LIMITATIONS TO EXERCISE TOLERANCE IN TYPE 1 DIABETES: THE ROLE OF PULMONARY OXYGEN UPTAKE KINETICS AND PRIMING EXERCISE

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ABSTRACT

We compared the time constant ($\tau_{\dot{V}O2}$) of the fundamental phase of pulmonary oxygen uptake ($\dot{V}O_2$) kinetics between young adult males with type 1 diabetes and healthy controls. We also assessed the impact of priming exercise on $\tau_{\dot{V}O2}$, critical power, and muscle deoxygenation in a subset of participants with type 1 diabetes. 17 males with type 1 diabetes and 17 healthy male controls performed moderate-intensity exercise to determine $\tau_{\dot{V}O2}$. A subset of 7 participants with type 1 diabetes performed an additional eight visits, whereby critical power, $\tau_{\dot{V}O2}$ and muscle deoxyhaemoglobin + myoglobin ([HHb+Mb]; via near-infrared spectroscopy) kinetics (described by a time constant, $\tau_{[HHb+Mb]}$) were determined with (PRI) and without (CON) a prior 6-minute bout of heavy exercise. $\tau_{\dot{V}O2}$ was greater in participants with type 1 diabetes compared to controls (type 1 diabetes: 50±13 vs. control: 32±12 s; *P*<0.001). Critical power was greater in PRI compared to CON (PRI: 161±25 W vs. CON: 149±22 W; *P*<0.001), whereas $\tau_{\dot{V}O2}$ (PRI: 36±15 vs. CON: 50±21 s; *P*=0.006) and $\tau_{[HHb+Mb]}$ (PRI: 10±5 vs. CON: 17±11 s; *P*=0.037) were reduced in PRI compared to CON. Type 1 diabetes patients showed slower pulmonary $\dot{V}O_2$ kinetics when compared to controls; priming exercise speeded $\dot{V}O_2$ and [HHb + Mb] kinetics, and increased critical power in a subgroup with type 1 diabetes. These data therefore represent the first characterisation of the power-duration relationship in type 1 diabetes, and the first experimental evidence that $\tau_{\dot{V}O2}$ is an independent determinant of critical power in this population.

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KEYWORDS: Type 1 diabetes, exercise tolerance, oxygen uptake kinetics, critical power, priming exercise, oxidative metabolism, near-infrared spectroscopy, muscle deoxygenation kinetics

List of abbreviations:

1/T, linear power-inverse of time model; ANOVA, analysis of variance; $A_{\dot{V}O_2}$, amplitude of the fundamental oxygen uptake response; $A_{[HHb+Mb]}$, amplitude of the muscle [deoxyhaemoglobin + deoxymyoglobin] response; BMI, body mass index; CON, control; Cr, creatine; GET, gas exchange threshold; [HbO_2 + MbO_2], [oxyhaemoglobin + oxymyoglobin]; [HHb + Mb], [deoxygenated haemoglobin + myoglobin]; [L^-], blood [lactate]; MRT, mean response time; NIRS, near-infrared spectroscopy; PA-R, physical activity rating scale; PCr, phosphocreatine; PFA, perceived functional ability; PRI, priming condition; P-T, hyperbolic power-time model; SD, standard deviation; $TD_{[HHb + Mb]}$, time delay before the onset of the rise in muscle [deoxyhaemoglobin + deoxymyoglobin]; $TD_{S\dot{C}V_{O2}}$, time delay before the onset of the oxygen uptake slow component; [THb + Mb], [total haemoglobin + myoglobin]; $\dot{V}O_2$, oxygen uptake; $\dot{V}O_{2\,(b)}$, baseline oxygen uptake; WR1-WR4, constant work rate trials used to determine critical power and *W'*; W-T, linear work-time model; $\tau_{[HHb+Mb]}$, time constant for the increase in muscle [deoxyhaemoglobin + deoxymyoglobin] kinetics; $\tau_{\dot{V}\,O2}$, time constant for the fundamental phase of oxygen uptake kinetics

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68 **NEW & NOTEWORTHY**

69 Patients with type 1 diabetes demonstrated slower $\dot{V}O_2$ kinetics when compared to healthy
70 controls. Furthermore, a prior bout of high-intensity exercise speeded $\dot{V}O_2$ kinetics and
71 increased critical power in people with type 1 diabetes. Prior exercise speeded muscle
72 deoxygenation kinetics, indicating that $\dot{V}O_2$ kinetics in type 1 diabetes are limited primarily
73 by oxygen extraction and/or intracellular factors. These findings highlight the potential for
74 interventions that decrease metabolic inertia for enhancing exercise tolerance in this
75 condition.

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INTRODUCTION

People with type 1 diabetes have an elevated risk of cardiovascular disease and shorter life expectancy (46, 69). Consequently, individuals with type 1 diabetes are recommended to engage in regular exercise (16), which reduces cardiovascular disease risk via improvements in glycaemic control, blood lipid profile and endothelial function (14). However, there is evidence that exercise tolerance is impaired in individuals with type 1 diabetes (34–36, 44, 45, 60, 64), which is itself a barrier to exercise training (10) as well as a potent predictor of cardiovascular and overall mortality (55). Despite the importance of regular exercise in the management of type 1 diabetes, the mechanism(s) of impaired exercise tolerance observed in this population remains unknown.

The capacity to tolerate high-intensity exercise is described by a hyperbolic function of external power output, defined by two parameters: critical power and *W'*(40, 51, 52, 62). Critical power represents the asymptote of this relationship, whereas *W'* is a finite work capacity available above critical power (40, 51, 52, 62). Critical power corresponds to the highest work rate that can be sustained without progressive contributions from non-oxidative metabolism (2, 15), and is thus fundamental to exercise tolerance. Despite the importance of critical power in determining exercise tolerance, its physiological antecedents have previously remained poorly understood. However, data from our laboratory has shown in healthy individuals that critical power, and by extension exercise tolerance, is determined by the rate of increase in pulmonary oxygen uptake ($\dot{V}O_2$, a proxy for muscle $\dot{V}O_2$ kinetics, 26) at the onset of exercise (24–28), specifically the fundamental phase time constant ($\tau_{\dot{V}O2}$).

Despite the importance of $\dot{V}O_2$ kinetics in determining exercise tolerance (24–27), their high prognostic value (63), and the finding that exercise tolerance may be impaired in

type 1 diabetes (34–36, 44, 45, 60, 64), no previous study has assessed $\dot{V}O_2$ kinetics and/or critical power in adults with type 1 diabetes. The first hypothesis of the present study was therefore that $\dot{V}O_2$ kinetics would be slower in individuals with type 1 diabetes compared to a group of healthy controls similar for age- and physical activity status.

Slowed $\dot{V}O_2$ kinetics are typically due to derangements in O_2 delivery and/or O_2 utilisation (65). Consequently, a prior bout of heavy-intensity priming exercise (i.e. a bout of exercise below critical power but above the lactate threshold performed prior to subsequent exercise), which improves O_2 delivery and intracellular O_2 utilisation during subsequent exercise (22, 31, 32, 39), has been demonstrated to speed $\dot{V}O_2$ kinetics in healthy individuals with slow $\dot{V}O_2$ kinetics but without type 1 diabetes (8, 33, 66). Given the potential for slowed $\dot{V}O_2$ kinetics in individuals with type 1 diabetes, as implied by their poor exercise tolerance, priming exercise may speed the $\dot{V}O_2$ kinetics (i.e. reduce $\tau_{\dot{V}O2}$) and increase critical power in this population. Therefore, the second hypothesis of the present study was that priming exercise would speed pulmonary $\dot{V}O_2$ kinetics and increase critical power in individuals with type 1 diabetes. In both cases, muscle deoxygenation was non-invasively assessed via continuous interrogation of the exercising muscle via near-infrared spectroscopy (NIRS) to assess the relative importance of O_2 supply and demand in determining $\dot{V}O_2$kinetics.

METHODS

Ethical approval

This study was conducted in two parts. Part 1 compared pulmonary $\dot{V}O_2$ kinetics between a group of recreationally active males with type 1 diabetes with a group of controls similar in age- and physical activity status. Part 2 investigated the influence of priming exercise on

pulmonary $\dot{V}O_2$ kinetics and critical power in a subgroup of males with type 1 diabetes. Both studies were conducted according to the Declaration of Helsinki and all procedures were approved by the National Health Services Research Ethics Committee. All participants provided written informed consent to participate in this study.

Participants

In Part 1, 17 males with type 1 diabetes and 17 healthy males without type 1 diabetes similar for age, BMI and level of physical activity (Table 1) gave written informed consent to take part. Participants with type 1 diabetes were free from any diabetes complications and were not taking any medications other than insulin. No participant in either group smoked. Participants with type 1 diabetes were recruited from the diabetes outpatient clinics at the Royal Liverpool and Broadgreen University Hospitals NHS Trust. Control participants were recruited from the university and general populations. Part 2 used a subgroup of 7 males with type 1 diabetes that participated in Part 1. For the type 1 diabetes group, the following exclusion criteria were employed: 1) history of stroke, congestive heart failure, hypertension, or cardiopulmonary disease, 2) current smoking or smoking within the last 12 months, 3) autonomic or distal neuropathy, 4) HbA1c > 9.0%, 5) hypoglycaemia unawareness or 6) taking any medications other than insulin.

Pre-exercise safety procedures

Exercise only commenced when blood glucose concentrations were between 7-12 mmol.L^{-1} (mg/100mL) (57). When pre-exercise blood glucose concentrations were >12 mmol.L^{-1}, testing was either abandoned or delayed until blood glucose concentration was between 7-12 mmol.L^{-1}. When pre-exercise blood glucose concentration was <7 mmol.L^{-1}, participants ingested ~30 g simple carbohydrates to bring blood glucose levels back to within the desired

range before exercise commenced (57). Dextrose tablets were freely available throughout testing in the case of a precipitous drop in blood glucose concentration. In addition, participants were told to make pre-exercise adjustments to their insulin dosing regimen in line their usual practice and current guidelines (57).

General experimental procedures.

Participants visited the laboratory on 2 (Part 1) or 10 (Part 2) separate occasions over a 2-8-week period. Each test was scheduled at the same time of day (±2 h) with at least 24 h separating visits. Participants were instructed to avoid alcohol and strenuous exercise within the 24 h preceding each exercise test and not to consume caffeine within the preceding 6 h. Prior to Visit 1, each participant completed the Physical Activity Rating Scale (PA-R) and a Perceived Functional Ability (PFA) questionnaire (23). Participants were also asked to record their 24 h dietary intake and were asked to replicate this in the 24 h preceding each subsequent visit. Testing was conducted in a well-ventilated laboratory maintained between 18-21^{o}C. All exercise tests were performed on an electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands). Saddle height/angle and handlebar height/angle were recorded at the first test and replicated for subsequent visits. During the first trial, participants were instructed to cycle at a self-selected cadence between 70-90 rev/min (which was recorded and replicated in each subsequent visit). Strong verbal encouragement was provided during all exhaustive tests. Task failure was defined as the point at which cadence dropped below 50 rev/min and was recorded to the nearest second.

Experimental procedures – Part 1

Participants visited the laboratory on two separate occasions during Part 1. Height and weight were recorded upon arrival to the laboratory in Visit 1. Participants then undertook an

178 incremental ramp test until the limit of tolerance to establish $\dot{V}O_2$ peak, gas exchange
179 threshold (GET, a non-invasive estimate of the lactate threshold), and the power output for
180 the subsequent visit. The exercise test consisted of 3-minutes of baseline pedalling at 30 W,
181 followed by a continuous, ramped increase in work rate of either 20 (*n* = 5 for both groups)
182 or 25 $W.min^{-1}$ (*n* = 12 for both groups) until task failure. Selection of the ramp rate for each
183 individual participant was made based on the participant's physical characteristics and self-
184 reported physical activity levels. Ventilatory and gas exchange variables were measured
185 continuously breath-by-breath throughout each test. $\dot{V}O_2$ peak was defined as the final 30 s
186 average value recorded during the test. The GET was estimated via visual procedures as
187 previously described (24). The mean response time (MRT) for $\dot{V}O_2$ was defined as the time
188 between the beginning of the ramp test and intersection between baseline $\dot{V}O_2$ (average
189 $\dot{V}O_2$ measured during last 30 s of baseline; $\dot{V}O_{2b}$) and backwards extrapolation of the $\dot{V}O_2$-
190 time relationship (7). The MRT was then utilised to calculate the power output equivalent to
191 a given $\dot{V}O_2$ for all subsequent visits (including Part 2). Capillary blood samples were obtained
192 at rest, immediately prior to the onset of the ramp test (i.e. final 30 s of baseline pedalling),
193 and immediately following exhaustion. Capillary blood samples were analysed for blood
194 glucose concentration using a portable analyser (Accutrend Plus, Roche Diagnostics,
195 Switzerland) and blood lactate concentration ($[L^-]$) was determined using a Biosen lactate
196 analyser (Biosen C-Line, EKF, Germany).

197 In Visit 2, participants performed 3 minutes of baseline pedalling at 20 W immediately
198 before undertaking four successive 6-minute bouts of moderate-intensity exercise (i.e. below
199 the GET) at a work rate corresponding to 70% GET, each separated by 10 minutes of pedalling

at 20 W. Capillary blood samples were obtained at rest, and 30 seconds prior to each transition to 70% GET.

Experimental procedures – Part 2.

Part 2 featured eight additional visits for 7 participants with type 1 diabetes who took part in Part 1. During these visits participants were required to exercise to task failure at four fixed severe-intensity (i.e. above critical power) power outputs on two separate occasions. The goal of this range of power outputs was to produce exercise tolerance times between 2-15 minutes. These power outputs are subsequently referred to as WR1, WR2, WR3, and WR4, with WR1 being the lower and WR4 being the highest power outputs, respectively. Each exercise intensity was performed once with priming exercise (PRI) and once without priming exercise (CON). CON consisted of 3 minutes of baseline pedalling at 20 W, after which a rapid (<1 s) step increase to the required power output was abruptly applied, and participants exercised until task failure. In PRI, participants performed 3 minutes of baseline pedalling at 20 W before a rapid step increase to a power output of 20%Δ (i.e. [20% of the difference between GET and $\dot{V}O_2$ peak] + GET) for 6 minutes. Upon completion of this priming bout of exercise, participants rested for 7 minutes, before performing a further 3 minutes of baseline pedalling at 20 W (providing 10 minutes rest between priming and the subsequent constant work rate bouts) and subsequently, a rapid step increase to the required power output was applied until task failure was reached. For both CON and PRI, blood glucose and [L^-] samples were obtained at rest, during the last minute of baseline pedalling preceding the exhaustive constant work rate bout, and immediately following task failure.

***Measurements*.**

Participants wore a silicone face mask (Hans Rudolph, Kansas, United States) with a flow sensor (Geratherm Respiratory, GmbH, Germany), which was attached in turn via a capillary line to a metabolic cart (Blue Cherry, Geratherm Respiratory, GmbH, Germany) that was used to measure pulmonary gas exchange and ventilation breath-by-breath throughout all tests. Gases of known concentration were used to calibrate gas analysers, and a 3-liter syringe (Hans Rudolph, Kansas City, MO) was used to calibrate flow sensors.

During each test, continuous non-invasive measurements of muscle oxygenation/deoxygenation status were made via a frequency-domain multi-distance NIRS system (Oxiplex TS, ISS, Champaign, USA) with light-source detector separation distances of 2.25 – 3.75 cm. This NIRS device provides absolute measures of underlying tissue deoxygenated ([HHb + Mb]), oxygenated ([HbO_2 + MbO_2]) and total ([THb + Mb]) haemoglobin + myoglobin concentration. The flexible NIRS probe was held firmly in place longitudinally along the belly of the right *vastus lateralis* muscle midway between the greater trochanter and the lateral condyle of the tibia. The NIRS probe was calibrated prior to each testing session using a calibration block of known absorption and scattering coefficients. Calibration was then cross-checked using a second block of known but distinctly different absorption and scattering coefficients. To account for the influence of adipose tissue thickness on the NIRS signal, we employed a previously employed correction factor (9, 17) to facilitate between-group comparisons. Adipose tissue thickness was measured using skinfold callipers (Harpenden Skinfold Caliper, Baty International, UK).

Data analysis.

The breath-by-breath $\dot{V}O_2$ data from each exercise bout were examined to exclude errant breaths >4 standard deviations (SD) from the local 5-breath mean. Edited $\dot{V}O_2$ data were then

linearly interpolated to provide second-by-second values. The $\dot{V}O_2$ and [HHb + Mb] data from the four moderate transitions (Part 1) and the four bouts of heavy priming exercise (Part 2) were then time-aligned and ensemble averaged to produce a single dataset. The severe-intensity criterion bouts for the determination of critical power and W' in each condition were not repeated, hence the $\dot{V}O_2$ and [HHb + Mb] data from each of these were modelled independently (Part 2). The following monoexponential model with time delay (Eq. 1) was then used to fit the $\dot{V}O_2$ and [HHb + Mb] data:

$$Y_{(t)} = Y_{(b)} + A_Y * (1 - e^{-(t - TD/\tau)}) \quad (1)$$

Where $Y_{(t)}$ is the value of the independent variable at time t, $Y_{(b)}$ is the baseline value measured over the final 30 seconds of baseline pedalling, A_Y is the amplitude of increase in Y above baseline, TD is the time delay and τ is the time constant of the response.

For $\dot{V}O_2$, the first 20 s of data (i.e. representative of the "cardiodynamic" phase) were removed before modelling. During moderate exercise, data from the entirety of the 6-minute exercise bout were modelled. For heavy and severe exercise, a $\dot{V}O_2$ slow component occurs which delays the onset of a steady-state, and if not accounted for obscures the precise modelling of the fundamental phase of $\dot{V}O_2$ kinetics. Therefore, during the modelling process the fundamental phase was isolated from the time of onset of the $\dot{V}O_2$ slow component ($TD_{S\dot{C}V_{O2}}$). This was achieved by progressively increasing the fitting window in 1-s increments to end-exercise and observing the modelled value of $\tau_{\dot{V}O2}$ and χ^2 each time. The time point at which a departure from "flatness" in the plot of $\tau_{\dot{V}O2}$ and/or χ^2 versus time occurred was taken as $TD_{S\dot{C}V_{O2}}$, thus providing the fitting window for defining the values of the fundamental phase parameters. The amplitude of the $\dot{V}O_2$ slow component was

268 determined by calculating the difference between the end exercise $\dot{V}O_2$ (i.e. mean $\dot{V}O_2$ over
269 final 30 s of exercise) and $A_{\dot{V}_{O_2}}$+$\dot{V}O_{2\,(b)}$. The functional gain of the fundamental $\dot{V}O_2$ response
270 was also calculated by dividing $A_{\dot{V}_{O_2}}$ by the change in work rate (i.e. $A_{\dot{V}_{O_2}}$/Δ work rate).

271 For [HHb + Mb], data preceding the time point at which the [HHb + Mb] signal
272 increased above 1 SD of the pre-transition baseline value were removed. On occasions where
273 [HHb + Mb] decreased after exercise onset, data preceding the first point showing a sustained
274 increase in [HHb + Mb] were removed from the modelling process. Although [HHb + Mb] data
275 were modelled with TD allowed to vary freely such that the fit could be optimised, the point
276 at which [HHb + Mb] began to increase is presented as $TD_{[HHb\ +\ Mb]}$ this is the more
277 physiologically relevant parameter. For [HHb + Mb] during moderate exercise, the model
278 fitting window was constrained to 120 seconds. For [HHb + Mb] during heavy and severe
279 exercise, the model fitting window was constrained to $TD_{S\dot{C}V_{O_2}}$. The amplitude of the [HHb
280 + Mb] slow component was calculated by subtracting the average value of [HHb + Mb] during
281 the final 30 s of exercise from the absolute [HHb + Mb] response (i.e. $[HHb + Mb]_{(b)} + A_{[HHb+Mb]}$).

282 The mean values for [HbO_2 + MbO_2] and [THb + Mb] were determined at baseline (30 s
283 preceding each transition), at 30 s and 120 s into the exercise transition (15 s bin centred on
284 30 and 120 s), and at end exercise (final 30 s) to facilitate comparisons between conditions.
285 These particular time points were chosen to allow comparisons between conditions early in
286 the transition during the phase II increase in $\dot{V}O_2$ before the onset of the $\dot{V}O_2$ slow
287 component and after the $\dot{V}O_2$ slow component had developed fully (i.e. at task failure).

288 In Part 2, critical power and W' were estimated from the time-to-task-failure and
289 power data using three models: the hyperbolic power-time (P-T) model (Equation 4); the
290 linear work-time (W-T) model, where the total work done is plotted against time (Equation

291 5); and the linear inverse-of-time (1/T) model (Equation 6), where power output is plotted
292 against the inverse of time:

293 (3) $P = W' / T + CP$

294 (4) $W = CP * T + W'$

295 (5) $P = W' * (1/T) + CP$

296 The standard errors of the estimates (SEE) associated with CP and W' were expressed as a
297 coefficient of variation (CV) relative to the parameter estimate. The model with the lowest
298 average CV across conditions for each individual was then used for all subsequent analyses.

299 ***Statistical analyses***.

300 In Part 1, descriptive variables, data from the ramp incremental test and kinetic parameters
301 were compared between groups using independent samples *t*-tests. Differences in [HbO_2 +
302 Mb] and [THb + Mb] between groups were compared via a mixed model ANOVA. In Part 2,
303 two-way (condition * work rate) analyses of variance (ANOVA) were used to compare
304 differences in all kinetic parameters (i.e. $\dot{V}O_2$ and [HHb + Mb]); whereas three-way (condition
305 * work rate * time) ANOVAs were used to compare differences in blood [L^-], [glucose], [HbO_2
306 + MbO_2], and [THb + Mb]. Bonferroni-corrected pairwise comparisons were used to locate
307 any significant main or interaction effects. Student's paired *t* tests were used to compare
308 differences in critical power and W' between conditions. All data are presented as mean ± SD
309 unless otherwise stated. For clarity, and to highlight values for parameters measured across
310 all four severe-intensity work rates, the overall mean across work rates ± SD is presented in
311 text, with work rate-specific mean ± SD presented in tables. All statistical analyses were
312 performed in SPSS (IBM, New York, USA). Statistical significance was accepted at $p < 0.05$.

313 **RESULTS**

314 ***Part 1.***

315 The groups did not differ for any descriptive, anthropometric, or physical activity-related
316 variable (Table 1, all $p > 0.05$). $\dot{V}O_2$ peak relative to body mass (type 1 diabetes: 36.4 ± 4.7,
317 controls: 41.4 ± 8.7 $ml.kg^{-1}.min^{-1}$, $p = 0.045$), the peak power attained during the ramp test
318 normalised for body mass (type 1 diabetes: 3.3 ± 0.4, controls: 3.7 ± 0.7 $W.kg^{-1}$, $p = 0.038$),
319 and the GET relative to body mass (type 1 diabetes: 19 ± 2, controls: 22 ± 3 $ml.kg^{-1}.min^{-1}$, $p =$
320 0.022) were lower in the type 1 diabetes group when compared to the control group (Table
321 1).

322 Parameters of the $\dot{V}O_2$ kinetics are presented in Table 2, whereas the group mean
323 $\dot{V}O_2$ responses are depicted in Figure 1. $\tau_{\dot{V}O2}$ was greater in the type 1 diabetes group
324 compared to the controls (type 1 diabetes: 50 ± 13 s, controls: 32 ± 12 s, $p < 0.001$). There
325 were no differences with respect to any other parameter of the $\dot{V}O_2$ kinetics (Table 2).

326 The parameters of the [HHb + Mb] kinetics are presented in Table 3, whereas the
327 group mean [HHb + Mb] responses are depicted in Figure 2. $\tau_{[HHb+Mb]}$ was greater (type 1
328 diabetes: 22 ± 15, controls: 12 ± 6 seconds, $p = 0.017$) whereas $TD_{[HHb+Mb]}$ was shorter in the
329 group with type 1 diabetes when compared to the controls (type 1 diabetes: 10 ± 4, controls:
330 17 ± 5 seconds, $p < 0.001$). No other parameter of the [HHb + Mb] kinetics differed between
331 groups (Table 3). There were no differences between groups with respect to [HbO_2 + Mb] and
332 [THb + Mb] (all comparisons $p > 0.05$).

333 ***Part 2.***

Participant characteristics from Part 2 are reported in Table 1. Priming exercise was conducted at an average intensity of 111 ± 25 W (19 ± 12 %Δ), and resulted in an elevated blood [L^-] immediately prior to the exhaustive constant work rate trials when compared to CON (CON = 1.63 ± 0.32 vs. PRI = 4.18 ± 1.19 mmol.L^{-1}, p = 0.001) with no differences in end-exercise blood [L^-] (CON = 11.8 ± 2.5 vs. PRI = 11.6 ± 2.4 mmol.L^{-1}, p = 0.576). $\tau_{\dot{V}O2}$ determined from the four ensemble-averaged heavy intensity bouts of priming exercise was 51 ± 14 seconds.

For each participant, the $\dot{V}O_2$ peak obtained in the incremental tests did not differ from that obtained in the constant work rate trials by more than 3%, confirming true attainment of $\dot{V}O_2$ max (61; Figure 3). The group mean $\dot{V}O_2$ responses to severe exercise at a representative work rate in each condition are presented in Figure 4. $\tau_{\dot{V}O2}$ was smaller in PRI compared to CON (CON = 50 ± 21 vs. PRI = 36 ± 15 seconds, p = 0.006), however there were no differences between conditions for any other parameters of the $\dot{V}O_2$ kinetics (Table 4).

Individual fit optimisation resulted in the W-T model being used for 5 participants, the 1/T model being used for 1 participant, and the hyperbolic P-T model for 1 participant. Critical power was greater in PRI when compared to CON (CON = 149 ± 22 W, CV = 2 ± 1% *vs.* PRI = 161 ± 25 W, CV = 2 ± 1%; p < 0.001, Figure 5), whereas W' was reduced in PRI compared to CON (CON = 16.5 ± 5.2 kJ, CV = 6 ± 3 % *vs.* PRI = 13.6 ± 3.5 kJ, CV = 7 ± 2 %; p = 0.024).

The group mean [HHb + Mb] responses to exercise at a representative work rate in each condition are depicted in Figure 6. $\tau_{[HHb+Mb]}$ was reduced in PRI compared to CON (CON: 17 ± 11 s vs. PRI: 10 ± 5; p = 0.037), however there were no other differences with respect to any

parameters of the [HHb + Mb] kinetics. [HbO_2 + MbO_2] and [THb + Mb] did not differ significantly between conditions (both $p > 0.05$).

DISCUSSION

This study demonstrates that type 1 diabetes is characterised by a marked slowing of $\dot{V}O_2$ kinetics, compared to healthy individuals similar in age and physical activity status. These findings are important because we have previously shown $\dot{V}O_2$ kinetics to be a central determinant of critical power, and thus exercise tolerance, which in turn is strongly related to prognosis and clinical outcomes (63). In addition to impairments to $\dot{V}O_2$ peak and the GET that have been demonstrated previously (34–36, 44, 45, 60, 64) therefore, these data suggest that slow $\dot{V}O_2$ kinetics are contributory to impaired exercise tolerance in type 1 diabetes. Moreover, and consistent with our hypotheses, we also found that "priming" exercise resulted in faster $\dot{V}O_2$ kinetics and a greater critical power when compared to the control condition. These data therefore represent the first characterisation of the power-duration relationship in type 1 diabetes, and the first experimental evidence that $\tau_{\dot{V}O2}$ is an independent determinant of critical power in this population.

Central to the interpretation of the data in Part 1 the present study is the degree to which the two groups were matched for possible confounding variables, such as age, physical activity status, and BMI. In this respect, it was endeavoured to match the participants for these variables between groups on an individual basis, and the averages for age, BMI, and physical activity were not different between the groups (Table 1). Furthermore, the recruitment of participants with any history of comorbidities and complications, cardiovascular or otherwise, was specifically avoided. Collectively, these precautions permit high confidence that the differences observed between groups are primarily attributable to

379 the presence or absence of type 1 diabetes, rather than the presence of comorbidities,
380 reduced physical activity status or differences in age.

381 ***Oxygen uptake kinetics and exercise tolerance***

382 Aerobic fitness is an important determinant of cardiovascular risk (1), and
383 cardiovascular risk is already substantially higher in individuals with type 1 diabetes compared
384 to individuals without diabetes (46). The findings from Part 1 are therefore clinically relevant
385 to individuals living with type 1 diabetes, suggesting that interventions aimed at mitigating
386 cardiovascular risk and improving life expectancy in type 1 diabetes necessitate a strong focus
387 on improvement of aerobic fitness. The $\tau_{\dot{V}O2}$ value observed in the type 1 diabetes group was
388 ~50 seconds, a value that is similar to that previously reported in healthy older adults with a
389 mean age of 69 years (13). These findings concur with the numerical (although non-
390 significant) slowing of $\dot{V}O_2$ kinetics reported by Nadeau et al. (56) in youth with type 1
391 diabetes. Thus, the present findings demonstrate that type 1 diabetes results in an
392 impairment in $\dot{V}O_2$ kinetics that is equivalent to >30 years of ageing, a finding that broadly
393 supports the recent suggestion that type 1 diabetes may be considered as a condition of
394 accelerated muscle ageing (49).

395 The present study (Part 2) also shows that a bout of heavy-intensity priming exercise
396 speeded $\dot{V}O_2$ kinetics (i.e. reduced $\tau_{\dot{V}O2}$) with a concomitant increase in critical power of
397 ~8% compared to the control condition. These data thus add to the growing body of evidence
398 (24–28) that $\tau_{\dot{V}O2}$ and critical power are causally related. The putative explanation given for
399 this inverse, causal relationship between $\tau_{\dot{V}O2}$ and critical power is that critical power
400 represents the highest work rate for which the accumulation of the O_2 deficit may be
401 stabilised, and thus a metabolic steady-state attained (53, 65). $\tau_{\dot{V}O2}$ determines the size of

the O_2 deficit (71, 72), thus a faster $\dot{V}O_2$ response will minimise reliance on substrate level phosphorylation, in turn reducing muscle metabolic perturbation (e.g. reduced Δ[PCr], Δ[Cr], Δ[ADP], Δ[ATP]) and fatigue-related metabolite accumulation during the rest-to-exercise transition (72). The resultant effect is an increase in the highest work rate that can be attained for a given magnitude of O_2 deficit accumulation, otherwise known as critical power. Since critical power is fundamental to the capacity to tolerate exercise, the increased $\tau_{\dot{V}O2}$ in type 1 diabetes demonstrated in part 1 therefore likely underpins the impaired exercise tolerance in this population (present study; 38, 64).

Data derived from NIRS showed that the group with type 1 diabetes demonstrated a shorter $TD_{[HHb+Mb]}$ and greater $\tau_{[HHb+Mb]}$, as compared to health controls (Part 1). Given the slower $\dot{V}O_2$ kinetics observed in the type 1 diabetes group, the shorter $TD_{[HHb+Mb]}$ is likely representative of an impairment in muscle O_2 availability during the early phase (i.e. 10-20 s) of exercise. This interpretation is supported by the observation of substantially impaired muscle O_2 delivery during contractions in rats with diabetes (6, 42, 67), and blunted exercise-induced rises in blood volume in humans with type 1 diabetes (38). On the other hand, the greater $\tau_{[HHb+Mb]}$ in the type 1 diabetes group likely indicates impairments to the capacity to increase intracellular O_2 utilisation (i.e. muscle $\dot{V}O_2$) to an extent that is proportionally more important than any reduction in O_2 delivery. Hence, the data obtained via NIRS from Part 1 suggest that derangements in both muscle O_2 delivery and utilisation underpin the slow $\dot{V}O_2$ kinetics observed in individuals with type 1 diabetes, as compared to healthy controls.

Priming exercise has the capacity to enhance both muscle O_2 delivery and utilization at the onset of exercise (22, 32, 39). In Part 2, the effect of priming exercise on critical power could therefore have been via an independent effect of enhanced O_2 availability, rather than

a reduced $\tau_{\dot{V}O2}$ per se (28). However, the reduction in $\tau_{[HHb+Mb}$ (i.e. muscle deoxygenation kinetics were speeded) afforded by priming exercise, alongside an unchanged $TD_{[HHb+Mb]}$, indicates that the salutary effect of priming exercise on $\dot{V}O_2$ kinetics and critical power were due more so to an upregulation of intracellular O_2 utilisation as compared to any enhancements to O_2 delivery. This interpretation is bolstered by the observation that in our type 1 diabetes population neither [THb + Mb] or [HbO_2 + MbO_2] were improved immediately before or during exercise following priming exercise. Indeed, the augmentation of the intracellular determinants of $\dot{V}O_2$ following priming exercise is well documented (22, 32, 39), and the notion that $\dot{V}O_2$ kinetics are primarily limited by intracellular oxidative metabolic inertia in type 1 diabetes is supported by several lines of evidence. For instance, biopsy data indicate that young, active individuals with type 1 diabetes demonstrate ultrastructural alterations in mitochondria that impair mitochondrial bioenergetics and reduce mitochondrial capacity despite no loss of muscle capillary density (38, 48–50), findings which are largely supported by magnetic resonance spectroscopy studies of oxidative metabolism in this population (18, 19, 41). These findings are in stark contrast to other clinical conditions such as heart failure (68), type II diabetes (5), and peripheral arterial disease (4) where $\dot{V}O_2$ kinetics are limited due to impaired O_2 delivery. In type 1 diabetes, therefore, our data strongly suggest that $\dot{V}O_2$ kinetics, and in turn critical power and exercise tolerance, are primarily limited by impaired intracellular (i.e. mitochondrial) utilisation of O_2, rather than due to O_2 delivery impairments . Furthermore, these derangements to cellular metabolism can, at least partially, be reversed via a prior bout of priming exercise, presumably via an upregulation of enzyme activation at potentially limiting sites within the oxidative respiratory chain such as the pyruvate dehydrogenase complex (31, 32).

448 ***Limitations***

449 Our data suggest that in type 1 diabetes, impairments to O_2 utilisation are the primary
450 limiting factor to $\dot{V}O_2$ kinetics, and by extension exercise tolerance. However, our findings do
451 point towards impaired O_2 delivery (as indicated by the reduced $TD_{[HHb+Mb]}$) being contributory
452 in the exercise intolerance observed in type 1 diabetes. Central measures of O_2 availability
453 (i.e. cardiac output, heart rate, etc.) were not included in the present study, therefore a role
454 for impaired central O_2 delivery also cannot be excluded. However, NIRS primarily monitors
455 changes in the oxygenation status of the microvasculature (i.e. at the sites of gas exchange)
456 and is thus likely to more closely represent the factors limiting skeletal muscle respiration in
457 the interrogated region when compared to central measures of O_2 delivery (3, 20, 21, 30).
458 However, our NIRS measurements were conducted at a single, superficial site on the *vastus*
459 *lateralis*, yet skeletal muscle deoxygenation (43), blood flow (37) and metabolism (11) are
460 spatially and temporally heterogeneous during exercise. Moreover, the reductions in the
461 number of capillaries supporting flow and red blood cell flux in animal models of both type 1
462 (42, 67) and type 2 diabetes (58) would predict a more heterogeneous distribution of
463 perfusion and wide range of O_2 delivery-to-$\dot{V}O_2$ ratios across the exercising muscle mass. This
464 latter suggestion is supported by the notion that alterations in the endothelial glycocalyx in
465 diabetes may result in heterogeneous microvascular perfusion (47). Hence, although we have
466 concluded that enhancements to intracellular metabolism were primarily responsible for the
467 faster $\dot{V}O_2$ kinetics observed following priming in the present study, it is possible that this
468 was not the case in other, unmeasured muscular regions. Indeed a more heterogeneous
469 matching of blood flow-to-$\dot{V}O_2$ could independently account for the reduced $TD_{[HHb + Mb]}$
470 observed in the type 1 diabetes patients examined herein. Furthermore, a limitation of the

present study is that only males were studied. Female participants were excluded from the present study due to concerns that the relatively greater adiposity in females compared to males with type 1 diabetes (70) would blunt the NIRS signal. Indeed, it has recently been demonstrated that the effect of type 1 diabetes on mitochondrial bioenergetics is dependent upon sex (36). Future research should therefore determine whether females with type 1 diabetes also exhibit similar impairments in key parameters of aerobic metabolism.

Significance

Since critical power fundamentally underpins the capacity to tolerate exercise, our findings in type 1 diabetes of impaired $\tau_{\dot{V}O2}$ and causative relationship between $\tau_{\dot{V}O2}$ and critical power have important implications for the development of interventions to enhance aerobic fitness in this patient group. Indeed, our finding of impairments in each of the most important parameters of aerobic function, (i.e. $\dot{V}O_2$ peak, GET, $\tau_{\dot{V}O2}$ & critical power) in type 1 diabetes supports recent suggestions that the current physical activity recommendations (16) may be insufficient to offset the deleterious effects of this disorder on aerobic function (50). An increased volume of physical activity/exercise training may therefore be required to prevent the pernicious effects of type 1 diabetes on various components of the oxidative respiratory chain, in particular the intracellular O_2 utilisation pathways. Moreover, our data suggest that interventions that can specifically improve the speed of the $\dot{V}O_2$ kinetics will enhance exercise tolerance in this population. Since exercise tolerance is a potent predictor of cardiovascular risk and all-cause mortality in type 1 diabetes (12, 54, 55, 59), we may assume that improving $\tau_{\dot{V}O2}$ via interventions that augment intracellular O_2 utilisation and O_2 extraction would be an effective therapeutic target.

Conclusions.

494 This study demonstrated impaired exercise tolerance and aerobic function in a group of
495 physically active males with type 1 diabetes in moderate glycaemic control without micro- or
496 macrovascular disease complications when compared to a group of healthy controls similar
497 for age- and physical activity-status. This is the first assessment of $\dot{V}O_2$ kinetics in adults with
498 type 1 diabetes, and we demonstrate a profound slowing of the $\dot{V}O_2$ kinetics (i.e. increased
499 $\tau_{\dot{V}O2}$) in the type 1 diabetes group relative to the control group. The injurious effects of type
500 1 diabetes on the aerobic phenotype noted herein are likely to contribute to the burden
501 associated with the disease and its secondary complications. Furthermore, given the reduced
502 $\tau_{\dot{V}O2}$ and concomitant increase in critical power following priming exercise in Part 2, the
503 present data identifies for the first time the increased $\tau_{\dot{V}O2}$ as being causative for the exercise
504 intolerance inherent in type 1 diabetes. The slow [HHb + Mb] kinetics in type 1 diabetes (Part
505 1) and subsequent speeding with priming exercise (Part 2), strongly suggest that the
506 impairments to $\dot{V}O_2$ kinetics and exercise tolerance in type 1 diabetes are due primarily to
507 derangements in intracellular oxidative metabolism and/or O_2 extraction, rather than O_2
508 delivery. These findings highlight $\tau_{\dot{V}O2}$ as a therapeutic target for interventions aimed at
509 improving exercise tolerance and cardiovascular risk, most pertinently via repairs to
510 intracellular metabolism and muscle O_2 extraction.

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515 **DATA AVAILABILITY**

516 Data are available upon request from the authors.

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DUALITY OF INTEREST

The authors declare that there is no duality of interest associated with this manuscript.

CONTRIBUTION STATEMENT

RPG, SM, DMR and PJW conceived and designed the project, RPG collected and analysed the data, RPG, SM, DMR, PJW, SNS and SK interpreted the data. RPG drafted the manuscript and all authors revised it critically. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All people designated as authors qualify for authorship, and all those who qualify for authorship are listed. RPG is the guarantor for the work and/or conduct of the study, had full access to all the data in the study and takes responsibility for the integrity of data and the accuracy of the data analysis, and controlled the decision to publish.

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FIGURE LEGENDS

Figure 1. Parameters of the $\dot{V}O_2$ kinetics for moderate-intensity exercise (70% gas exchange threshold) in Part 1. Type 1 diabetes group (T1D) shown as clear circles; control group (CON) shown as black circles. Panel A: Individual data showing the oxygen uptake kinetics fundamental phase time constant values ($\tau_{\dot{V}O2}$) for each participant in both groups. Solid black line represents the group mean. * indicates significant difference between groups ($P < 0.001$). Panel B: Group mean $\dot{V}O_2$ responses to moderate exercise, with group mean $\tau_{\dot{V}O2}$ values displayed. Error bars removed for clarity.

Figure 2. Parameters of the muscle [HHb + Mb] kinetics for moderate exercise in Part 1. Type 1 diabetes group shown as clear circles; control group shown as black circles, dashed vertical line represents onset of exercise. Panel A: Group mean [HHb + Mb] responses to moderate exercise. Panel B: Group mean [HHb + Mb] responses during the first 30 seconds of exercise. $TD_{[HHb+Mb]}$ values were significantly different between groups ($P < 0.001$). Panel C: Group mean [HHb + Mb] responses to moderate exercise, normalised as a percentage of the amplitude of the response, with $\tau_{[HHb+Mb]}$ values displayed. $\tau_{[HHb+Mb]}$ values were significantly different between groups ($P = 0.017$).

Figure 3. $\dot{V}O_2$ responses to the incremental ramp test (black circles) in a representative participant, and $\dot{V}O_2$ peak values attained during the constant work rate trials used for determination of critical power in CON (clear circles) and PRI (black triangles). Black square represents $\dot{V}O_2$ value attained during the final 30 s of heavy-intensity priming exercise. Dashed vertical lines indicate the boundaries partitioning exercise intensity domains, i.e. the gas exchange threshold (GET) and critical power (CP) in both CON and PRI.

Horizontal dashed lines represent the $\dot{V}O_2$ peak value attained during ramp incremental exercise ± 3%. Note that the $\dot{V}O_2$ peak values attained during ramp and constant work rate exercise differ by less than 3% in all cases, confirming attainment of a true $\dot{V}O_2$ max in all trials. Redrawn from Poole & Jones (61) using data from the present study.

Figure 4. Group mean $\dot{V}O_2$ responses to WR 1 during the rest-to-exercise transition (panel A) in the control condition (black squares) and the primed condition (clear triangles) in Part 2, normalised as a percentage of their fundamental phase amplitude. Exponential model fits are displayed as thick grey lines. Panel B displays the same data, however the final data point represents the average time to exhaustion in each condition.

Figure 5. Critical power measured in the control (CON) and primed (PRI) conditions in Part 2. Group mean ± SD (n = 7) are shown as open bars, and individual participant changes are shown as dashed black lines. * indicates significant difference between conditions ($P < 0.001$).

Figure 6. Group mean [HHb + Mb] kinetic responses to WR 1 during the rest-to-exercise transition in the control condition (black squares) and the primed condition in Part 2 (clear triangles), normalised as a percentage of the fundamental phase amplitude. Exponential model fits are displayed as thick grey lines.

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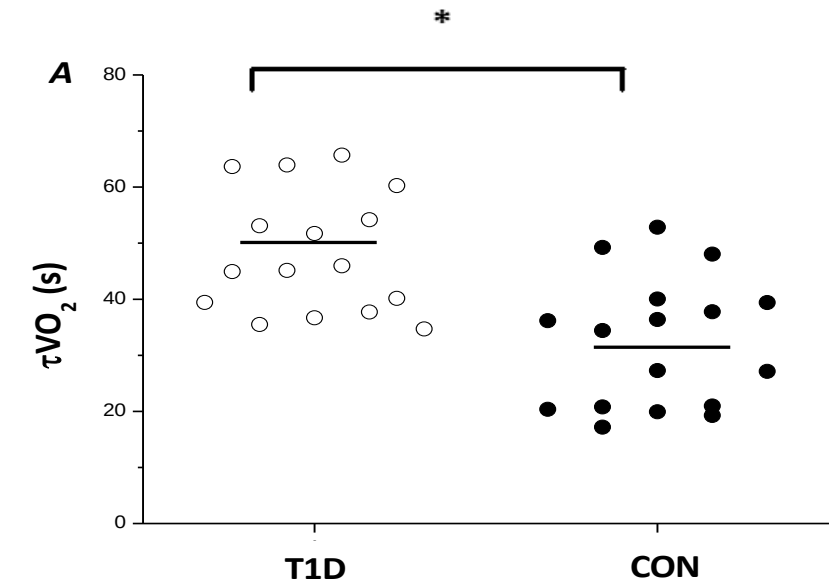
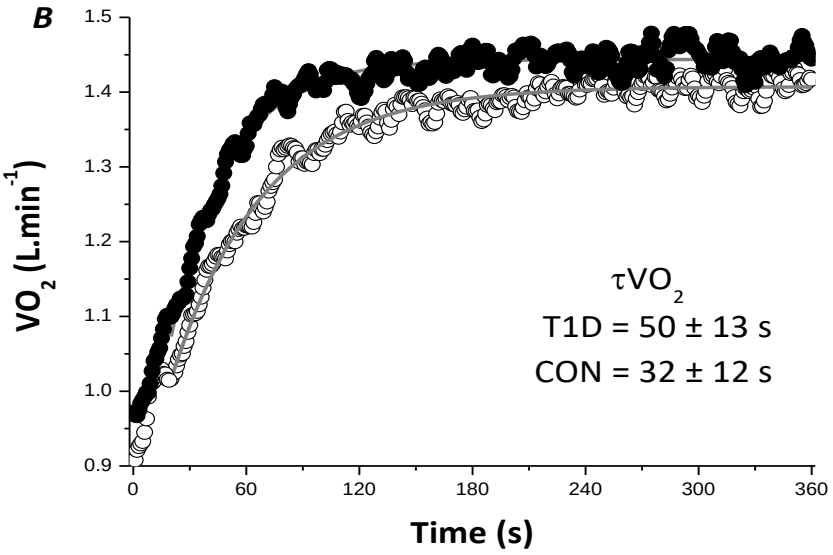
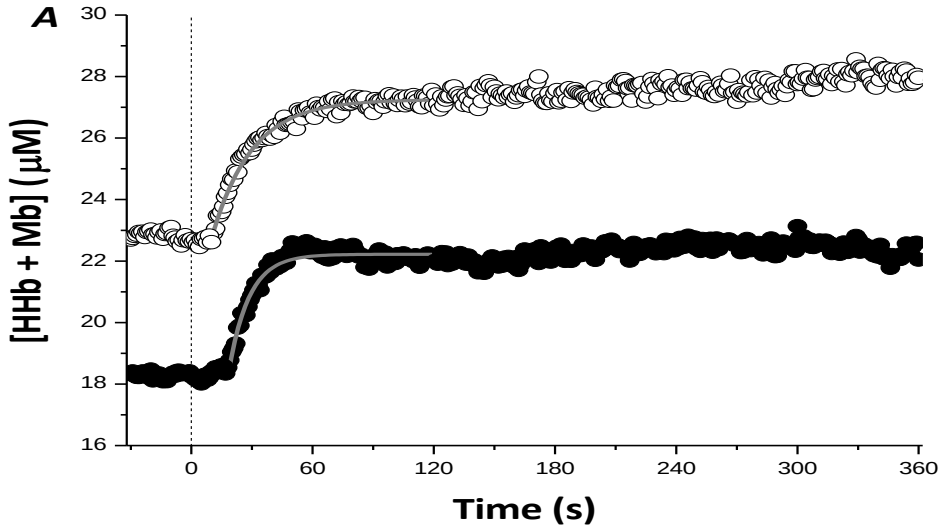
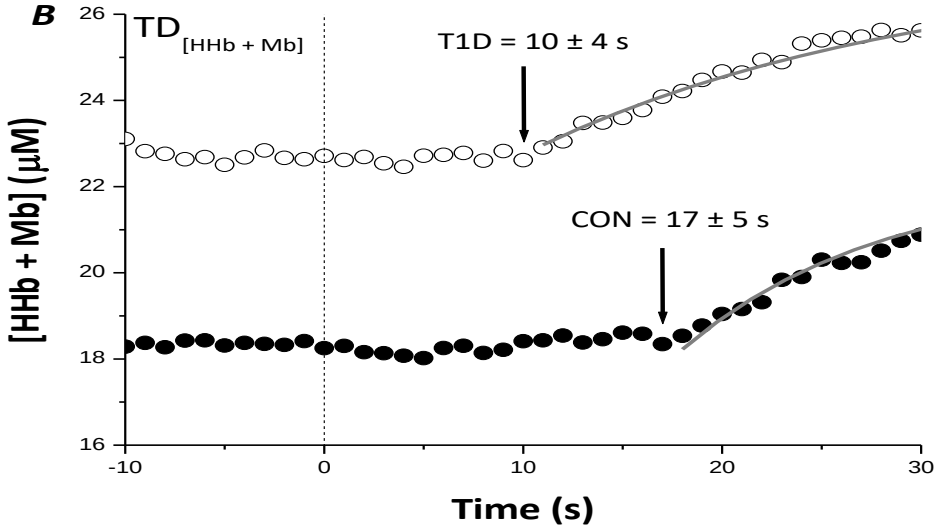
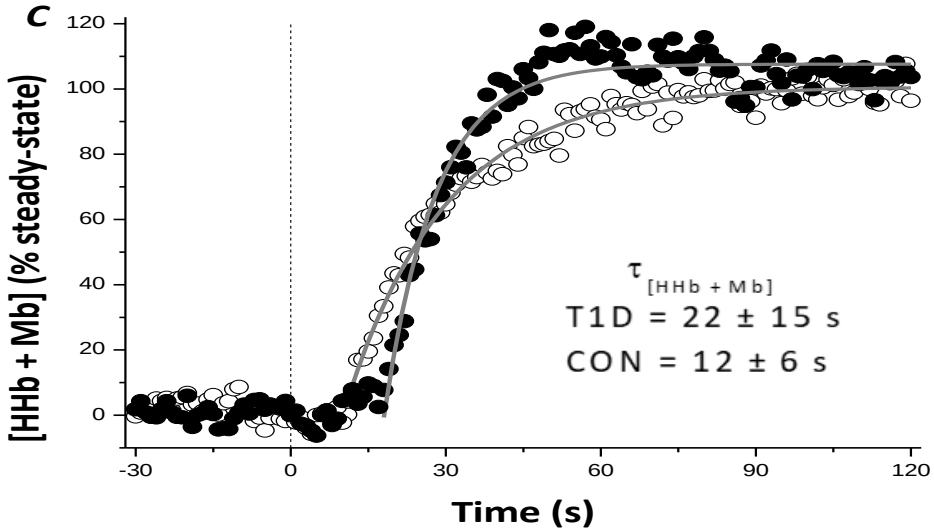
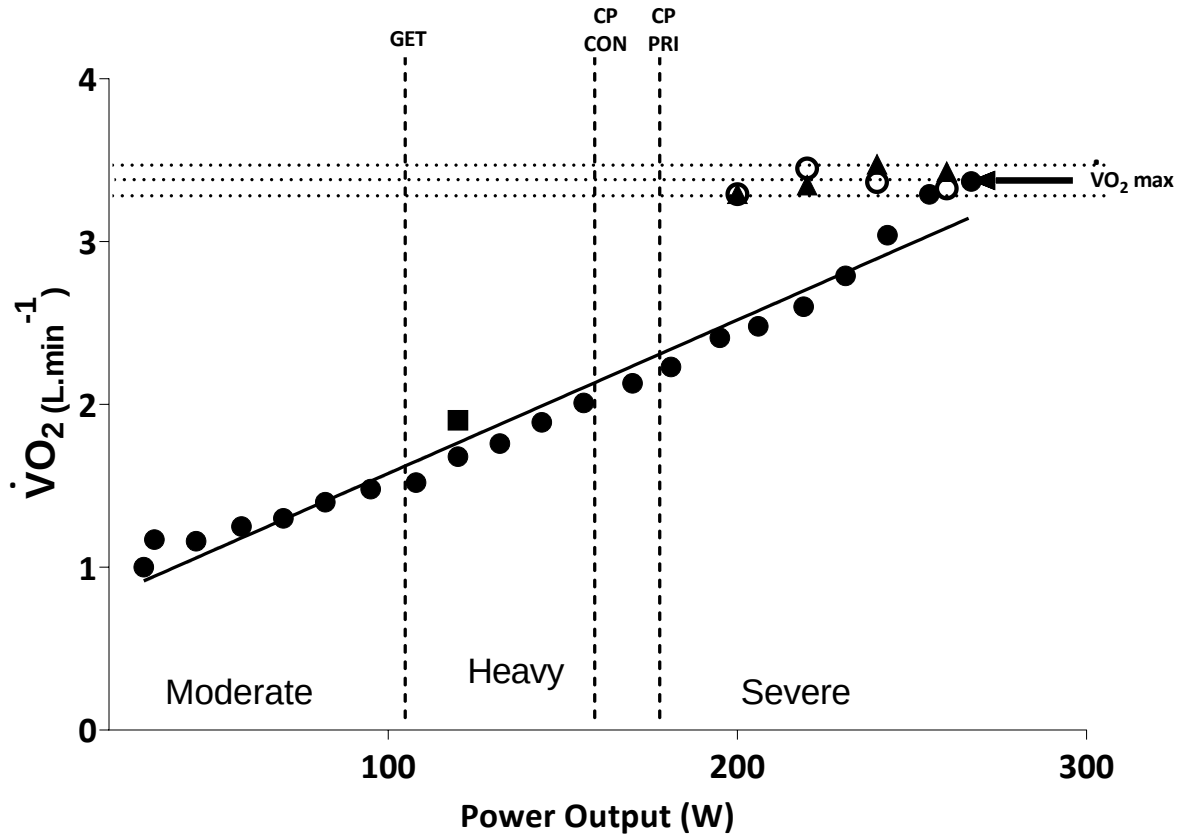

*
A
80
60
40
20
0
τVO2 (s)
T1D
CON

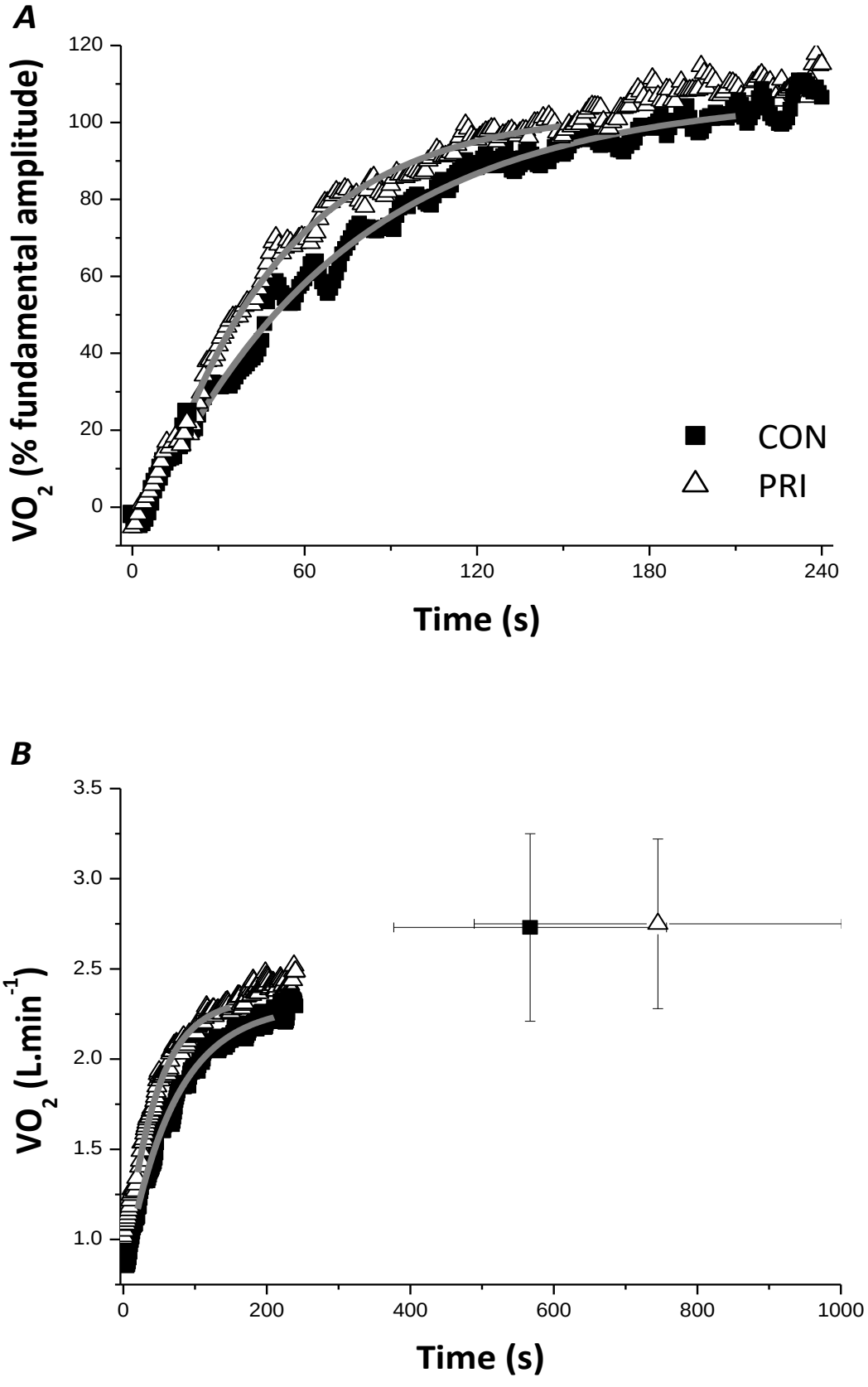

B
1.5
1.4
1.3
1.2
1.1
1.0
0.9
VO2 (L.min-1)
0
60
120
180
240
300
360
Time (s)
τVO2
T1D = 50 ± 13 s
CON = 32 ± 12 s

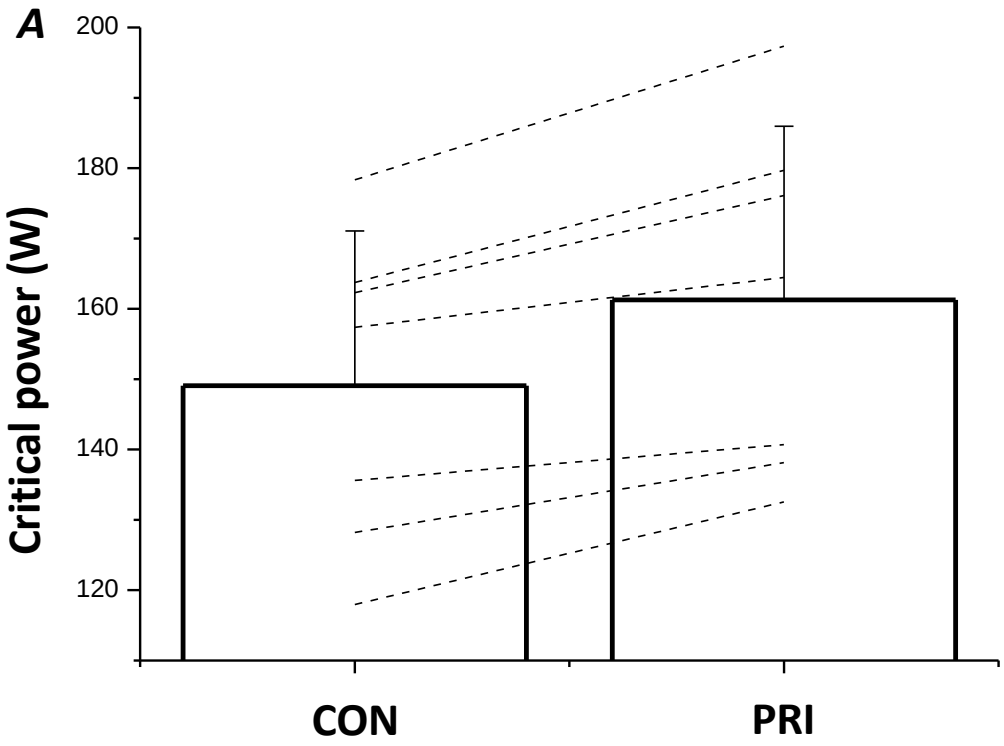

A
[HHb + Mb] (µM)
Time (s)


B
TD [HHb + Mb]
T1D = 10 ± 4 s
CON = 17 ± 5 s
[HHb + Mb] (µM)
Time (s)


C
τ [HHb + Mb]
T1D = 22 ± 15 s
CON = 12 ± 6 s
[HHb + Mb] (% steady-state)
Time (s)


GET
CP
CON
CP
PRI
4
3
2
1
0
$\dot{V}O_2$ (L.min^{-1})
$\dot{V}O_2$ max
Moderate
Heavy
Severe
100
200
300
Power Output (W)


A
VO2 (% fundamental amplitude)
120
100
80
60
40
20
0
0
60
120
180
240
Time (s)
CON
PRI
B
VO2 (L.min-1)
3.5
3.0
2.5
2.0
1.5
1.0
0
200
400
600
800
1000
Time (s)


A
200
180
160
140
120
Critical power (W)
CON
PRI

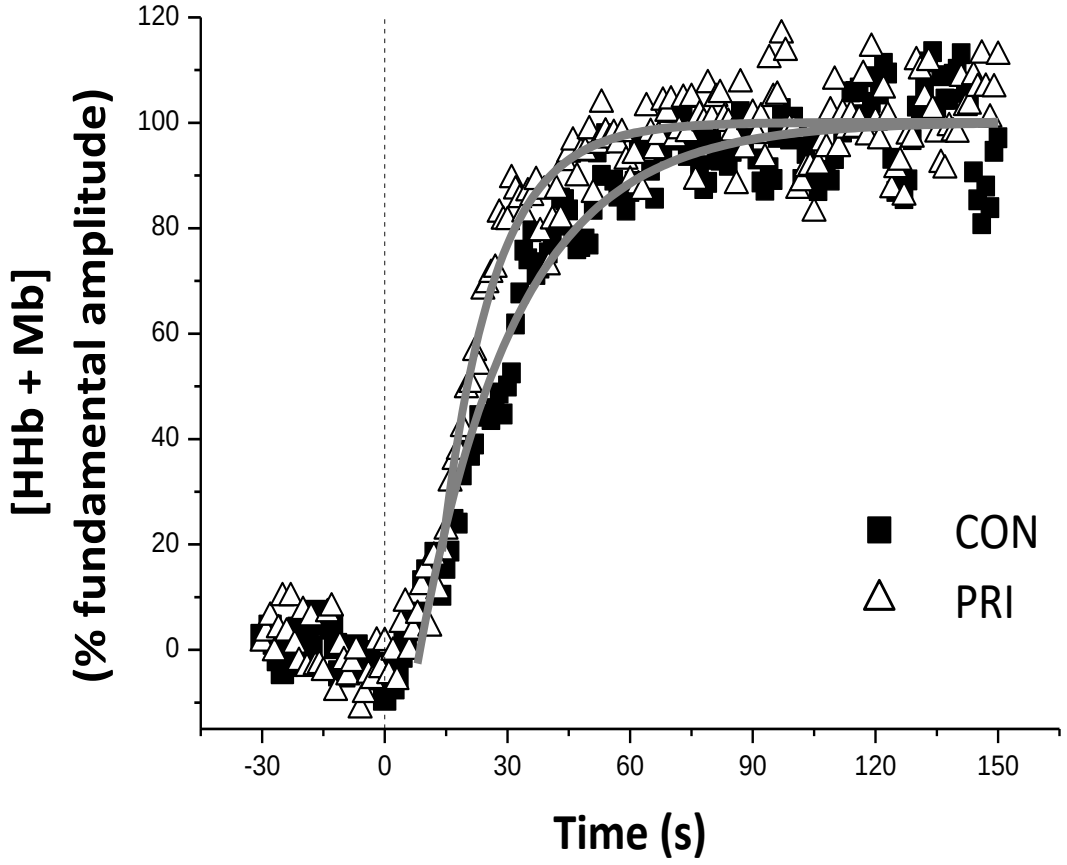

[HHb + Mb]
(% fundamental amplitude)
120
100
80
60
40
20
0
-30
0
30
60
90
120
150
Time (s)
CON
PRI

Table 1. Participant characteristics.

	Part 1		Part 2
Characteristic	Control (*n* = 17)	Type 1 diabetes (*n* = 17)	Type 1 diabetes (*n* = 7)
Age (years)	33 ± 15	33 ± 13	39 ± 17
Weight (kg)	79 ± 15	78 ± 11	81 ± 8
Height (cm)	181 ± 5	178 ± 6	179 ± 6
BMI (kg/m^2)	24.1 ± 4.1	24.7 ± 2.9	25.1 ± 2.5
HbA_{1c} (mmol/mol)	-	56.6 ± 10.2	56.5 ± 7.7
HbA_{1c} (%)	-	7.3 ± 0.9	7.3 ± 0.7
Diabetes duration (years)	-	15 ± 13	14 ± 17
Diabetes diagnosis (years of age)	-	18 ± 8	25 ± 10
Physical activity rating scale score	5.1 ± 1.5	5.2 ± 2.0	5.1 ± 2.0
Perceived functional ability score	15.7 ± 5.4	15.8 ± 4.1	15.7 ± 3.0
Light physical activity (h/week)	1.0 ± 1.5	1.3 ± 0.9	1.4 ± 0.9
Moderate physical activity (h/week)	2.5 ± 1.4	2.0 ± 1.1	2.0 ± 1.1
Vigorous physical activity (h/week)	1.6 ± 1.3	1.6 ± 1.2	1.7 ± 1.1
Peak power (W)	267 ± 60	236 ± 47	246 ± 29
Peak power ($W \cdot kg^{-1}$)	3.69 ± 0.69	3.27 ± 0.39 *	3.06 ± 0.17
$\dot{V}O_2$ peak ($L.min^{-1}$)	3.24 ± 0.86	2.87 ± 0.63	2.73 ± 0.46
$\dot{V}O_2$ peak ($ml \cdot kg^{-1} \cdot min^{-1}$)	41.4 ± 8.7	36.4 ± 4.7 *	33.7 ± 3.4
Gas exchange threshold ($L.min^{-1}$)	1.68 ± 0.26	1.51 ± 0.24 *	1.42 ± 0.12
Gas exchange threshold ($ml.kg^{-1}.min^{-1}$)	19 ± 2	22 ± 3 *	18 ± 1
Gas exchange threshold (W)	100 ± 16	87 ± 16 *	82 ± 17

Data are means ± SD, * indicates significantly different from control group ($P < 0.05$). Physical activity rating scale and perceived functional ability score are derived from questionnaires, with each being scored on scales of 1-10 and 1-20, respectively.

Table 2. Pulmonary oxygen uptake kinetics during moderate-intensity cycle exercise in Part 1.

Parameter	Control (*n* = 17)	Type 1 diabetes (*n* = 17)
$\dot{V}O_2$ baseline, L.min^{-1}	0.98 ± 0.17	0.93 ± 0.21
$TD_{\dot{V}_{O2}}$, s	15 ± 10	12 ± 7
$\tau_{\dot{V}O2}$, s	32 ± 12	50 ± 13 *
$A_{\dot{V}_{O2}}$, L.min^{-1}	0.47 ± 0.14	0.42 ± 0.12
Gain, ml.min^{-1}.W^{-1}	9.4 ± 2.1	9.7 ± 2.1
End-ex $\dot{V}O_2$, L.min^{-1}	1.44 ± 0.23	1.35 ± 0.30

$TD_{\dot{V}_{O2}}$, fundamental time delay; $\tau_{\dot{V}O2}$, fundamental time constant; $A_{\dot{V}_{O2}}$, fundamental amplitude; Gain, increase in fundamental phase $\dot{V}O_2$ per unit increase in power output; End-ex $\dot{V}O_2$, end-exercise $\dot{V}O_2$. * indicates significantly different from the control group ($P < 0.001$).

Table 3. Muscle deoxygenation kinetic responses to moderate-intensity cycle exercise in Part 1.

Parameter	Control (*n* = 17)	Type 1 diabetes (*n* = 17)
$[HHb+Mb]_{(b)}$, µM	17.9 ± 9.2	21.9 ± 9.8
$TD_{[HHb+Mb]}$, s	17 ± 5	10 ± 4 *
$\tau_{[HHb+Mb]}$, s	12 ± 6	22 ± 15 *
$A_{[HHb+Mb]}$, µM	5.2 ± 4.2	5.1 ± 4.5
$[HHb+Mb]_{(b)} + A_{[HHb+Mb]}$, µM	23.0 ± 10.6	25.4 ± 14.8
[HHb+Mb] end-ex, µM	21.3 ± 11.8	28.3 ± 14.7

$[HHb+Mb]_{(b)}$, mean [HHb+Mb] over last 30 s of baseline; $TD_{[HHb+Mb]}$, time delay before exponential rise in [HHb+Mb]; $\tau_{[HHb+Mb]}$, time constant of [HHb+Mb] response; $A_{[HHb+Mb]}$, amplitude of [HHb+Mb] response; [HHb+Mb] end-ex, mean [HHb+Mb] over last 30 seconds of exercise. * indicates significantly different from control ($P < 0.05$).

Table 4. Pulmonary oxygen uptake responses to severe intensity cycle exercise in Part 2.

Baseline (L.min^{-1})	CON	PRI
WR 1	0.92 ± 0.30	1.07 ± 0.16
WR 2	1.00 ± 0.19	0.88 ± 0.17
WR 3	0.92 ± 0.33	0.88 ± 0.24
WR 4	0.92 ± 0.15	0.95 ± 0.25
TD (s)		
WR 1	14 ± 6	11 ± 7
WR 2	12 ± 8	14 ± 11
WR 3	13 ± 6	18 ± 10
WR 4	5 ± 8	11 ± 7
$\tau_{\dot{V}O2}$ (s)		
WR 1	53 ± 21	42 ± 19
WR 2	48 ± 22	33 ± 14
WR 3	49 ± 29	33 ± 12
WR 4	50 ± 16	35 ± 13
A (L.min^{-1})		
WR 1	1.29 ± 0.33	1.23 ± 0.32
WR 2	1.38 ± 0.41	1.46 ± 0.36
WR 3	1.61 ± 0.33	1.51 ± 0.32
WR 4	1.73 ± 0.38	1.54 ± 0.43
Absolute *A* (L.min^{-1})		
WR 1	2.21 ± 0.43	2.30 ± 0.42
WR 2	2.37 ± 0.50	2.35 ± 0.38
WR 3	2.53 ± 0.53	2.39 ± 0.45
WR 4	2.66 ± 0.41	2.49 ± 0.55
Gain, ml.min^{-1}.W^{-1}		
WR 1	8.02 ± 1.54	7.73 ± 1.20
WR 2	7.43 ± 1.28	8.21 ± 1.03
WR 3	7.91 ± 0.66	7.67 ± 1.66
WR 4	7.67 ± 0.91	7.12 ± 1.42
SC (L.min^{-1})		
WR 1	0.53 ± 0.30	0.45 ± 0.20
WR 2	0.45 ± 0.26	0.44 ± 0.25
WR 3	0.12 ± 0.14	0.30 ± 0.30

WR 4	0.15 ± 0.18	0.20 ± 0.19
End-ex (L.min^{-1})		
WR 1	2.73 ± 0.52	2.75 ± 0.47
WR 2	2.82 ± 0.43	2.78 ± 0.52
WR 3	2.61 ± 0.59	2.67 ± 0.56
WR 4	2.73 ± 0.51	2.71 ± 0.59

$\dot{V}O_2$, oxygen uptake; baseline, average value over final 30 s of baseline pe
fundamental time delay; $\tau_{\dot{V}O2}$, fundamental time constant; *A*, fundamental a
Absolute *A*, baseline + fundamental amplitude; Gain, increase in fundamental phase
unit increase in power output; SC, magnitude of the slow component; end-ex,
value over final 30 s of exercise; CON, control condition in Part 2; PRI, primed conditi
2. * indicates significant main effect of condition ($P < 0.01$).