3	85	19	1	14	13	70	34	32	16
12	124	97	4	16	0	49	19	97	21
21	-34	23	11	20	10	108	36	33	31
22	-15	7	11	20	14	153	72	21	31
33	-76	31	29	16	8	156	11	39	45
41	-26	6	18	9	1	98	8	7	28
Mean	17	35	11	17	9	107	35	38	29
SD	84	36	11	3	6	48	23	30	11

Muscle deoxygenation mean response times during 'primed' heavy-intensity exercise initiated from an elevated baseline

MRT (s)					
MICT DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
4	44	44	32	46	54
7	16	22	18	39	40
8	22	22	26	55	34
15	14	32	62	36	48
20	14	16	32	42	42
24	22	22	30	26	30
28	22	28	30	30	30
30	164	118	62	58	96
39	48	50	38	26	30
Mean	41	39	37	40	45
SD	48	32	15	12	21

MRT (s)					
LVHIIT DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
34	15	66	28	40	18
35	14	20	24	20	24
36	70	28	32	22	30
45	44	26	20	44	26
47	14	24	41	34	40
48	11	14	26	23	77
49	30	22	66	36	36
Mean	28	29	34	31	36
SD	22	17	16	10	20

MRT (s)					
CON DSP ID	Week 0	Week 3	Week 6	Week 9	Week 12
3	38	38	24	24	52
12	30	16	32	20	14
21	66	66	44	12	32
22	156	43	22	109	96
33	30	16	38	54	44
41	66	12	22	22	22
Mean	64	36	32	44	48
SD	54	21	9	40	31

Heart rate kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 0.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	120	29	5	102	149
7	116	27	6	167	143
8	125	35	0	77	160
15	157	17	3	79	174
17	137	17	34	150	154
20	153	23	11	79	176
23	120	27	4	86	147
24	155	17	2	80	172
28	147	25	5	112	172
30	132	20	5	13	152
39	132	15	1	100	147
Mean	136	23	7	95	159
SD	15	6	9	41	12

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	125	22	5	92	147
34	149	17	8	74	166
35	148	18	6	82	166
36	138	24	4	67	162
45	132	31	0	116	163
47	152	21	3	94	173
48	152	30	12	112	182
49	141	22	1	113	163
Mean	142	23	5	94	165
SD	10	5	4	19	10

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	128	19	9	100	147
10	125	25	0	93	150
12	139	25	1	61	164
18	145	14	17	55	159
21	134	20	6	46	154
22	132	28	1	70	160
31	159	21	5	67	180
33	129	27	5	67	156
41	139	27	2	126	166
Mean	137	23	5	76	160
SD	10	5	5	25	10

Heart rate kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 3.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	115	25	0	74	140
7	106	27	3	162	133
8	123	31	3	88	154
15	145	19	1	78	164
17	123	7	1	71	130
20	134	22	3	94	156
23	108	22	1	65	130
24	143	20	3	72	163
28	127	28	1	88	155
30	127	18	11	88	145
39	135	12	2	108	147
Mean	126	21	3	90	147
SD	13	7	3	27	13

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	123	24	0	92	147
34	147	16	12	95	163
35	138	20	7	96	158
36	128	25	0	89	153
45	131	27	0	105	158
47	129	24	0	102	153
48	154	24	1	75	178
49	132	23	2	80	154
Mean	135	23	3	92	158
SD	11	3	4	10	9

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	128	23	7	116	151
10	116	17	0	44	133
12	144	31	6	98	175
18	142	24	10	72	166
21	126	28	4	69	155
22	126	30	0	56	156
31	149	25	6	64	174
33	126	40	0	98	166
41	143	27	20	106	170
Mean	133	27	6	80	161
SD	11	6	6	25	14

Heart rate kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 6.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	103	31	0	60	133
7	108	21	2	161	129
8	125	35	0	81	160
15	145	14	11	71	159
17	124	12	0	60	136
20	129	17	3	65	146
23	100	22	0	42	121
24	154	21	11	131	175
28	120	25	1	88	145
30	131	20	7	89	151
39	119	13	7	91	132
Mean	123	21	4	85	144
SD	17	7	5	34	16

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	123	22	1	77	145
34	132	23	8	98	155
35	132	18	0	58	150
36	120	23	0	73	143
45	120	32	0	84	152
47	125	21	2	65	146
48	136	29	1	82	165
49	139	26	4	100	165
Mean	128	24	2	80	153
SD	7	5	3	15	9

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	123	21	1	96	144
10	116	15	1	60	131
12	130	37	7	93	167
18	143	21	2	80	164
21	137	12	7	53	149
22	135	31	0	69	166
31	149	24	7	56	173
33	133	32	11	96	165
41	152	2	9	106	154
Mean	135	22	5	79	157
SD	12	11	4	20	14

Heart rate kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 9.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	101	25	1	43	126
7	100	23	0	118	123
8	129	23	7	57	152
15	128	21	0	62	148
17	126	13	6	150	139
20	134	13	3	45	147
23	117	19	10	51	136
24	150	25	3	134	175
28	116	25	0	64	141
30	123	18	0	98	140
39	130	11	3	85	141
Mean	123	19	3	82	142
SD	14	5	3	38	14

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	123	23	0	91	146
34	133	25	0	75	159
35	129	20	7	60	149
36	124	24	2	90	148
45	128	26	2	61	154
47	140	17	4	98	157
48	142	22	21	58	164
49	128	26	2	84	153
Mean	131	23	5	77	154
SD	7	3	7	16	6

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	120	21	5	75	141
10	116	20	0	62	136
12	135	31	0	72	166
18	145	17	12	77	162
21	131	28	8	60	158
22	129	33	1	90	162
31	154	25	3	55	179
33	140	32	5	99	172
41	164	22	9	106	186
Mean	137	26	5	77	162
SD	16	6	4	18	16

Heart rate kinetics responses during 'primed' heavy-intensity exercise initiated from an elevated baseline at week 12.

MICT DSP ID	Baseline	A1	TD1	Tau	END A
4	118	21	3	73	139
7	97	23	0	105	119
8	119	29	1	57	148
15	131	19	0	65	150
17	122	13	2	103	135
20	133	16	2	55	149
23	112	17	5	51	129
24	150	22	1	115	172
28	116	26	1	57	142
30	120	15	1	56	134
39	130	11	7	106	141
Mean	123	19	2	77	142
SD	14	6	2	25	14

LVHIIT DSP ID	Baseline	A1	TD1	Tau	END A
26	118	19	0	65	137
34	124	21	10	84	145
35	128	20	5	68	148
36	118	20	2	80	138
45	128	26	2	61	154
47	142	19	0	100	161
48	142	25	0	100	167
49	120	30	0	120	150
Mean	128	22	2	85	150
SD	10	4	3	21	10

CON DSP ID	Baseline	A1	TD1	Tau	END A
3	122	21	1	116	143
10	106	19	8	65	124
12	151	21	4	75	173
18	141	22	4	51	163
21	108	22	0	75	130
22	121	4	0	75	125
31	141	31	5	49	173
33	132	29	3	89	161
41	153	28	17	103	181
Mean	131	22	5	78	152
SD	17	8	5	22	22

Appendix 7.7. Piloting data raw data.

Table 1. ***Participant characteristics***

Sex (m/f)	5/0
Age (yr)	26.2 (5.4)
Body mass (kg)	93.6 (27.2)
BMI (kg.m^{-2})	27.5 (5.7)
VO_{2max} (mL.kg^{-1}.min^{-1})	37.6 (4.1)

Data are mean (SD). BMI, body mass index; VO_{2max}, maximum oxygen uptake.

Table 2. ***VO_2 kinetics responses following priming exercise during moderate-intensity exercise during the piloting study***

	'Unprimed' (*n* = 5)	W-to-W 'primed'(*n* = 5)	50% Δ 'primed'(*n* = 5)
VO_2 Baseline (L.min^{-1})	1.0 (0.3)	1.1 (0.3)	1.0 (0.1)
A (L.min^{-1})	1.3 (0.2)	1.2 0.1)	1.4 (0.2)
TD (s)	13 (6)	14 (3)	19 (8)
τVO_{2P} (s)	31 (5)	23 (2)*	24 (4)*
End A (L.min^{-1})	2.3 (0.3)	2.3 (0.4)	2.3 (0.3)

Data are mean (SD). * signifies significantly different from 'unprimed' (P < 0.05). VO_2, oxygen uptake; A, amplitude; TD, time delay; τVO_{2P}, phase II time constant.

Table 3. ***VO_2 kinetics responses following priming exercise during heavy-intensity exercise during the piloting study.***

	'Unprimed' (*n* = 5)	**W-to-W 'primed'(*n* = 5)**	**50% Δ 'primed'(*n* = 5)**
VO_2 Baseline ($L.min^{-1}$)	1.8 (0.9)	2.4 (0.4)	2.3 (0.2)
A ($L.min^{-1}$)	0.8 (0.2)	0.8 (0.2)	0.9 (0.2)
TD (s)	19 (5)	17 (5)	15 (3)
τVO_{2P} (s)	28 (2)	30 (6)	29 (6)
VO_{2SC} A ($L.min^{-1}$)	0.32 (0.1)	0.2 (0.1)*	0.2 (0.1)*
VO_{2SC} TD (s)	134 (19)	135 (23)	138 (21)
End A ($L.min^{-1}$)	2.6 (0.9)	3.2 (0.6)	3.2 (0.5)

Data are mean (SD). * signifies significantly different from 'unprimed' ($P < 0.05$). VO_2, oxygen uptake; A, amplitude; TD, time delay; τVO_{2P}, phase II time constant, VO_{2SC}; slow component.

Participant characteristics

Participant	Sex	Age	Stature (m)	Body Mass (kg)	BMI (kg.m2)	Maximum (L/min)	Maximum (mL/kg/min)	Peak power output (W)
PSP 1	M	25.8	1.7	77.5	26.82	3.842	49.6	304.0
PSP 2	M	24.9	1.79	79.0	24.66	3.145	39.8	275.0
PSP 3	M	22.9	1.75	64.0	20.90	2.697	42.1	238.0
PSP 4	M	34.2	1.93	124.4	33.40	4.340	34.9	343.0
PSP 5	M	22.9	1.86	107.0	30.93	3.575	33.4	294.0
	Mean	26.2	1.83	93.6	27.5	3.4	37.6	288
	S.D.	5.4	0.08	27.2	5.7	0.7	4.1	44

VO_2 kinetics responses during moderate-intensity exercise following priming exercise.

ID	Condition	Baseline	A1	TD1	Tau	END A
PSP 1	Unprimed	0.93	1.50	23	24	2.42
PSP 2	Unprimed	0.88	1.28	10	35	2.16
PSP 3	Unprimed	0.82	1.11	14	32	1.93
PSP 4	Unprimed	1.51	1.14	9	33	2.65
PSP 5	Unprimed	0.88	1.26	10	28	2.24
Mean	Mean	1.00	1.26	13	31	2.28
SD	SD	0.29	0.15	6	5	0.27

ID	Condition	Baseline	A1	TD1	Tau	END A
PSP 1	Wtow Primed	1.07	1.39	12	23	2.46
PSP 2	Wtow Primed	0.91	1.23	14	25	2.15
PSP 3	Wtow Primed	0.74	1.07	20	26	1.81
PSP 4	Wtow Primed	1.63	1.15	14	22	2.78
PSP 5	Wtow Primed	0.94	1.30	12	20	2.24
Mean	Mean	1.06	1.23	14	23	2.29
SD	SD	0.34	0.12	3	2	0.36

ID	Condition	Baseline	A1	TD1	Tau	END A
PSP 1	Delta Primed	1.14	1.34	28	21	2.48
PSP 2	Delta Primed	0.94	1.30	25	26	2.24
PSP 3	Delta Primed	0.85	1.11	16	27	1.97
PSP 4	Delta Primed	0.85	1.77	11	25	2.63
PSP 5	Delta Primed	0.93	1.30	14	18	2.24
Mean	Mean	0.95	1.37	19	24	2.31
SD	SD	0.12	0.24	8	4	0.25

VO_2 kinetics responses during heavy-intensity exercise following priming exercise.

PSP ID	Condition	Baseline	A1	TD1	Tau	A2	TD2	End A
1	Unprimed	0.24	0.88	13	27	0.41	130	1.12
2	Unprimed	2.16	0.79	19	27	0.36	127	2.94
3	Unprimed	1.88	0.51	21	23	0.33	112	2.40
4	Unprimed	2.69	1.00	26	26	0.29	137	3.70
5	Unprimed	2.15	0.87	14	28	0.21	163	3.02
Mean	Mean	1.82	0.81	19	26	0.32	134	2.63
SD	SD	0.93	0.18	5	2	0.08	19	0.96

PSP ID	Condition	Baseline	A1	TD1	Tau	A2	TD2	End A
1	WtoW Primed	2.53	0.92	10	26	0.26	111	3.45
2	WtoW Primed	2.13	0.79	19	27	0.22	157	2.91
3	WtoW Primed	1.87	0.54	19	28	0.22	155	2.40
4	WtoW Primed	2.86	1.00	23	40	0.16	142	3.86
5	WtoW Primed	2.29	0.87	14	28	0.14	110	3.15
Mean	Mean	2.33	0.82	17	30	0.20	135	3.16
SD	SD	0.38	0.18	5	6	0.05	23	0.55

PSP ID	Condition	Baseline	A1	TD1	Tau	A2	TD2	End A
1	Delta Primed	2.45	1.12	14	28	0.20	130	3.57
2	Delta Primed	2.27	0.82	18	37	0.14	168	3.09
3	Delta Primed	2.02	0.47	14	23	0.17	116	2.49
4	Delta Primed	2.67	0.91	17	24	0.28	127	3.58
5	Delta Primed	2.28	0.94	11	34	0.18	151	3.23
Mean	Mean	2.34	0.85	15	29	0.19	138	3.19
SD	SD	0.24	0.24	3	6	0.05	21	0.45

Appendix 7.8. Ethical Approval Letter

Ethics and Medical Research Committee

ELM PARK, DUBLIN 4

Tel. (01) 2214117 Fax (01) 2214428

email: joan.mcdonnell@ucd.ie or jacinta.mcmanus@ucd.ie

2nd February, 2015.

Professor D. O'Shea,

Consultant Endocrinologist,

St. Vincent's University Hospital,

Elm Park,

Dublin 4.

Re: - The effect of age and sex on the time course and mechanisms of adaptation cardiovascular and metabolic health with exercise training in type 2 diabetes. Revised Standard Application Form vs 2 29/01/15 clean and track change. Local Checklist version 1 03/12/2014. Revised Protocol Version 2 29/01/15 clean and track changes. Revised PIL/Consent (Type 2 Diabetes) Version 2 29/01/15 clean and track changes. Questionnaires Version 1 03/12/2014. Advert (Type 2 Diabetes Participant). PIL/Consent (Healthy Volunteers). Advert (Healthy Volunteers). Three day Diary.

Dear Professor O'Shea,

We have received the revised documents from Ms. Norita Gildea which were requested at the Ethics and Medical Research Committee meeting held on Wednesday 7th January 2015 at which the above study was reviewed.

Following review of the revised documents, this study is now granted full ethical approval.

Yours sincerely,

Dr. E. McKone,

Chairman,

Ethics & Medical Research Committee

cc Ms Norita Gildea, Trinity College Dublin.