1 **TITLE**

2 Priming exercise accelerates pulmonary oxygen uptake kinetics during "work-to-work" cycle exercise in middle-

3 aged individuals with type 2 diabetes.

4 **AUTHORS**

5 Norita Gildea[1], Joel Rocha[2], Donal O'Shea[34], Simon Green[5], Mikel Egaña[2]

6 **AFFILIATIONS & ADDRESSES**

7 1.   Department of Physiology, School of Medicine, Trinity College Dublin, Dublin Ireland.

8 2.   Division of Sport and Exercise Sciences, Abertay University, Dundee, UK.

9 3.   Department of Endocrinology, St. Columcille's Hospital, Dublin, Ireland.

10 4.   Department of Endocrinology and Diabetes Mellitus, St. Vincent's University Hospital, Dublin, Ireland.

11 5.   Schools of Health Sciences and Medicine, Western Sydney University, Sydney, Australia.

12

13 **CONTACT INFORMATION (corresponding author):**

14 Mikel Egaña

15 Department of Physiology, School of Medicine

16 Trinity College Dublin

17 Dublin 2, Ireland.

18 E-mail: megana@tcd.ie

19 Telephone: +353 1 896 1770

20 Fax: +353 1 679 3545

21 ORCID: https://orcid.org/0000-0003-1984-9250
22

Abstract

Purpose The time constant of phase II pulmonary oxygen uptake kinetics ($\dot{V}O_2\tau_p$) is increased when high-intensity exercise is initiated from an elevated baseline (work-to-work). A high-intensity priming exercise (PE), which enhances muscle oxygen supply, does not reduce this prolonged $\dot{V}O_2\tau_p$ in healthy active individuals, likely because $\dot{V}O_2\tau_p$ is limited by metabolic inertia (rather than oxygen delivery) in these individuals. Since $\dot{V}O_2\tau_p$ is more influenced by oxygen delivery in type 2 diabetes (T2D), this study tested the hypothesis that PE would reduce $\dot{V}O_2\tau_p$ in T2D during work-to-work cycle exercise. *Methods* Nine middle-aged individuals with T2D and nine controls (ND) performed four bouts of constant-load, high-intensity work-to-work transitions, each commencing from a baseline of moderate-intensity. Two bouts were completed without PE and two were preceded by PE. The rate of muscle deoxygenation ([HHb+Mb]) and surface integrated electromyography (iEMG) were measured at the right and left vastus lateralis respectively. *Results* Subsequent to PE, $\dot{V}O_2\tau_p$ was reduced ($P=0.001$) in T2D (from 59±17 to 37±20s) but not ($P=0.24$) in ND (44±10 to 38±7s). The amplitude of the $\dot{V}O_2$ slow component ($\dot{V}O_2A_s$) was reduced ($P=0.001$) in both groups (T2D: 0.16±0.09 to 0.11±0.04l/min; ND: 0.21±0.13 to 0.13±0.09l/min). This was accompanied by a reduction in ΔiEMG from the onset of $\dot{V}O_2$ slow component to end-exercise in both groups ($P<0.001$), while [HHb+Mb] kinetics remained unchanged. *Conclusions* PE accelerates $\dot{V}O_2\tau_p$ in T2D, likely by negating the O_2 delivery limitation extant in the unprimed condition, and reduces the $\dot{V}O_2A_s$ possibly due to changes in muscle fibre activation.

Keywords: near-infrared spectroscopy, oxygen extraction, cycling, oxygen uptake slow component, electromyography.

Abbreviations:

A: Amplitude

CP: Critical power

HR: Heart rate

HHb+Mb: deoxygenated haemoglobin and myoglobin

iEMG: Surface integrated electromyography

MRT: Mean response time

ND: Non-diabetic controls

53 NIRS: Near-infrared spectroscopy

54 PE: Priming exercise

55 TD: Time delay

56 T2D: Type 2 diabetes

57 TOI: Tissue oxygenation index

58 $\dot{V}CO_2$: Expired carbon dioxide

59 $\dot{V}_E$: Minute ventilation

60 $\dot{V}O_2$: Oxygen uptake

61 $\dot{V}O_{2peak}$: Peak oxygen uptake

62 VT: Ventilatory threshold

63 w-to-w: Work-to-work transition

64 τ: time constant

65 $\Delta50\%$: the sum of the power output at VT and 50% of the difference between the power output at VT and

66 $\dot{V}O_{2peak}$

67 $\Delta iEMG_{end-TDs}$: Difference between iEMG values at end-exercise and at the time point equivalent to the onset of

68 TD.

69

Introduction

Type 2 diabetes mellitus (T2D), having reached epidemic proportions in the last two decades, poses one of the main threats to human health in the 21st century. Of significant concern for this clinical population is the consistent demonstration of a reduced maximal exercise capacity (Green et al. 2015), which is independently correlated with cardiovascular and all-cause mortality (Kodama et al. 2009). Furthermore, pulmonary oxygen uptake ($\dot{V}O_2$) kinetics during moderate-intensity (i.e. below ventilatory threshold, (VT)) exercise is significantly blunted by ~30% in young and middle-aged individuals with uncomplicated T2D (Mac Ananey et al. 2011; O'Connor et al. 2015; O'Connor et al. 2012; Kiely et al. 2015; Bauer et al. 2007; Regensteiner et al. 1998). This is evidenced by a prolonged time constant of the primary phase of the $\dot{V}O_2$ kinetics response ($\dot{V}O_2\ \tau_p$) which has been considered to be a determinant of exercise tolerance (Jones and Poole 2005). Although not universal (Poitras et al. 2015; Copp et al. 2010), substantial evidence exists to suggest that the impairments in $\dot{V}O_2\ \tau_p$ in uncomplicated T2D are influenced by limitations in peripheral oxygen (O_2) delivery in the lower limbs (Kiely et al. 2014; Bauer et al. 2007; MacAnaney et al. 2011). In contrast, in non-diabetic active individuals presenting with a fast $\dot{V}O_2$ kinetics, $\dot{V}O_2\ \tau_p$ appears to be limited by the adjustment of specific metabolic pathways (i.e. oxidative capacity of contracting skeletal muscle) rather than O_2 delivery.

In healthy active individuals, the initiation of a transition to heavy-intensity [> VT and < critical power (CP)] or severe-intensity (> CP) upright cycling from a moderate-intensity (< VT) baseline, referred to as work-to-work (w-to-w), elicits a significantly longer $\dot{V}O_2\ \tau_p$ than an on-transition from rest or 'unloaded' cycling (Hughson and Morrissey 1982; Goulding et al. 2018; Wilkerson and Jones 2007, 2006; Dimenna et al. 2009; DiMenna et al. 2008). This prolonged $\dot{V}O_2\ \tau_p$ may relate to a constrained cellular respiration in the already active muscle fibres (Nederveen et al. 2017), or a larger recruitment of fast twitch (type II) muscle fibres to meet the augmented metabolic demand (Whipp 1994; Barstow et al. 1996). In these healthy active individuals a prior bout of high-intensity priming exercise (PE) does not alter this prolonged $\dot{V}O_2\ \tau_p$ in subsequent w-to-w transitions. This is likely because during high-intensity exercise a prior PE appears to facilitate convective and diffusive components of muscle O_2 delivery (Gerbino et al. 1996; Sahlin et al. 2005; Jones et al. 2006) rather than muscle metabolic pathways. In this regard, DiMenna et al. (DiMenna et al. 2010b) reported that PE significantly reduced $\dot{V}O_2\ \tau_p$ during severe-intensity w-to-w cycling in the supine posture, where O_2 delivery is limited due to a loss of gravity-enhanced perfusion pressure in active muscle. These effects were, therefore, likely owing to an enhanced distribution of blood flow to active muscles following priming (DiMenna et al. 2010b). Despite PE not influencing

4

100 $\dot{V}O_2 \tau_p$ during heavy/severe-intensity w-to-w upright cycling in healthy active participants, PE reduces the mean

101 response time (MRT) of the overall $\dot{V}O_2$ dynamic response by increasing the amplitude of the $\dot{V}O_2$ primary phase

102 ($\dot{V}O_2 A_p$) and/or blunting the amplitude of the $\dot{V}O_2$ slow component ($\dot{V}O_2 A_s$), which have been associated with

103 a PE-induced reduction in the requirement for type II muscle fibre activation, and thus, an improved metabolic

104 stability of type I fibres (DiMenna et al. 2008).

105

106 Given that T2D is a disease that affects the vasculature and limits the O_2 supply to contracting muscle, the

107 combination of a PE intervention with the w-to-w model may offer further insight into potential mechanisms

108 implicated in the impaired $\dot{V}O_2$ kinetics response demonstrated by these individuals. Accordingly, the aim of the

109 present study was to investigate the influence of PE on $\dot{V}O_2$ kinetics during w-to-w upright cycling exercise

110 transitions in middle-aged individuals with T2D. We hypothesized that PE would speed $\dot{V}O_2 \tau_p$ in the subsequent

111 high-intensity w-to-w transition in individuals with T2D. Given that muscle fibre distribution appears to be altered

112 in individuals with T2D (Marin et al. 1994) with reports showing a 2-fold increase in type IIb fibres (Mogensen

113 et al. 2007), together with the notion that PE induces a reduction in type II muscle fibre activation, we also

114 hypothesised that PE would reduce the $\dot{V}O_2 A_s$ in individuals with T2D. In attempting to explore the mechanistic

115 basis of any PE-induced effect on $\dot{V}O_2$ kinetics in T2D, the rate of muscle deoxygenation (i.e., deoxygenated

116 haemoglobin and myoglobin, HHb+Mb) and muscle electromyography (EMG) were measured to assess the

117 alterations on muscle fractional O_2 extraction and motor unit activation, respectively.

118

119 **Methods**

120 *Participants*

121 Eighteen individuals, 9 with uncomplicated T2D (5 males/4 females) and 9 healthy controls (5 males/4 females)

122 volunteered to participate in this study (Table 1). Non-diabetic controls (ND) were recruited from the general

123 population, whilst participants with T2D were recruited from the Diabetes Outpatient Clinics of St. Columcille's

124 Hospital (Louglinstown, Co. Dublin) and St. Vincent's University Hospital (SVUH, Dublin 4) following chart

125 review. To avoid the potential confounding effects of age on the T2D-related impairments in exercise tolerance,

126 previously established in men (Wilkerson et al. 2011; O'Connor et al. 2015), we limited the age of participants to

127 < 60 yr.

128 Three female participants were premenopausal (1 T2D and 2 ND) and five were postmenopausal (3 T2D and 2

129 ND) not undergoing hormone replacement therapy. Participants were classified as physically inactive by self-

5

130 report (≤ 1.5 h.week^{-1} of moderate-intensity exercise in the preceding 6 months), which was confirmed by the use

131 of 5-day RT3 triaxial accelerometry (Stayhealthy Inc, CA) in a subset of participants (Table 1) (Rowlands et al.

132 2004). All participants with T2D had a clinical history of diabetes between 3 and 11 years (mean ± SD = 7.3 ±

133 4.0 yrs.), were treated by oral hypoglycaemic agents and had adequately controlled HbA$_{1c}$ levels (<8.5%). None

134 of the participants with T2D were taking insulin or beta-blockers and all participants were non-smokers (had not

135 smoked during the 12-month period preceding the study). One of the healthy controls was on a prescriptive

136 medication (statins, *n* = 1), and individuals with T2D were taking oral (*n* = 8) and/or subcutaneous (*n* =1)

137 hypoglycaemic prescription medications (metformin, *n* = 5; sulphonylurea, *n* = 1; glucagon-like peptide 1, *n* = 1;

138 sodium glucose cotransporter-2 inhibitors, *n* = 1; dipeptidyl peptidase-4 inhibitors, *n* = 1). In addition, 3

139 individuals with T2D were taking antihypertensive prescription drugs (angiotensin converting enzyme inhibitor

140 & calcium channel blocker, *n* = 2; angiotensin II receptor blocker, *n* = 1) and statins. All participants displayed

141 no clinical evidence of coronary artery disease (12-lead electrocardiogram treadmill stress test following the Bruce

142 protocol), peripheral arterial disease (0.9 < Ankle-Brachial Index, ABI, < 1.3), kidney dysfunction (consistent

143 urinary protein > 200 mg.dl^{-1}) or liver dysfunction (urinary creatinine levels > 2.2 mg.dl^{-1}). All participants

144 provided written informed consent prior to participation. The study was approved by the Faculty of Health

145 Sciences' Research Ethics Committee, Trinity College Dublin, and St Vincent's Healthcare Ethics and Medical

146 Research Committee, and was performed in line with the principles outlined by the Declaration of Helsinki.

147

148 *Study Protocol*

149 *Overview*. Following the satisfactory completion of the 12-lead ECG stress test, all participants completed two

150 visits to the laboratory. The controls undertook these tests in the cardiovascular performance laboratory in the

151 Department of Physiology, Trinity College Dublin; whilst individuals with T2D did so in the exercise testing

152 facility in St. Columcille's Hospital. In the first visit all participants performed a ramp incremental (RI) cycling

153 test to exhaustion to determine $\dot{V}O_{2peak}$ (see *visit 1*). In the second visit participants performed four w-to-w step

154 transitions to high-intensity exercise commencing from a baseline of moderate-intensity exercise. Two of these

155 transitions were completed without PE and the other two transitions were undertaken preceded by a PE (see *visit*

156 *2*). All exercise tests were carried out in an upright position on an electrically braked cycle ergometer (Excalibur

157 Sport; Lode B.V., Groningen, Netherlands). All participants were asked to refrain from consuming alcohol,

158 caffeine and non-prescribed nutritional supplements as well as avoiding any strenuous exercise in the 24 hours

159 prior to testing. All premenopausal participants were tested during the mid-follicular phase (days 5-12) of the

160 menstrual cycle to avoid potential differences, even though the phase of the menstrual cycle does not seem to

161 affect the $\dot{V}O_2$ kinetics response (Mattu et al. 2020). The mid-follicular phase was self-determined.

162

163 *Visit 1: Ramp incremental cycling test to exhaustion*. The test started with an initial workload of 10 W for 2 min

164 (i.e. 'unloaded' cycling). This was followed by 10-15 W/min increments in power output for women or 15-20

165 W/min increments for men based on participants' activity levels. Pedalling rate was held constant at an

166 individually selected cadence between 60-75 revolutions per minute (rpm) and was maintained throughout all

167 further testing. Failure in a test was determined as a drop in cadence exceeding 10 rpm for >5 s. Peak workload

168 was the power output achieved at the point of failure. $\dot{V}O_{2peak}$ was the highest $\dot{V}O_2$ value (15-s average) attained

169 during the test. The first ventilatory threshold (VT) was determined by visual inspection as the $\dot{V}O_2$ at which

170 $\dot{V}_E/\dot{V}O_2$ exhibited a systematic non-linear increase without a concomitant increase in $\dot{V}_E/\dot{V}CO_2$ and the deflection

171 point of $\dot{V}CO_2$ vs. $\dot{V}O_2$ (V-slope method) during the ramp incremental test (Beaver et al. 1986). The respiratory

172 compensation point (RCP) was estimated by identifying the second non-linear increase of $\dot{V}_E$ and $\dot{V}CO_2$, whereby

173 an increase in $\dot{V}_E/\dot{V}O_2$ is accompanied by an increase of $\dot{V}_E/\dot{V}CO_2$ (Wasserman and McIlroy 1964).

174

175 *Visit 2: Priming effect on high-intensity work-to-work cycling exercise*. All participants performed four separate

176 w-to-w transitions to constant-load high-intensity cycling at 50% delta (Δ50%; the sum of the power output at VT

177 and 50% of the difference between the power output at VT and $\dot{V}O_{2peak}$ obtained during the ramp incremental test)

178 each commencing from an elevated baseline of 80% VT (80% of each participant's VT). For all participants the

179 power output at Δ50% was higher or the same than at RCP (see results). Given that in the present study the mean

180 response times of $\dot{V}O_2$ during the ramp cycle exercise (Keir et al. 2018) were not accounted for when calculating

181 these target power outputs, it is likely that power outputs at RCP (and at VT) were slightly overestimated. Thus,

182 it is reasonable to assume that the Δ50% intensity for participants in the present study was within the lower region

183 of the severe intensity domain (> critical power). The order of these bouts was fixed for all participants (Fig 1).

184 Each transition consisted of 3 min of "unloaded" cycling at 10W, immediately followed by 6 min of moderate-

185 intensity (80% VT) cycling which in turn was immediately followed by 6 min of high-intensity (Δ50%) cycling.

186 Two of these w-to-w transitions were completed without PE (unprimed w-to-w) and two bouts were undertaken

187 preceded by a bout of PE (primed w-to-w). The unprimed w-to-w bout was used as PE. A pilot study carried out

188 in our laboratory in young control individuals ($n = 6$) demonstrated that when a w-to-w bout was used as PE, its

189 effect on subsequent w-to-w $\dot{V}O_2$ and [HHb+Mb] kinetics was not different compared with a condition where a

7

190 single 6-min 50% Δ bout was used as PE. Exercise was performed continuously with changes in power output

191 initiated as a step function without giving prior warning to the individual. There was a 12 min rest period between

192 each of the cycling bouts, except following the first primed w-to-w bout where participants remained seated in a

193 chair for 45 min. This resting period has been shown to be sufficient for physiological parameters to return to

194 baseline levels, and therefore, not to influence $\dot{V}O_2$ kinetics responses during subsequent exercise (Burnley et al.

195 2006). Eight participants (4 from each group) failed to complete 6 min of exercise at Δ50% during the w-to-w

196 bouts in the unprimed condition, so only physiological responses collected over the same period (i.e., <6 min,

197 range 2.5 – 5 min) during the unprimed and primed conditions were analysed. Heart rate (HR), gas

198 exchange/ventilatory variables, muscle oxygenation & deoxygenation and muscle EMG were continuously

199 measured during each cycling bout.

200

201 *Measurements*

202 During exercise, participants wore a facemask to continuously collect expired air using an online metabolic system

203 (Innocor, Innovision A/S, Odense, Denmark) that measured airflow using a pneumotachometer. Carbon dioxide

204 analysis was performed by using a photoacoustic gas analyser and oxygen was analysed using an oxygen sensor

205 (Oxigraf Inc., USA) based on the principle of laser diode absorption spectroscopy. The system was calibrated

206 prior to each test as per manufacturer's recommendations. Both the oxygen sensor and photoacoustic gas analyser

207 require multi-point calibration that is routinely performed by the manufacturer every 6-12 months. Analysis of

208 expired air allowed determination of pulmonary O_2 uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$)

209 and the respiratory exchange ratio breath-by-breath. HR was recorded every 5 s (Polar S610i, Polar Ltd, Finland),

210 with peak HR defined as the highest HR attained within the last 15 s prior to termination of the test.

211

212 A continuous wave NIRS system (Hamamatsu Niro 200Nx; Hamamatsu Photonics, Hamamatsu, Japan), was used

213 to determine muscle oxygenation status non-invasively through the spatially resolved spectroscopy technique and

214 modified Beer-Lambert principle with three wavelengths of emitting light (λ = 735, 810, and 850 nm). The

215 theoretical basis of NIRS and its use in exercise measurements have been described in detail elsewhere (Ferrari et

216 al. 2011) but briefly, this technique estimates the optical density changes of oxygenated (O_2Hb+Mb) and

217 deoxygenated haemoglobin and myoglobin ($HHb+Mb$) based on the oxygen dependency of absorption changes

218 for near-infrared light in these proteins. As the vastus lateralis (VL) muscle is a dominant locomotor muscle during

219 cycling, the present study examined the concentration of $HHb+Mb$ ($\Delta[HHb+Mb]$), and tissue oxygenation index

220 (TOI) of the right vastus lateralis (VL) muscle. After shaving, cleaning and drying the skin, the probes were placed

221 on the belly of the muscle, 5-8 cm above the lateral femoral condyle, parallel to the major axis of the thigh with a

222 3 cm spacing between the emitter and receiver. The probes were housed in a black rubber holder and secured on

223 the skin surface with bi-adhesive tape and then covered with a dark elastic bandage, which minimised extraneous

224 movement and the intrusion of stray light throughout the exercise protocol. Since the depth of the measured area

225 was estimated to be approximately one-half the distance between the emitter and the receiver (~1.5 cm), the

226 present study determined the thickness of the skin and adipose tissue at the site of the probe placement via 2D

227 ultrasound operating in B-mode (Zonare Ultra Smart Cart, Software version 4.7, USA), to ensure that data largely

228 represented absorption of near-infrared light in muscle tissue and not in subcutaneous fat. Individuals presenting

229 with adiposity >1.5 cm over the site of interrogation on the vastus lateralis were excluded from the study.

230

231 Neuromuscular activity of the vastus lateralis muscle of the left leg was measured using surface electromyography

232 (EMG). The area of the belly of the muscle was shaved and cleaned using a sterile alcohol wipe and the electrodes

233 were placed in a bipolar Ag/AgCl arrangement 25mm apart (centre to centre) and in a plane which was estimated

234 to be parallel to the direction of the muscle shortening during contraction, while a third ground electrode was

235 placed on the left hip. The electrodes were taped in place and covered in a cloth bandage to prevent excessive

236 movement during exercise. The EMG signal was measured using a Powerlab 26T (AD instruments, Sydney,

237 Australia) at a sampling frequency of 1,000 Hz. All raw EMG data were demeaned and band passed filtered

238 between 20 and 500 Hz with the filtered data then used to calculate integrated EMG (iEMG). Filtered data was

239 rectified and then integrated for every 50 ms of EMG activity. The iEMG data were averaged in 15 s intervals

240 throughout exercise, with these values normalized to the average measured during 15–165 s of unloaded cycling

241 before the initial transition. Therefore, all iEMG data were calculated as a percentage of the initial unloaded

242 cycling phase. Data from repeat trials were averaged, and iEMG at the time point equivalent to the onset of the

243 $\dot{V}O_2$ slow component (TD_s, see *data analysis*) (the 15 s interval before the TD_s time point) and at end exercise

244 (last 15 s of exercise) were calculated. $\Delta iEMG_{end\text{-}TDs}$ was calculated as the difference between iEMG values at

245 end-exercise and at the time point equivalent to the onset of TD_s. The EMG recordings were re-started prior to

246 each w-to-w transition (i.e. upon initiation of the 3 min "unloaded" cycling) and were continuously measured for

247 the duration of each w-to-w transition.

248

249 *Data analysis*

250 *$\dot{V}O_2$ Kinetics:* The breath-by-breath $\dot{V}O_2$ data for each transition were linearly interpolated to provide second-by-

251 second values and time aligned such that time 0 represented the onset of exercise. Data from each transition were

252 ensemble-averaged to yield a single, average response for each individual and further time-averaged into 5 s bins.

253 During the moderate-intensity bouts, 5 participants (2 T2D and 3 ND during both conditions) revealed a small

254 $\dot{V}O_2$ slow component suggesting that the power outputs in these participants were slightly above their VT. This

255 was likely because the mean response times of $\dot{V}O_2$ during the ramp cycle exercise were not accounted for when

256 calculating the target power outputs (Keir et al. 2018). Thus, averaged and smoothed responses for each participant

257 for moderate-intensity exercise were fitted to either a monoexponential (*Eq. 1*) or biexponential (*Eq. 2*) function,

258 while for high-intensity exercise responses were fitted to a biexponential function

259

260 $$\dot{V}O_2(t) = \dot{V}O_2 \text{ baseline} + A_p \left[1 - e^{-(t-TDp)/\tau p}\right] \cdot F1 \qquad (1)$$

261 $$\dot{V}O_2(t) = \dot{V}O_2 \text{ baseline} + A_p \left[1 - e^{-(t-TDp)/\tau p}\right] \cdot F1 + A_s \left[1 - e^{-(t-TDs)/\tau s}\right] \cdot F2 \qquad (2)$$

262

263 where $\dot{V}O_2(t)$ represents the absolute $\dot{V}O_2$ at a given time *t*; $\dot{V}O_2$ baseline (for moderate-intensity, in *Eq's 1 & 2*)

264 is the mean $\dot{V}O_2$ in the final 30 s of unloaded cycling, whereas $\dot{V}O_2$ baseline (for high-intensity, in *Eq. 2*) is the

265 mean $\dot{V}O_2$ in the final 60 s of the moderate-intensity cycling exercise preceding the step transition to high-intensity

266 cycling exercise; A_p and A_s, are the amplitudes of the increase in $\dot{V}O_2$ for the primary and slow component phases;

267 TD_p and TD_s are the time delays of these phases, and τ_p and τ_s are the time constants of the phases, defined as the

268 duration of time for which $\dot{V}O_2$ increases to a value equivalent to 63% of the amplitude. The conditional

269 expressions F1 and F2 limit the fitting of the phase to the period at and beyond the time delay associated with that

270 phase. The first 20 s of data after the onset of exercise (i.e., the phase I $\dot{V}O_2$ response) were deleted, while still

271 allowing TD to vary freely (to optimize accuracy of parameter estimates (Murias et al. 2011)). The MRT was

272 calculated through the fitting of a monoexponential curve to provide information on the "overall" $\dot{V}O_2$ kinetics

273 during the high-intensity exercise bout, with no distinction made for the various phases of the response. The $\dot{V}O_2$

274 data were fit using a weighted least-squares non-linear regression procedure (TableCurve 2D, Systat, USA). Data

275 points lying outside the 95% prediction interval during the initial fit of a model were excluded. For moderate-

276 intensity exercise only estimates representing the primary phase are presented. Whilst the presence of a slow

277 component was detected in 5 participants during the moderate-intensity bouts, the presence of this phase does not

278 appear to significantly affect the parameter estimates of the earlier phases (Wilkerson et al. 2004). The end-

279 exercise $\dot{V}O_2$ response, referred to as End A, was calculated as the averaged $\dot{V}O_2$ over the last 30 s. Because the

280 asymptomatic value (A_s) of the exponential term describing the $\dot{V}O_2$ slow component may represent a higher

281 value than is actually reached at the end of the exercise, the actual amplitude of the slow component was calculated

282 as the absolute difference between the End A and $\dot{V}O_2$ baseline + A_p. The amplitude of the slow component was

283 also described relative to the entire $\dot{V}O_2$ response [i.e. $A_s / (A_p + A_s)$]. The functional "gain" of the primary $\dot{V}O_2$

284 response (G_p) was calculated as the difference between $\dot{V}O_2$ A_p and $\dot{V}O_2$ baseline normalized to the difference in

285 power outputs between the moderate-intensity exercise and unloaded cycling; and the functional gain of the entire

286 response at the end of the high-intensity exercise bout (i.e. end-exercise gain) was calculated in a similar manner.

287

288 *[HHb+Mb] kinetics and TOI.* To provide information on muscle deoxygenation throughout the protocol, we

289 modelled the [HHb+Mb] response for moderate- and high-intensity exercise, fitting the data to either a

290 monoexponential (*Eq. 1*) or biexponential (*Eq. 2*) function (see above). In the moderate-intensity exercise the 5

291 participants who showed a small $\dot{V}O_2$ slow component also showed a [HHb+Mb] slow component, so, for these

292 participants data were fitted using a biexponential function, but only estimates representing the primary phase are

293 presented. As per the $\dot{V}O_2$ data, the NIRS-derived Δ[HHb+Mb] data for each transition were linearly interpolated

294 to provide second-by-second values and time aligned. Data from each transition were ensemble-averaged to yield

295 a single average response for each individual, and further time-averaged into 5 s bins. A time delay (TD) at the

296 onset of exercise occurs in the [HHb+Mb] profile before it increases with an exponential like time course

297 (DeLorey et al. 2003) which has been interpreted to reflect a tight coupling between muscle O_2 uptake and local

298 O_2 delivery (DeLorey et al. 2003). This was determined in the present study via visual inspection as a systematic

299 increase above the pre-transition level. [HHb+Mb] data were fitted from the end of this TD to the end of the

300 exercise bout. For the moderate- and high-intensity exercise, the time course for the primary phase of the

301 Δ[HHb+Mb] response, referred to as the effective response time ($\tau'\Delta$[HHb+Mb]), was determined from the sum

302 of the TD and τ from the onset of exercise. TOI was determined at baseline (30 s prior to each transition to the

303 moderate-intensity domain), at every minute during the moderate-intensity cycling exercise; at min 1 and 2 into

304 the high-intensity exercise transition (15 s bins centred on every 60 s), and at the end exercise (final 30 s) to allow

305 comparisons between conditions in all participants.

306

Statistical analysis

308 Prior to analysis, normal distribution was assessed using the Shapiro-Wilk's test. Physical characteristics and

309 physiological responses derived from the ramp test between groups were compared using the unpaired Student's

t-test for parametric analyses, or the Mann-Whitney U test for non-parametric analyses. The kinetics parameter estimates for $\dot{V}O_2$ and [HHb+Mb], and $\Delta iEMG_{end\text{-}TDs}$ responses were analysed by using a two-way repeated measures ANOVA [condition (unprimed, primed) x diabetes status (T2D, ND)] and the post hoc Tukey test. TOI responses at different time points within the w-to-w transitions were compared using a 3-way repeated measures ANOVA (time x condition x diabetes status). Finally, correlations between PE-induced absolute changes in $\dot{V}O_2$ A_s and $\Delta iEMG_{end\text{-}TDs}$ were established using the Pearson product-moment correlation coefficient (Pearson r). A power analysis indicated that 9 participants per group were required to detect a PE-induced reduction of ~30% in $\dot{V}O_2$ τ_p during the w-to-w transitions (primary outcome) with a power of 0.80 and alpha of 0.05. This was based on previously published data on the effect of PE on subsequent $\dot{V}O_2$ τ_p during cycling w-to-w transitions in the supine posture (i.e. when O_2 delivery to the active muscles was reduced at the outset) (DiMenna et al. 2010b). Statistical significance was accepted as $P < 0.05$. All values are expressed as mean ± standard deviation (SD) or as median and interquartile ranges for data that were deemed not normally distributed.

Results

Physical characteristics and activity levels.

Participants' physical characteristics are presented in Table 1. Both groups were well matched according to sex, age, body mass, body mass index and activity levels. As expected, participants with T2D displayed higher HbA_{1c} and fasting plasma glucose levels.

Performance data from ramp incremental cycling test

Absolute $\dot{V}O_{2peak}$ (T2D: 1.94 ± 0.53 L.min^{-1}; ND: 2.47 ± 0.54 L.min^{-1}; $P = 0.049$) and $\dot{V}O_{2peak}$ normalised to body mass (T2D: 22.4 ± 4.3 mL.kg^{-1}.min^{-1}; ND: 29.7 ± 7.7 mL.kg^{-1}.min^{-1}; $P = 0.012$) were significantly reduced in individuals with T2D compared with healthy controls while peak power output tended to be lower in T2D (T2D: 149 ± 45 W; ND: 192 ± 57 W; $P = 0.092$). The power outputs equivalent to 80% VT were lower in T2D (T2D: 64 ± 17 W; ND: 96 ± 44 W; $P = 0.043$) while power outputs equivalent to Δ50% (T2D: 116 ± 33 W; ND: 158 ± 58 W; $P = 0.076$) and RCP (T2D: 112 ± 33 W; ND: 153 ± 55 W; $P = 0.073$) showed a tendency to be reduced in diabetes.

Effect of PE on $\dot{V}O_2$ kinetics, EMG and NIRS-derived responses during high-intensity exercise of the w-to-w transition

340 *$\dot{V}O_2$ kinetics.* The parameter estimates of the $\dot{V}O_2$ kinetics response for the high-intensity exercise bouts with and

341 without a prior PE are presented in Table 2, and responses for representative individuals are shown in Fig 2. In

342 the unprimed transition the $\dot{V}O_2$ τ_p and overall $\dot{V}O_2$ MRT were significantly ($P = 0.035$ & $P = 0.049$ respectively)

343 longer in T2D compared with controls. PE resulted in a significant reduction in the $\dot{V}O_2$ MRT in both groups,

344 while $\dot{V}O_2$ τ_p values were also reduced following PE in T2D ($P = 0.001$) but not in controls ($P = 0.24$). Subsequent

345 to PE $\dot{V}O_2$ A_s was reduced in both groups ($P = 0.001$) while $\dot{V}O_2$ A_p was elevated (main effect, priming condition,

346 $P = 0.015$).

347 *$\Delta[HHb+Mb]$ kinetics.* Kinetics parameters for $\Delta[HHb+Mb]$ as well as TOI baseline & amplitude values are

348 displayed in Table 3 while TOI values during the w-to-w transitions are shown in Fig 3. In the unprimed condition,

349 the parameter estimates for the $[HHb+Mb]$ kinetics responses were similar between groups. PE induced a

350 reduction in the $\Delta[HHb+Mb]$ A_p in both groups (main effect, priming condition, $P = 0.004$), but it did not affect

351 the effective response time of the $\Delta[HHb+Mb]$ response in either group. TOI values were higher during the primed

352 high-intensity exercise bout in both groups (main effect, priming condition, $P = 0.002$). The magnitude of the

353 change in TOI from baseline to end-exercise was not affected by prior PE. Participants with T2D showed lower

354 TOI than controls (main effect, diabetes status, $P = {<}0.001$).

355 *EMG.* Representative iEMG responses during the w-to-w transitions are shown in Fig 4, while relative iEMG

356 responses between the time points equivalent to end-exercise and the onset of $\dot{V}O_2$ slow component are shown in

357 Fig 5. The $\Delta iEMG_{end\text{-}TDs}$ was significantly reduced subsequent to PE in both groups (main effect, priming

358 condition, $P = {<}0.001$) (T2D unprimed: 22 ± 18 %, T2D primed: $1 \pm 10\%$; controls unprimed: $30 \pm 37\%$, controls

359 primed: $3 \pm 20\%$). Absolute changes in $\dot{V}O_2$ A_s and $\Delta iEMG_{end\text{-}TDs}$ from unprimed to primed conditions were not

360 correlated in controls ($r = 0.09$, $P = 0.85$), or among individuals with T2D ($r = 0.49$, $P = 0.22$).

361

362 *Effect of PE on $\dot{V}O_2$ kinetics and NIRS-derived responses at moderate-intensity exercise of the w-to-w transition*

363 The parameter estimates of the $\dot{V}O_2$ kinetics response for the moderate-intensity exercise bouts are presented in

364 Table 2. In both, the unprimed and primed conditions $\dot{V}O_2$ τ_p was significantly slower in T2D compared with

365 controls (main effect, group, $P = 0.016$), while PE accelerated $\dot{V}O_2$ τ_p in both groups (main effect, priming

366 condition, $P = 0.007$). Kinetics parameters for $\Delta[HHb+Mb]$ are displayed in Table 3. Parameter estimates were

367 similar between groups in the umprimed condition. PE did not affect the amplitude or the effective response time

368 of the $\Delta[HHb+Mb]$ response in either group. TOI responses were higher during the primed moderate-intensity

369 exercise bout in both groups (Fig 3 & Table 3). In addition, the magnitude of the change in TOI from baseline to

370 end-exercise was larger following PE in both groups (main effect, priming condition, $P < 0.001$).

371

372 **Discussion**

373 To our knowledge this is the first study to explore the influence of PE on the temporal relationship between the

374 adaptation of muscle O_2 consumption and delivery during high-intensity cycling initiated from a moderate-

375 intensity baseline in T2D. In agreement with our primary hypothesis, PE reduced $\dot{V}O_2$ τ_p during the high-intensity

376 cycling bout of the w-to-w transition in T2D in the absence of significant changes in the dynamic response of

377 $\Delta[HHb+Mb]$. Additionally, consistent with our second hypothesis, PE significantly reduced the $\dot{V}O_2$ A_s during

378 the high-intensity exercise bout, accompanied with a reduction in muscle electromyographic activity between the

379 end-exercise and the time point equivalent to the onset of $\dot{V}O_2$ slow component. Together, these priming effects

380 resulted in a reduction in the MRT of the overall $\dot{V}O_2$ response.

381

382 *Effect of PE on $\dot{V}O_2$ τ_p during high-intensity exercise of the w-to-w transition*

383 In the present study, PE did not significantly reduce $\dot{V}O_2$ τ_p during the subsequent high-intensity bout of the w-

384 to-w transition among ND participants; and these findings are consistent to those observed during unprimed and

385 primed upright severe-intensity w-to-w transitions (~42 vs. ~42 s respectively) in healthy individuals (DiMenna

386 et al. 2008). Given that PE facilitates convective and diffusive muscle O_2 delivery, (Gerbino et al. 1996; Sahlin

387 et al. 2005; Jones et al. 2006), our findings, and those by DiMenna et al (DiMenna et al. 2010b), suggest that the

388 $\dot{V}O_2$ τ_p responses in the control condition were not impaired by O_2 delivery limitation. In contrast, for T2D, $\dot{V}O_2$

389 τ_p responses during w-to-w transitions following PE were significantly reduced (~36% reduction) bringing the

390 $\dot{V}O_2$ τ_p in T2D on a par with control counterparts (~37 s). This effect was also evidenced in healthy participants

391 during severe-intensity cycling w-to-w transitions in the supine position (DiMenna et al. 2010b), thus,

392 compromising exercising muscle perfusion pressure and O_2 delivery (Egaña and Green 2005, 2007). Specifically,

393 PE subsequently induced a significant reduction in the lengthened $\dot{V}O_2$ τ_p during the supine posture, aligning it

394 with that observed in the unprimed upright posture. This was likely by negating the constrained O_2 delivery,

395 attributed to a loss of gravity-enhanced perfusion pressure in the active muscles (Jones et al. 2006; Egaña et al.

396 2013; Egaña et al. 2010a; Egaña et al. 2010b).

397

14

398   Given that the impaired $\dot{V}O_2$ τ_p in T2D appears to be mediated, at least in part by limitations in O_2 supply to

399   contracting muscle (Kiely et al. 2014; Bauer et al. 2007; MacAnaney et al. 2011), it is likely that the priming-

400   induced speeding in $\dot{V}O_2$ τ_p in T2D herein was elicited by an enhanced O_2 supply. The increased O_2 availability

401   at exercise onset in the primed exercise bout, evidenced by the elevated TOI further substantiates this notion. It is

402   likely that this was mediated by a PE-induced greater vasodilation and muscle blood flow at the onset of exercise

403   (Hughson et al. 2003; Gerbino et al. 1996) and increased lactic acidosis, via an enhanced blood-to-myocyte O_2

404   diffusion gradient through a rightward shift of the oxyhaemoglobin dissociation curve (Boning et al. 1991;

405   Wasserman et al. 1991); even if this effect is not apparent following prior arm cranking exercise (Fukuba et al.

406   2002). However, we cannot exclude the possibility that the priming-augmented $\dot{V}O_2$ τ_p observed herein, was also

407   partially mediated by the upregulation of rate-limiting mitochondrial oxidative enzymes (Gurd et al. 2006, 2009).

408

409   *Effect of PE on $\dot{V}O_2$ A_s and iEMG during high-intensity exercise of the w-to-w transition*

410   In the present study, in addition to decreasing $\dot{V}O_2$ τ_p, PE significantly reduced the amplitude of the $\dot{V}O_2$ slow

411   component during the high-intensity bout of the w-to-w transition in participants with T2D. In addition, despite

412   PE not influencing $\dot{V}O_2$ τ_p in the controls, PE reduced the $\dot{V}O_2$ A_s during the high-intensity bout, thus, shortening

413   the overall MRT of the $\dot{V}O_2$ response. These PE-induced reductions in the $\dot{V}O_2$ A_s, without altering $\dot{V}O_2$ τ_p in

414   healthy controls are in accordance with the literature centred on the influence of PE on heavy/severe-intensity

415   upright cycle exercise, both, from an elevated and an unloaded baseline (Burnley et al. 2006; Jones et al. 2008;

416   Jones et al. 2006; Scheuermann et al. 2001; Wilkerson and Jones 2007; Goulding et al. 2017; Burnley et al. 2000;

417   Fukuba et al. 2002); however, the governing mechanisms remain to be elucidated.

418

419   One such mechanism relates to priming-induced changes in the motor unit recruitment pattern. In this regard, in

420   the present study, the difference in iEMG between end-exercise and the time point equivalent to the onset of $\dot{V}O_2$

421   A_s (ΔiEMG$_{end-TDs}$) in the unprimed bout was significantly reduced following PE in both groups. Our findings are

422   consistent with reductions in ΔiEMG between end-exercise and min 2 during primed compared with unprimed

423   upright severe-intensity w-to-w cycling transitions in young active participants (DiMenna et al. 2008). Given the

424   transition to high-intensity exercise from an elevated baseline would mandate the recruitment of predominantly

425   type II muscle fibres, it is plausible that PE elicited a reduction in the requirement for additional type II muscle

426   fibre activation as the exercise proceeded, and as such, the associated $\dot{V}O_2$ cost of that activation was reduced

427   (DiMenna et al. 2008). Further extending this notion, DiMenna and colleagues (Dimenna et al. 2010a)

428 demonstrated a PE-induced reductions in the amplitudes of the [PCr] and $\dot{V}O_2$ slow components (50% and 46%

429 respectively) during prone knee-extension w-to-w transitions concomitant with a blunting of the ΔiEMG. A

430 reduction in the recruitment of these less efficient muscle fibres could serve to dampen the increase in the sustained

431 metabolic acidosis, deemed a likely driving force behind the slow components of both [PCr] and $\dot{V}O_2$, (Rossiter

432 et al. 2002; Krustrup et al. 2004). The combined iEMG and tissue oxygenation data in the present study may also

433 suggest a priming-enhanced distribution of intramuscular blood flow. Consequently, the anaerobic contribution

434 would decrease, precluding the recruitment of additional motor units, whilst favouring a more homogenous pool

435 of highly oxidative type 1 muscle fibres (DiMenna et al. 2010b). By the same token, we cannot negate the

436 upregulation of enzymatic processes within the type I fibres already recruited, improving the metabolic stability

437 within. Subsequently, a smaller reduction in [PCr] and Gibbs free energy of ATP hydrolysis, as well as a smaller

438 increase in [Pi] and [ADP] are ensured, thus sparing the activation of type 1 motor units herein.

439

440 Given that PE herein facilitated a reduction in the $\dot{V}O_2$ A_s of the severe-intensity w-to-w transition in individuals

441 with T2D, combined with a reduction in ΔiEMG$_{end\text{-}TDs}$ of that same bout, it is likely that the priming-induced

442 reduction in $\dot{V}O_2$ A_s herein may also be related to modified motor unit recruitment patterns. However, in addition,

443 given that type II fibres operate at a lower microvascular PO_2, the priming-enhanced O_2 delivery plausibly

444 increased the blood-to-myocyte flux and thus intramyocyte PO_2. This is all the more pertinent considering an

445 altered muscle fibre distribution has been evidenced in individuals with T2D (Marin et al. 1994) showing increased

446 proportions in type IIb fibres (Mogensen et al. 2007). However, it should be noted that given the variability

447 associated with measurement and normalisation of iEMG, some previous studies do not support the association

448 between neuromuscular activation and the $\dot{V}O_2$ slow component (Scheuermann et al. 2001). In addition, we did

449 not observe a significant correlation between PE-induced absolute reductions in ΔiEMG$_{end\text{-}TDs}$ with reductions in

450 A_s.

451

452 *Effect of PE on $\dot{V}O_2$ τ_p during moderate-intensity exercise of the w-to-w transition*

453 During the unprimed moderate-intensity cycling bout and in line with previous findings (reviewed by Green et al

454 (Green et al. 2015)), individuals with T2D displayed a significantly longer $\dot{V}O_2$ τ_p than their healthy counterparts

455 (~35 *vs.* ~44 s, respectively). Subsequent to PE both groups demonstrated similar reductions in the $\dot{V}O_2$ τ_p,

456 consistent with recent findings from our group in a larger number of middle-aged individuals with T2D (Rocha et

457 al. 2019), and in several previous studies involving young and older untrained healthy individuals presenting with

16

458 initially slow $\dot{V}O_2$ τ_p (DeLorey et al. 2004; Gurd et al. 2005; De Roia et al. 2012). NIRS-derived overall muscle

459 deoxygenation kinetics (τ'[HHb+Mb]) herein, were not affected by PE in any of the groups; therefore, it is likely

460 that the speeding of the $\dot{V}O_2$ kinetics response was attributed to a better matching of microvascular O_2 delivery to

461 utilisation.

462

463 *Limitations*

464 While a subset of participants (4 in each group) did not complete the required 6 min of high-intensity cycling

465 exercise during the w-to-w transitions, we believe this had little influence on the interpretation of our findings

466 given that the majority (8 in each group) completed at least 4 min of the bout and showed a clear $\dot{V}O_2$ slow

467 component phase. Although the current protocol did not allow the random assignment of unprimed and primed

468 conditions, this likely has a small impact on the results given that the sequence of the exercise transitions was the

469 same for all participants. We acknowledge the NIRS-derived oxygenation and deoxygenation data was limited to

470 one superficial muscle. Thus, the structural and functional heterogeneity extant within individual muscles, in

471 particular relating to vascularity and fibre type, fibre recruitment, vascular control, and blood flow (Koga et al.

472 2011; McDonough et al. 2005), in addition to variances identified both between muscles and within deep and

473 superficial muscle segments (Okushima et al. 2015; Saitoh et al. 2009), warrant consideration. Additionally, 3

474 participants with T2D were classified as hypertensive and also had hyperlipidaemia; whereas all controls

475 were normotensive, with one presenting with hyperlipidaemia. Further studies are needed to better establish if

476 the higher rates of hypertension and/or hyperlipidaemia observed within the T2D group in the present study may

477 have any significant impact on the findings presented herein.

478

Conclusions

480 The present study primarily demonstrated that priming exercise accelerates the primary time constant of $\dot{V}O_2$

481 during high-intensity w-to-w transitions in middle-aged individuals with T2D. This effect was likely mediated by

482 a priming-induced increase in O_2 delivery within the microvasculature of the working muscle, serving to alleviate

483 the metabolic strain to maintain $\dot{V}O_2$. In addition, PE decreased the amplitude of the $\dot{V}O_2$ slow component which

484 was likely influenced by an augmented motor unit recruitment pattern. Thus, from a physiological perspective the

485 combination of a PE intervention with the w-to-w model helps expand the insight that the impaired $\dot{V}O_2$ kinetics

486 in T2D are influenced by limitations in O_2 delivery. From a practical perspective, employing the work-to-work

487 protocol is of great relevance as it replicates metabolic transitions from light to higher metabolic rates akin to

488 those in daily life. Given individuals with T2D perceive light to moderate exercise as being more difficult than

489 healthy counterparts (Huebschmann et al. 2009), a more sedentary lifestyle is likely, which is independently

490 associated with worsening of cardiovascular outcomes in this burgeoning population. Therefore, the potential that

491 lies within an acute intervention such as priming or warm-up exercise which serves to heighten the oxidative

492 capacity of muscles and increase the therapeutic effect of exercise warrants further recognition.

493

Author contributions

495 N.G., J.R., M.E., D.O'S. and S.G. contributed to the study conception and design. N.G. and J.R. performed data

496 collection. N.G., and M.E. analysed data. N.G. and M.E. drafted the manuscript. S.G., D.O'S and J.R.

497 contributed to critically revising of this manuscript. All authors approved the final version.

498

502

Compliance with ethical standards

504 **Conflict of interest** Authors declare that they have no conflict of interest, financial or otherwise.

505

506

507 **REFERENCES**

508 Barstow TJ, Jones AM, Nguyen PH, Casaburi R (1996) Influence of muscle fiber type and pedal
509   frequency on oxygen uptake kinetics of heavy exercise. J Appl Physiol (1985) 81 (4):1642-
510   1650. doi:10.1152/jappl.1996.81.4.1642
511 Bauer TA, Reusch JE, Levi M, Regensteiner JG (2007) Skeletal muscle deoxygenation after the onset
512   of moderate exercise suggests slowed microvascular blood flow kinetics in type 2 diabetes.
513   Diabetes Care 30 (11):2880-2885. doi:dc07-0843 [pii]

514 10.2337/dc07-0843 [doi]
515 Beaver WL, Wasserman K, Whipp BJ (1986) A new method for detecting anaerobic threshold by gas
516   exchange. J Appl Physiol 60 (6):2020-2027
517 Boning D, Hollnagel C, Boecker A, Goke S (1991) Bohr shift by lactic acid and the supply of O_2 to
518   skeletal muscle. Respir Physiol 85 (2):231-243. doi:10.1016/0034-5687(91)90064-p
519 Burnley M, Doust JH, Jones AM (2006) Time required for the restoration of normal heavy exercise
520   VO2 kinetics following prior heavy exercise. J Appl Physiol 101 (5):1320-1327.
521   doi:00475.2006 [pii]

522 10.1152/japplphysiol.00475.2006 [doi]
523 Burnley M, Jones AM, Carter H, Doust JH (2000) Effects of prior heavy exercise on phase II
524   pulmonary oxygen uptake kinetics during heavy exercise. J Appl Physiol 89 (4):1387-1396
525 Copp SW, Hageman KS, Behnke BJ, Poole DC, Musch TI (2010) Effects of type II diabetes on
526   exercising skeletal muscle blood flow in the rat. J Appl Physiol (1985) 109 (5):1347-1353.
527   doi:10.1152/japplphysiol.00668.2010
528 De Roia G, Pogliaghi S, Adami A, Papadopoulou C, Capelli C (2012) Effects of priming exercise on the
529   speed of adjustment of muscle oxidative metabolism at the onset of moderate-intensity step
530   transitions in older adults. Am J Physiol Regul Integr Comp Physiol 302 (10):R1158-1166.
531   doi:10.1152/ajpregu.00269.2011
532 DeLorey DS, Kowalchuk JM, Paterson DH (2003) Relationship between pulmonary O_2 uptake kinetics
533   and muscle deoxygenation during moderate-intensity exercise. J Appl Physiol (1985) 95
534   (1):113-120. doi:10.1152/japplphysiol.00956.2002
535 DeLorey DS, Kowalchuk JM, Paterson DH (2004) Effects of prior heavy-intensity exercise on
536   pulmonary O_2 uptake and muscle deoxygenation kinetics in young and older adult humans. J
537   Appl Physiol (1985) 97 (3):998-1005. doi:10.1152/japplphysiol.01280.2003
538 Dimenna FJ, Fulford J, Bailey SJ, Vanhatalo A, Wilkerson DP, Jones AM (2010a) Influence of priming
539   exercise on muscle [PCr] and pulmonary O_2 uptake dynamics during 'work-to-work' knee-
540   extension exercise. Respir Physiol Neurobiol 172 (1-2):15-23. doi:10.1016/j.resp.2010.04.017
541 Dimenna FJ, Wilkerson DP, Burnley M, Bailey SJ, Jones AM (2009) Influence of extreme pedal rates
542   on pulmonary O_2 uptake kinetics during transitions to high-intensity exercise from an
543   elevated baseline. Respir Physiol Neurobiol 169 (1):16-23. doi:10.1016/j.resp.2009.08.001
544 DiMenna FJ, Wilkerson DP, Burnley M, Bailey SJ, Jones AM (2010b) Priming exercise speeds
545   pulmonary O_2 uptake kinetics during supine "work-to-work" high-intensity cycle exercise. J
546   Appl Physiol (1985) 108 (2):283-292. doi:10.1152/japplphysiol.01047.2009
547 DiMenna FJ, Wilkerson DP, Burnley M, Jones AM (2008) Influence of priming exercise on pulmonary
548   O_2 uptake kinetics during transitions to high-intensity exercise from an elevated baseline. J
549   Appl Physiol (1985) 105 (2):538-546. doi:10.1152/japplphysiol.90357.2008
550 Egaña M, Columb D, O'Donnell S (2013) Effect of low recumbent angle on cycling performance,
551   fatigue, and V O_2 kinetics. Med Sci Sports Exerc 45 (4):663-673.
552   doi:10.1249/MSS.0b013e318279a9f2
553 Egaña M, Green S (2005) Effect of body tilt on calf muscle performance and blood flow in humans. J
554   Appl Physiol (1985) 98 (6):2249-2258. doi:10.1152/japplphysiol.01235.2004
555 Egaña M, Green S (2007) Intensity-dependent effect of body tilt angle on calf muscle fatigue in
556   humans. Eur J Appl Physiol 99 (1):1-9. doi:10.1007/s00421-006-0308-4

Egaña M, O'Riordan D, Warmington SA (2010a) Exercise performance and VO2 kinetics during upright and recumbent high-intensity cycling exercise. Eur J Appl Physiol 110 (1):39-47. doi:10.1007/s00421-010-1466-y

Egaña M, Ryan K, Warmington SA, Green S (2010b) Effect of body tilt angle on fatigue and EMG activities in lower limbs during cycling. Eur J Appl Physiol 108 (4):649-656. doi:10.1007/s00421-009-1254-8

Ferrari M, Muthalib M, Quaresima V (2011) The use of near-infrared spectroscopy in understanding skeletal muscle physiology: recent developments. Philos Trans A Math Phys Eng Sci 369 (1955):4577-4590. doi:10.1098/rsta.2011.0230

Fukuba Y, Hayashi N, Koga S, Yoshida T (2002) VO(2) kinetics in heavy exercise is not altered by prior exercise with a different muscle group. J Appl Physiol (1985) 92 (6):2467-2474. doi:10.1152/japplphysiol.00207.2001

Gerbino A, Ward SA, Whipp BJ (1996) Effects of prior exercise on pulmonary gas-exchange kinetics during high-intensity exercise in humans. J Appl Physiol (1985) 80 (1):99-107. doi:10.1152/jappl.1996.80.1.99

Goulding RP, Roche DM, Marwood S (2017) Prior exercise speeds pulmonary oxygen uptake kinetics and increases critical power during supine but not upright cycling. Exp Physiol 102 (9):1158-1176. doi:10.1113/ep086304

Goulding RP, Roche DM, Marwood S (2018) Elevated baseline work rate slows pulmonary oxygen uptake kinetics and decreases critical power during upright cycle exercise. Physiol Rep 6 (14):e13802. doi:10.14814/phy2.13802

Green S, Egana M, Baldi JC, Lamberts R, Regensteiner JG (2015) Cardiovascular control during exercise in type 2 diabetes mellitus. J Diabetes Res 2015:654204. doi:10.1155/2015/654204

Gurd BJ, Peters SJ, Heigenhauser GJ, LeBlanc PJ, Doherty TJ, Paterson DH, Kowalchuk JM (2006) Prior heavy exercise elevates pyruvate dehydrogenase activity and speeds O2 uptake kinetics during subsequent moderate-intensity exercise in healthy young adults. J Physiol 577 (Pt 3):985-996. doi:10.1113/jphysiol.2006.112706

Gurd BJ, Peters SJ, Heigenhauser GJ, LeBlanc PJ, Doherty TJ, Paterson DH, Kowalchuk JM (2009) Prior heavy exercise elevates pyruvate dehydrogenase activity and muscle oxygenation and speeds O2 uptake kinetics during moderate exercise in older adults. Am J Physiol Regul Integr Comp Physiol 297 (3):R877-884. doi:10.1152/ajpregu.90848.2008

Gurd BJ, Scheuermann BW, Paterson DH, Kowalchuk JM (2005) Prior heavy-intensity exercise speeds VO2 kinetics during moderate-intensity exercise in young adults. J Appl Physiol (1985) 98 (4):1371-1378. doi:10.1152/japplphysiol.01028.2004

Huebschmann AG, Reis EN, Emsermann C, Dickinson LM, Reusch JE, Bauer TA, Regensteiner JG (2009) Women with type 2 diabetes perceive harder effort during exercise than nondiabetic women. Appl Physiol Nutr Metab 34 (5):851-857. doi:h09-074 [pii]

10.1139/h09-074 [doi]

Hughson R, Schijvens H, Burrows S, Devitt, D, Betik A, Hopman M (2003) Blood Flow and Metabolic Control at the Onset of Heavy Exercise. International Journal of Sport and Health Science 1 (1):9-18

Hughson RL, Morrissey M (1982) Delayed kinetics of respiratory gas exchange in the transition from prior exercise. J Appl Physiol Respir Environ Exerc Physiol 52 (4):921-929. doi:10.1152/jappl.1982.52.4.921

Jones AM, Berger NJ, Wilkerson DP, Roberts CL (2006) Effects of "priming" exercise on pulmonary O2 uptake and muscle deoxygenation kinetics during heavy-intensity cycle exercise in the supine and upright positions. J Appl Physiol (1985) 101 (5):1432-1441. doi:10.1152/japplphysiol.00436.2006

Jones AM, Poole DC (2005) Oxygen uptake dynamics: from muscle to mouth--an introduction to the symposium. Med Sci Sports Exerc 37 (9):1542-1550. doi:00005768-200509000-00014 [pii]

Jones AM, Wilkerson DP, DiMenna F, Fulford J, Poole DC (2008) Muscle metabolic responses to exercise above and below the "critical power" assessed using 31P-MRS. Am J Physiol Regul Integr Comp Physiol 294 (2):R585-593. doi:10.1152/ajpregu.00731.2007

Keir DA, Pogliaghi S, Murias JM (2018) The Respiratory Compensation Point and the Deoxygenation Break Point Are Valid Surrogates for Critical Power and Maximum Lactate Steady State. Med Sci Sports Exerc 50 (11):2375-2378. doi:10.1249/mss.0000000000001698

Kiely C, O'Connor E, O'Shea D, Green S, Egaña M (2014) Hemodynamic responses during graded and constant-load plantar flexion exercise in middle-aged men and women with type 2 diabetes. J Appl Physiol (1985) 117 (7):755-764. doi:10.1152/japplphysiol.00555.2014

Kiely C, Rocha J, O'Connor E, O'Shea D, Green S, Egana M (2015) Influence of menopause and Type 2 diabetes on pulmonary oxygen uptake kinetics and peak exercise performance during cycling. Am J Physiol Regul Integr Comp Physiol 309 (8):R875-883. doi:10.1152/ajpregu.00258.2015

Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H (2009) Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. Jama 301 (19):2024-2035. doi:10.1001/jama.2009.681

Koga S, Poole DC, Fukuoka Y, Ferreira LF, Kondo N, Ohmae E, Barstow TJ (2011) Methodological validation of the dynamic heterogeneity of muscle deoxygenation within the quadriceps during cycle exercise. Am J Physiol Regul Integr Comp Physiol 301 (2):R534-541. doi:10.1152/ajpregu.00101.2011

Krustrup P, Soderlund K, Mohr M, Bangsbo J (2004) The slow component of oxygen uptake during intense, sub-maximal exercise in man is associated with additional fibre recruitment. Pflugers Arch 447 (6):855-866. doi:10.1007/s00424-003-1203-z

Mac Ananey O, Malone J, Warmington S, O'Shea D, Green S, Egaña M (2011) Cardiac output is not related to the slowed o2 uptake kinetics in type 2 diabetes. Med Sci Sports Exerc 43 (6):935-942. doi:10.1249/MSS.0b013e3182061cdb

MacAnaney O, Reilly H, O'Shea D, Egaña M, Green S (2011) Effect of type 2 diabetes on the dynamic response characteristics of leg vascular conductance during exercise. Diab Vasc Dis Res 8 (1):12-21. doi:10.1177/1479164110389625

Marin P, Andersson B, Krotkiewski M, Bjorntorp P (1994) Muscle fiber composition and capillary density in women and men with NIDDM. Diabetes Care 17 (5):382-386

Mattu AT, Iannetta D, MacInnis MJ, Doyle-Baker PK, Murias JM (2020) Menstrual and oral contraceptive cycle phases do not affect submaximal and maximal exercise responses. Scand J Med Sci Sports 30 (3):472-484. doi:10.1111/sms.13590

McDonough P, Behnke BJ, Padilla DJ, Musch TI, Poole DC (2005) Control of microvascular oxygen pressures in rat muscles comprised of different fibre types. J Physiol 563 (Pt 3):903-913. doi:10.1113/jphysiol.2004.079533

Mogensen M, Sahlin K, Fernstrom M, Glintborg D, Vind BF, Beck-Nielsen H, Hojlund K (2007) Mitochondrial respiration is decreased in skeletal muscle of patients with type 2 diabetes. Diabetes 56 (6):1592-1599. doi:10.2337/db06-0981

Murias JM, Spencer MD, Kowalchuk JM, Paterson DH (2011) Influence of phase I duration on phase II VO2 kinetics parameter estimates in older and young adults. Am J Physiol Regul Integr Comp Physiol 301 (1):R218-224. doi:10.1152/ajpregu.00060.2011

Nederveen JP, Keir DA, Love LK, Rossiter HB, Kowalchuk JM (2017) Effect of heavy-intensity 'priming' exercise on oxygen uptake and muscle deoxygenation kinetics during moderate-intensity step-transitions initiated from an elevated work rate. Respir Physiol Neurobiol 235:62-70. doi:10.1016/j.resp.2016.09.013

O'Connor E, Green S, Kiely C, O'Shea D, Egana M (2015) Differential effects of age and type 2 diabetes on dynamic vs. peak response of pulmonary oxygen uptake during exercise. J Appl Physiol (1985) 118 (8):1031-1039. doi:10.1152/japplphysiol.01040.2014

21

658 O'Connor E, Kiely C, O'Shea D, Green S, Egaña M (2012) Similar level of impairment in exercise
659 performance and oxygen uptake kinetics in middle-aged men and women with type 2
660 diabetes. Am J Physiol Regul Integr Comp Physiol 303 (1):R70-76.
661 doi:10.1152/ajpregu.00012.2012
662 Okushima D, Poole DC, Rossiter HB, Barstow TJ, Kondo N, Ohmae E, Koga S (2015) Muscle
663 deoxygenation in the quadriceps during ramp incremental cycling: Deep vs. superficial
664 heterogeneity. J Appl Physiol (1985) 119 (11):1313-1319.
665 doi:10.1152/japplphysiol.00574.2015
666 Poitras VJ, Bentley RF, Hopkins-Rosseel DH, LaHaye SA, Tschakovsky ME (2015) Independent effect
667 of type 2 diabetes beyond characteristic comorbidities and medications on immediate but
668 not continued knee extensor exercise hyperemia. J Appl Physiol (1985) 119 (3):202-212.
669 doi:10.1152/japplphysiol.00758.2014
670 Regensteiner JG, Bauer TA, Reusch JE, Brandenburg SL, Sippel JM, Vogelsong AM, Smith S, Wolfel EE,
671 Eckel RH, Hiatt WR (1998) Abnormal oxygen uptake kinetic responses in women with type II
672 diabetes mellitus. J Appl Physiol 85 (1):310-317
673 Rocha J, Gildea N, O'Shea D, Green S, Egana M (2019) Influence of priming exercise on oxygen
674 uptake and muscle deoxygenation kinetics during moderate-intensity cycling in type 2
675 diabetes. J Appl Physiol (1985) 127 (4):1140-1149. doi:10.1152/japplphysiol.00344.2019
676 Rossiter HB, Ward SA, Kowalchuk JM, Howe FA, Griffiths JR, Whipp BJ (2002) Dynamic asymmetry of
677 phosphocreatine concentration and O(2) uptake between the on- and off-transients of
678 moderate- and high-intensity exercise in humans. J Physiol 541 (Pt 3):991-1002.
679 doi:10.1113/jphysiol.2001.012910
680 Rowlands AV, Thomas PW, Eston RG, Topping R (2004) Validation of the RT3 triaxial accelerometer
681 for the assessment of physical activity. Med Sci Sports Exerc 36 (3):518-524
682 Sahlin K, Sorensen JB, Gladden LB, Rossiter HB, Pedersen PK (2005) Prior heavy exercise eliminates
683 VO2 slow component and reduces efficiency during submaximal exercise in humans. J
684 Physiol 564 (Pt 3):765-773. doi:jphysiol.2005.083840 [pii]

685 10.1113/jphysiol.2005.083840 [doi]
686 Saitoh T, Ferreira LF, Barstow TJ, Poole DC, Ooue A, Kondo N, Koga S (2009) Effects of prior heavy
687 exercise on heterogeneity of muscle deoxygenation kinetics during subsequent heavy
688 exercise. Am J Physiol Regul Integr Comp Physiol 297 (3):R615-621.
689 doi:10.1152/ajpregu.00048.2009
690 Scheuermann BW, Hoelting BD, Noble ML, Barstow TJ (2001) The slow component of O(2) uptake is
691 not accompanied by changes in muscle EMG during repeated bouts of heavy exercise in
692 humans. J Physiol 531 (Pt 1):245-256. doi:10.1111/j.1469-7793.2001.0245j.x
693 Wasserman K, Hansen J, Sue D (1991) Facilitation of Oxygen Consumption by Lactic Acidosis During
694 Exercise. News Physiol Sci 6:29-34
695 Wasserman K, McIlroy MB (1964) DETECTING THE THRESHOLD OF ANAEROBIC METABOLISM IN
696 CARDIAC PATIENTS DURING EXERCISE. Am J Cardiol 14:844-852
697 Whipp BJ (1994) The slow component of O2 uptake kinetics during heavy exercise. Med Sci Sports
698 Exerc 26 (11):1319-1326
699 Wilkerson DP, Jones AM (2006) Influence of initial metabolic rate on pulmonary O2 uptake on-
700 kinetics during severe intensity exercise. Respir Physiol Neurobiol 152 (2):204-219.
701 doi:10.1016/j.resp.2005.10.001
702 Wilkerson DP, Jones AM (2007) Effects of baseline metabolic rate on pulmonary O2 uptake on-
703 kinetics during heavy-intensity exercise in humans. Respir Physiol Neurobiol 156 (2):203-211.
704 doi:10.1016/j.resp.2006.09.008
705 Wilkerson DP, Koppo K, Barstow TJ, Jones AM (2004) Effect of work rate on the functional 'gain' of
706 Phase II pulmonary O2 uptake response to exercise. Respir Physiol Neurobiol 142 (2-3):211-
707 223. doi:10.1016/j.resp.2004.06.001

708 Wilkerson DP, Poole DC, Jones AM, Fulford J, Mawson DM, Ball CI, Shore AC (2011) Older type 2
709   diabetic males do not exhibit abnormal pulmonary oxygen uptake and muscle oxygen
710   utilization dynamics during submaximal cycling exercise. Am J Physiol Regul Integr Comp
711   Physiol 300 (3):R685-692. doi:10.1152/ajpregu.00479.2010

712
713

Figure legends

716

Fig 1 Schematic representation of the protocol. Unprimed and primed work-to-work cycling step transitions performed at high-intensity cycling exercise (Δ50%; the sum of the power output at VT and 50% of the difference between the power output at VT and $\dot{V}O_{2peak}$), each commencing from an elevated baseline of moderate-intensity (power output corresponding to 80% of each participant's first ventilatory threshold, VT). All step transitions, each lasting 6 min, were preceded by 3 min of cycling at 10 W (i.e. 'baseline' cycling). Unprimed and primed work-to-work transitions were separated by 12 min of passive rest. The 2 step transitions (unprimed and primed work-to-work) were repeated following 45 min of passive rest within the same laboratory visit.

724

Fig 2. Oxygen uptake ($\dot{V}O_2$) responses for a representative individual with type 2 diabetes (A) and a healthy control (B) during high-intensity work-to-work cycling transitions without priming exercise (open circles) and with priming exercise (solid circles). The continuous lines of best fit illustrate the primary phase of the oxygen uptake ($\dot{V}O_2$) response. Note the relatively slower response of the primary phase of the $\dot{V}O_2$ response in the unprimed compared with the primed bout in T2D.

730

Fig 3. Mean $\pm$ SD total oxygenation index (TOI) at moderate and high-intensity exercise during the work-to-work transitions without priming exercise (open circles) and with priming exercise (solid circles) in T2D (A) and healthy controls (B). * $P < 0.05$ vs. unprimed within same diabetes status group (i.e. within controls or within Type 2 diabetes).

735

Fig 4: Integrated surface electromyographic (iEMG) responses for a representative individual with type 2 diabetes (A) and a healthy control (B) during moderate and high-intensity work-to-work cycling transitions without priming exercise (open circles) and with priming exercise (solid circles). The arrows indicate the time point equivalent to the onset of the $\dot{V}O_2$ slow component.

740

Fig 5: Individual and mean $\pm$ SD (*bar graph*) changes in integrated surface electromyographic (iEMG) responses between end-exercise and the time point equivalent to the oxygen uptake slow component ($\dot{V}O_2$ TD$_s$) (ΔiEMG$_{end-}$ $_{TDs}$) during high-intensity work-to-work transitions without priming exercise (unprimed) and with priming

744   exercise (primed) in T2D (A) and healthy controls (B). **P* < 0.05 vs. unprimed within same diabetes status group

745   (i.e. within controls or within Type 2 diabetes).

Fig 1

Click here to access/download;Figure;Fig 1 EJAP v2.pdf ±

Figure 1

Unprimed Work-To-Work

Primed Work-To-Work

50% Δ

80% VT

High-intensity

Mod-intensity

10W

12 min rest

0   3   9   15

50% Δ

80% VT

High-intensity

Mod-intensity

10W

27   30   36   42

Repeated after 45 min rest

Fig 2

Figure 2

Fig 3

Click here to access/download;Figure;Fig 3 TOI (%) EJAP.pdf ⬇

Figure 3

Fig 4

Figure 4

Fig 5
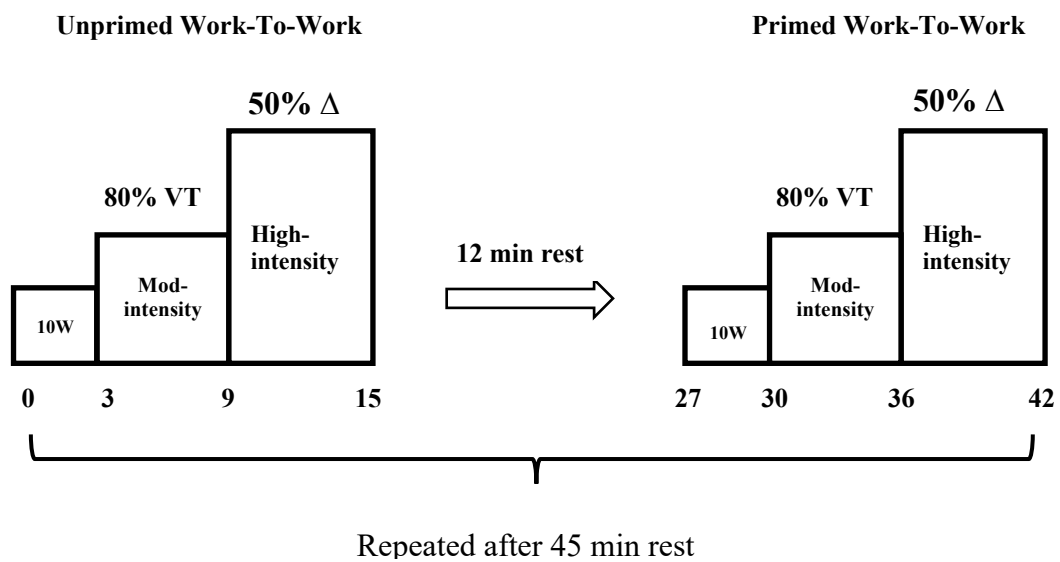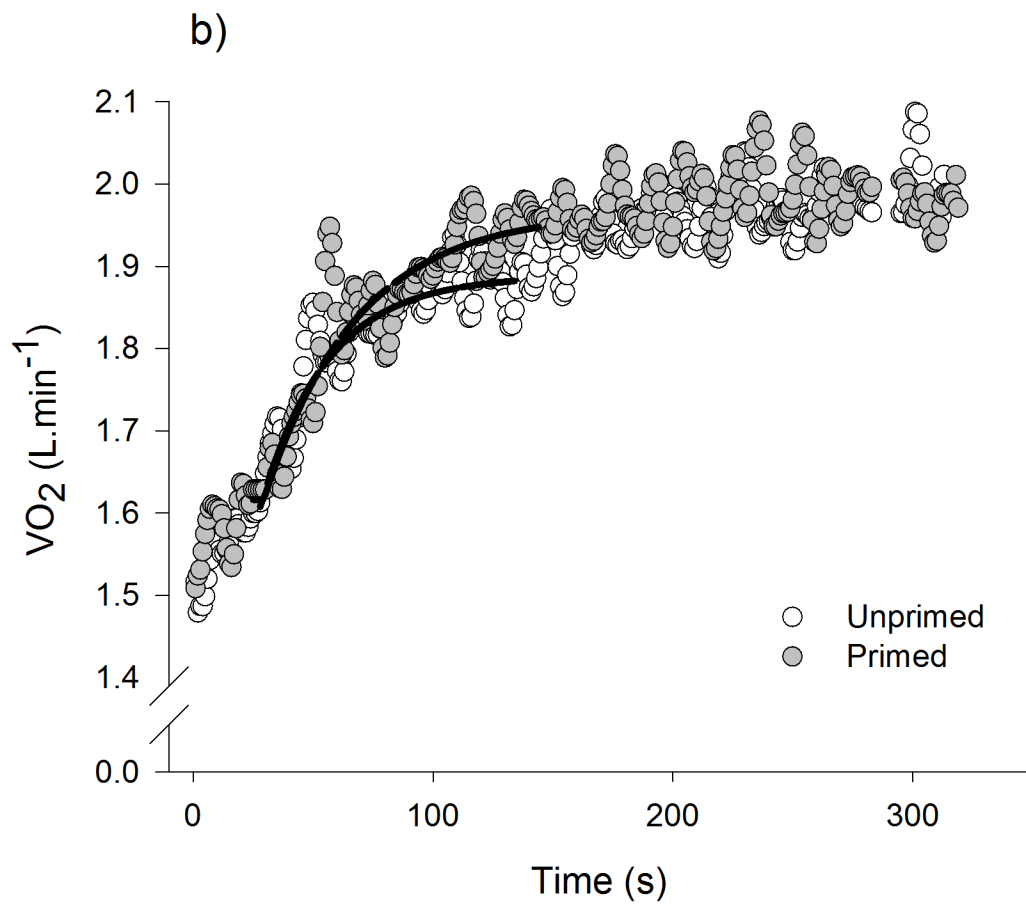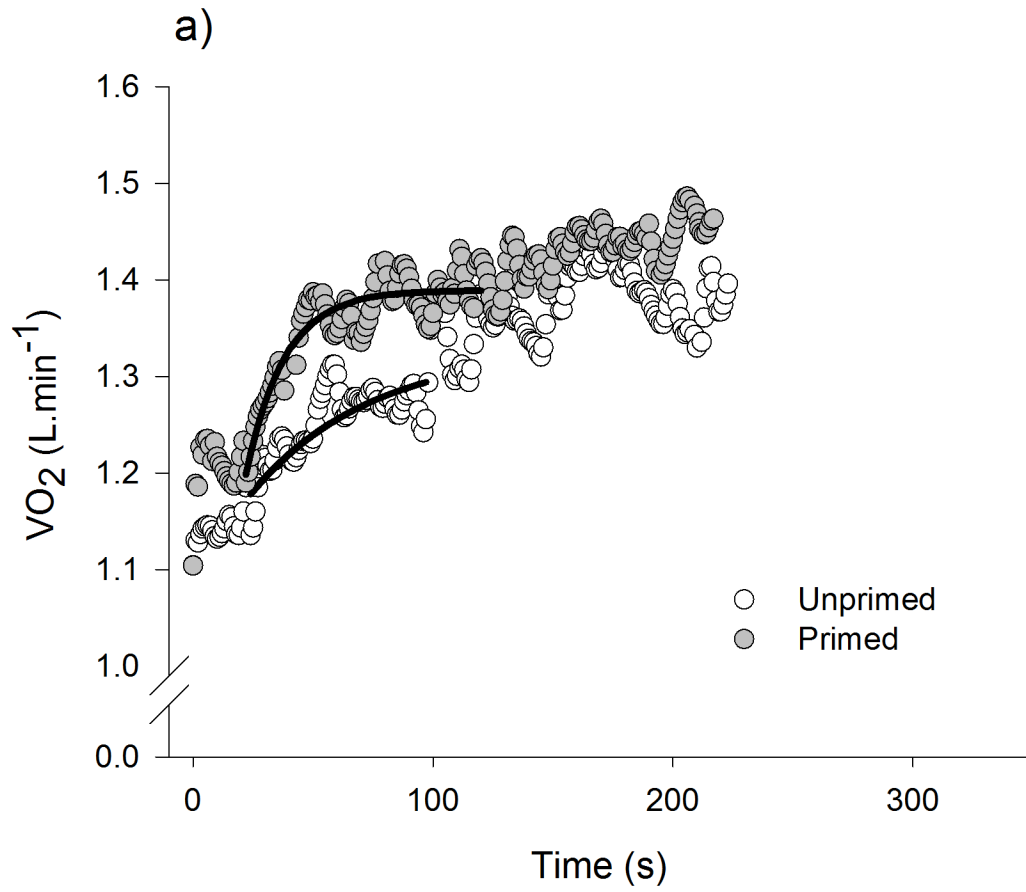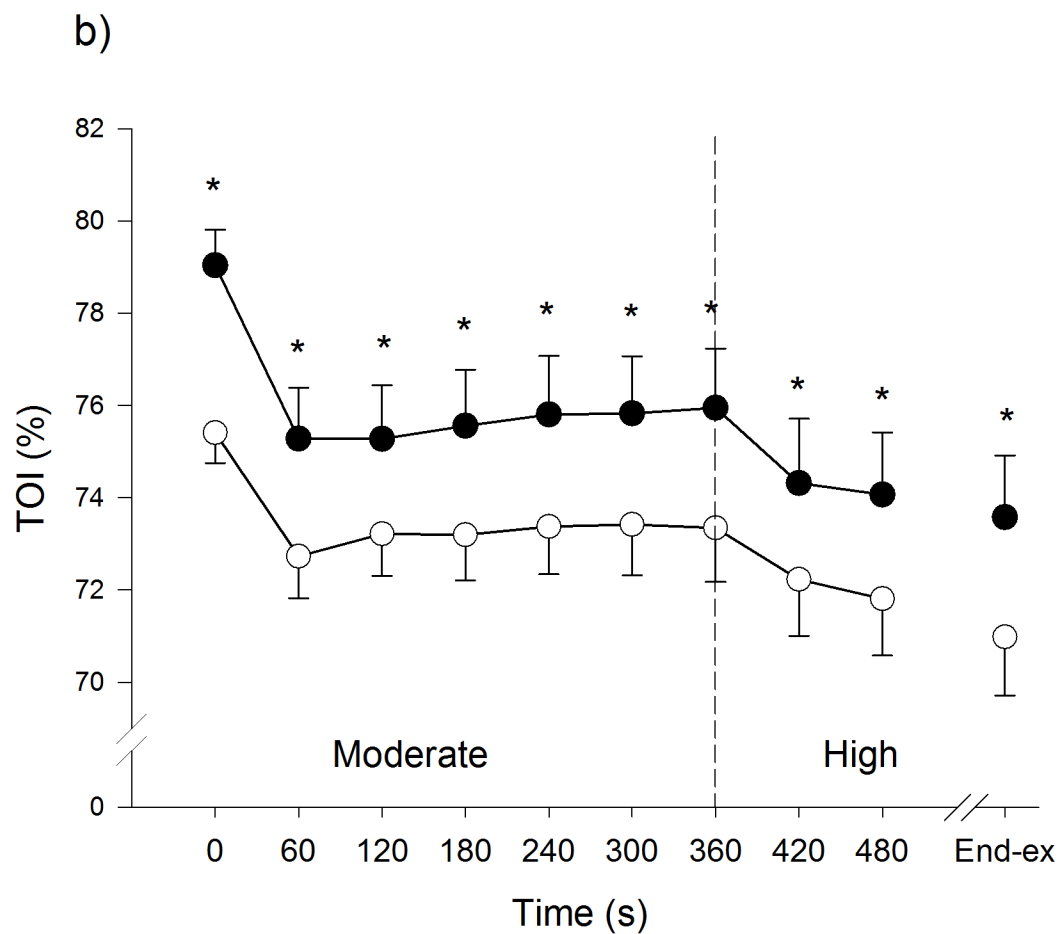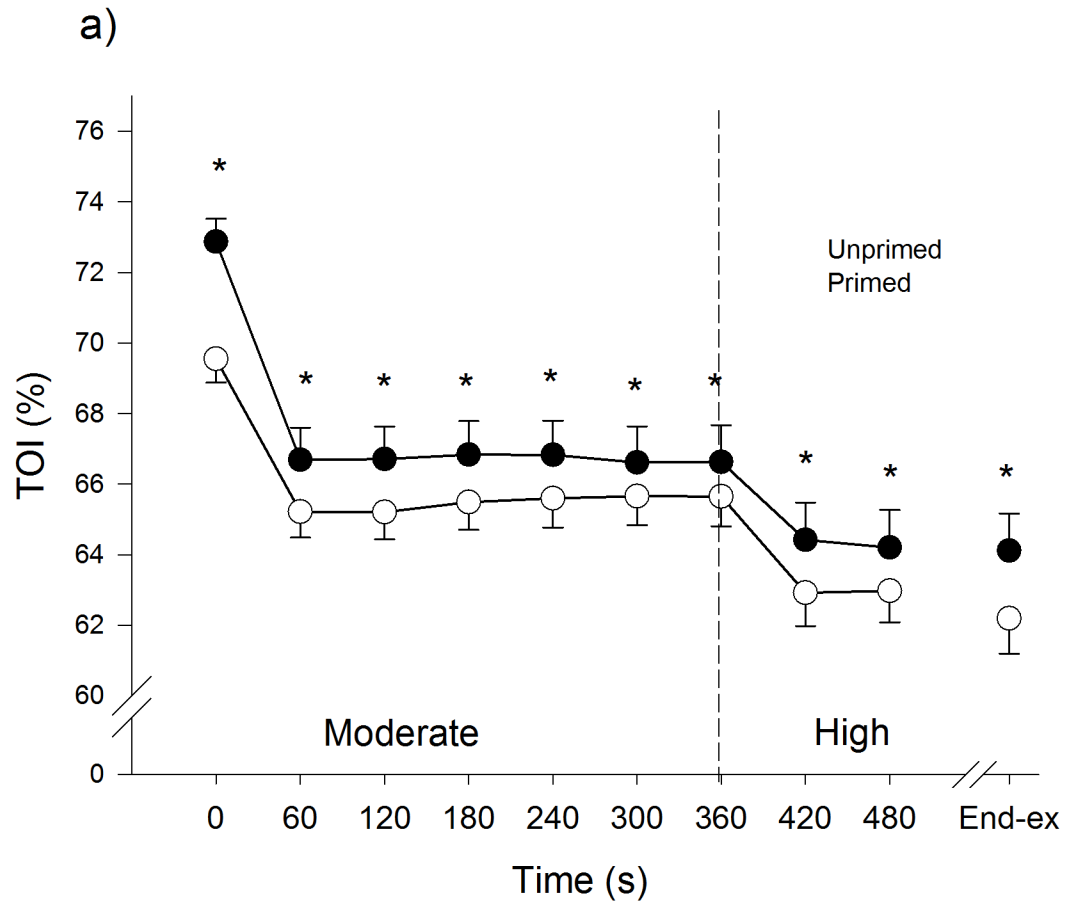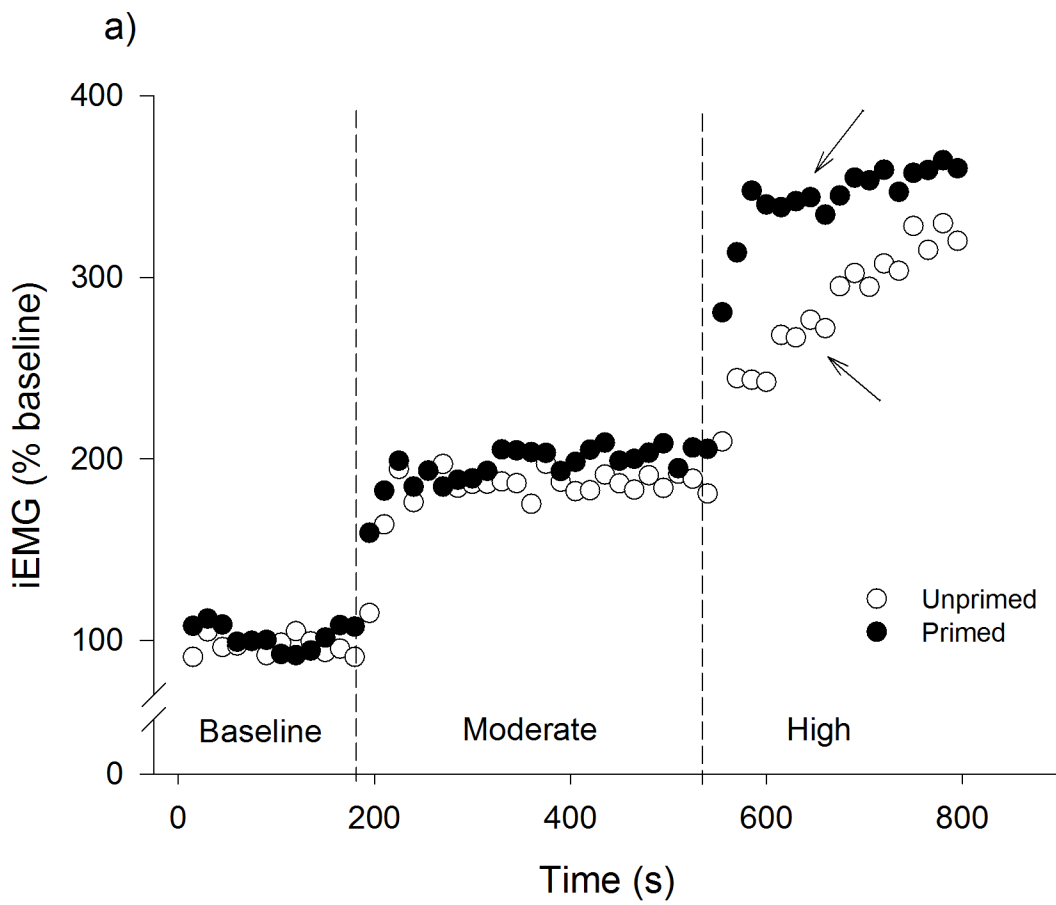
Figure 5
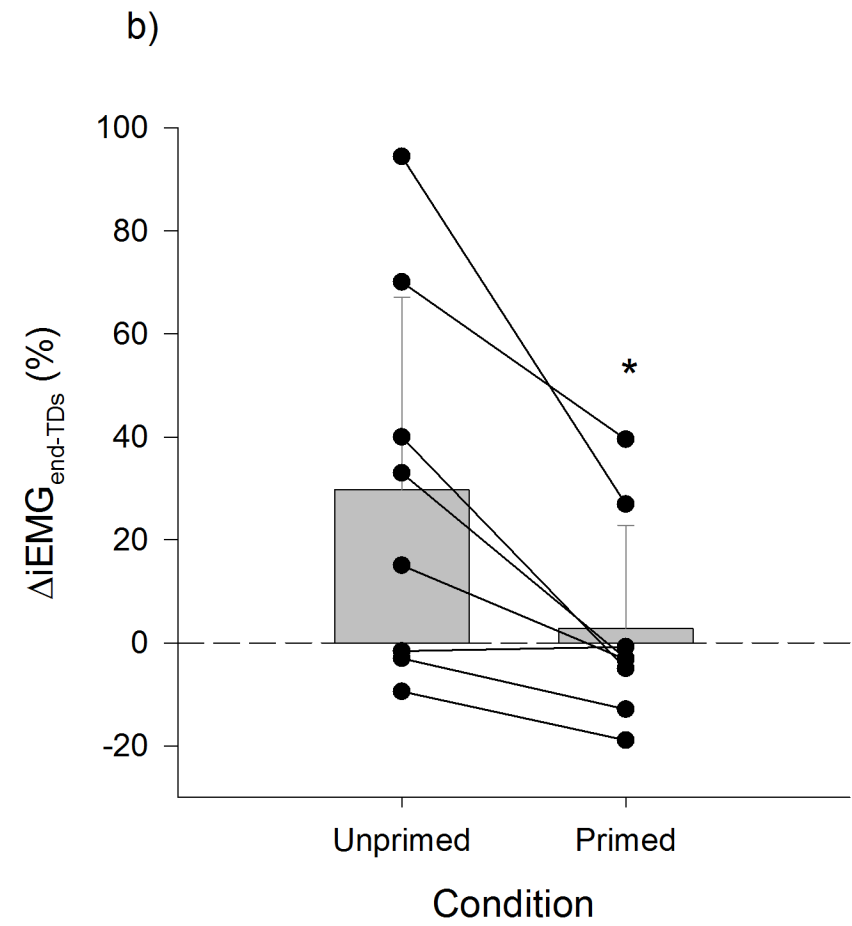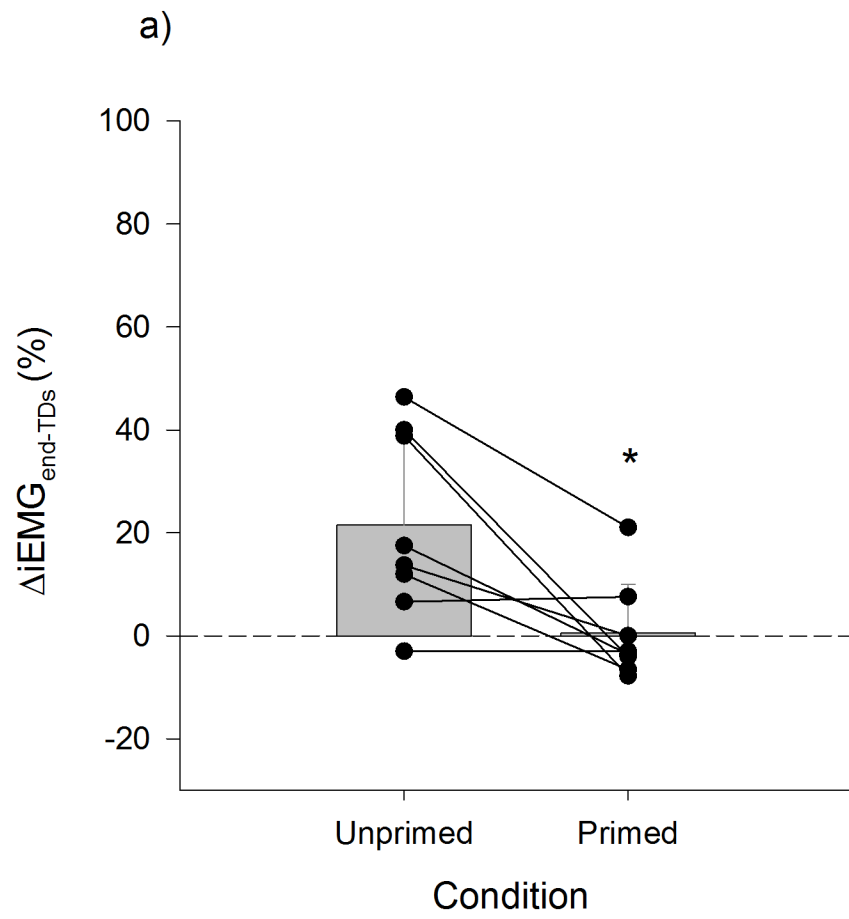
Table 1

Table 1. Physical characteristics and activity levels.
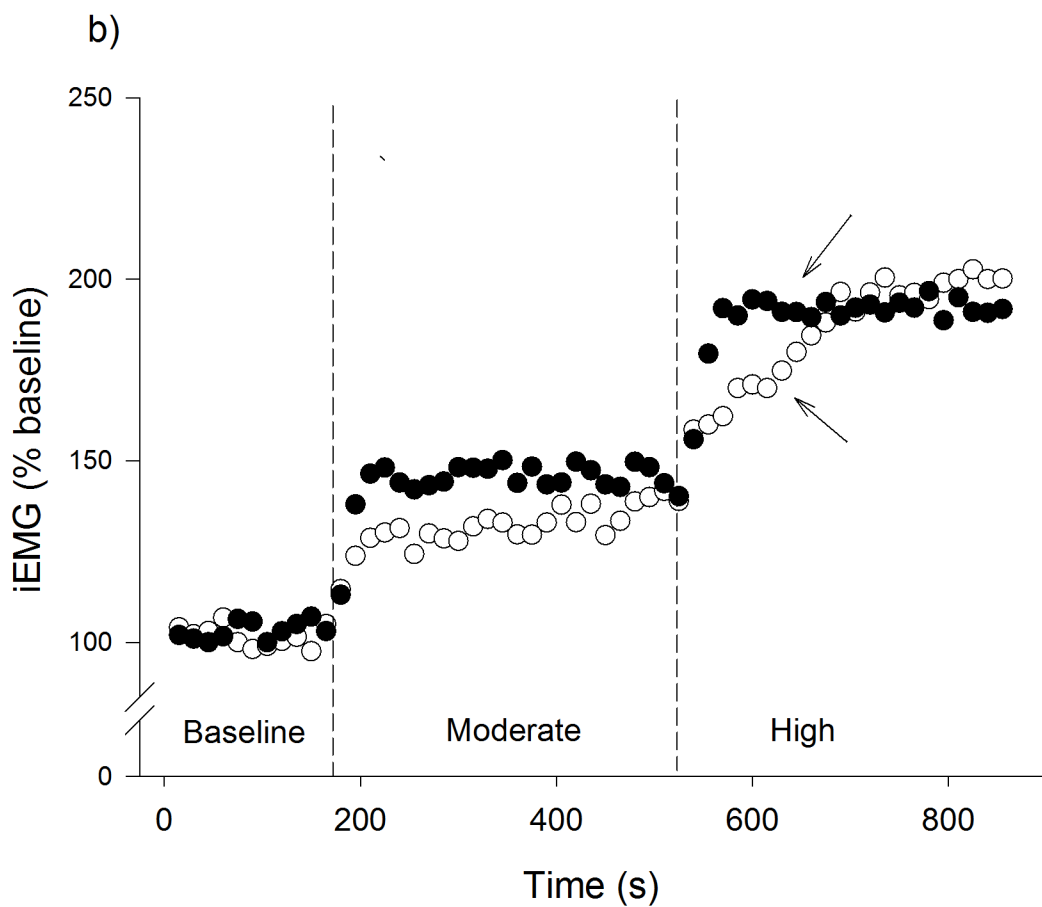
	Controls	T2D	P Value
n	9	9	
Physical characteristics			
Sex (male, female), n	5, 4	5, 4	
Age, yr	45 ± 12	48 ± 9	0.48
Stature, m	1.67 ± 0.07	1.70 ± 0.08	0.46
BMI, kg/m^2	*30 (4)*	*28 (8)*	0.72
Body Mass, kg	*82.0 (8.5)*	*79.0 (32.8)*	0.57
Fat layer VL, mm	*12.7 (10.2)*	*6.5 (2.8)*	0.23
HbA1c, %	*5.1 (0.2)**	*6.9 (1.4)*	0.02
FPG, mmol/L	4.4 ± 0.8*	7.2 ± 1.3	0.01
Time since diagnosis, yr		7.3 ± 4.0	
Total cholesterol, mmol/L	3.85 ± 0.88	4.50 ± 0.77	0.59
LDL-C, mmol/L	2.14 ± 0.86	2.43 ± 0.76	0.65
HDL-C, mmol/L	1.20 ± 0.17	1.00 ± 0.17	0.10
Triglycerides, mmol/L	1.12 ± 0.48	2.33 ± 1.29	0.07
Habitual physical activity			
Inactive, h/day	19.2 ± 1.7	18.3 ± 1.4	0.40
Light, h/day	3.8 ± 1.1	5.1 ± 1.3	0.13
Moderate, h/day	0.73 ± 0.50	0.48 ± 0.28	0.39
Vigorous, h/day	*0.20 (0.25)*	*0.05 (0.33)*	0.35

Values are means ± SD for variables that were normally distributed and median with interquartile range in parentheses for variables which showed significant skewness and were not normally distributed in one or both groups. n, no. of participants. Some variables have missing values, and the sample sizes are as follows: fat layer vastus lateralis (VL), $n = 7$ [nondiabetic control (ND)] and 8 [type 2 diabetes (T2D)]; glycosylated haemoglobin (HbA1c), $n = 4$ (ND) and 7 (T2D); fasting plasma glucose (FPG), $n = 6$ (ND) and 6 (T2D); total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides, $n = 6$ (ND) and 5 (T2D); habitual physical activity, $n = 6$ (ND) and 4 (T2D). BMI, body mass index; VL, vastus lateralis. *Significantly different from T2D ($P < 0.05$).

Table 2 R1

Table 2. Dynamic response characteristics of oxygen uptake ($\dot{V}O_2$) during moderate-intensity and high-intensity cycling exercise of the work-to-work transitions

	Unprimed		Primed	
	Controls	Type 2 diabetes	Controls	Type 2 diabetes
N	9	9	9	9
Moderate-intensity				
Baseline $\dot{V}O_2$, L/min	0.77 ± 0.13	0.89 ± 0.27	0.82 ±.11	0.90 ± 0.23
$\dot{V}O_2$ A_p, L/min	0.82 ± 0.44	0.50 ± 0.21	0.85 ± 0.51	0.51 ± 0.19
$\dot{V}O_2$ τ_p, s	34.6 ± 7.3†	43.8 ± 11.2	25.6 ± 7.7†*	33.2 ± 11.5*
CI$_{95}$ $\dot{V}O_2$ τ_p, s	4.4 ± 2.1	5.1 ± 1.9	4.0 ± 1.2	4.7 ± 0.8
$\dot{V}O_2$ end A, L/min	1.64 ± 0.54	1.44 ± 0.39	1.73 ± 0.65	1.43 ± 0.33
$\dot{V}O_2$ G_p mL.min^{-1}.W^{-1}	9.6 ± 1.7	9.4 ± 2.5	9.3 ± 2.3	9.5 ± 2.3
High-intensity	5.1 ± 1.9	5.1 ± 1.9	5.1 ± 1.9	5.1 ± 1.9
Baseline $\dot{V}O_2$, L/min	1.64 ± 0.54	1.44 ± 0.39	1.73 ± 0.65	1.43 ± 0.33
$\dot{V}O_2$ A_p, L/min	0.53 ± 0.15†	0.33 ± 0.12	0.55 ± 0.15†*	0.40 ± 0.16*
$\dot{V}O_2$ τ_p, s	43.6 ± 9.8†	58.6 ± 16.6	37.7 ± 6.9	37.2 ± 19.9*
CI$_{95}$ $\dot{V}O_2$ τ_p, s	8.8 ± 2.4	8.7 ± 2.9	9.0 ± 1.9	8.0 ± 2.8
$\dot{V}O_2$ A_s, L/min	0.21 ± 0.13	0.16 ± 0.09	0.13 ± 0.09*	0.11 ± 0.04*
$\dot{V}O_2$ A_s, %	27.5 ± 10.3	32.7 ± 11.0	18.5 ± 10.6*	22.5 ± 7.5*
$\dot{V}O_2$ TD_s, s	127 ± 47	119 ± 7	129 ± 50	106 ± 43
$\dot{V}O_2$ end A, L/min	2.37 ± 0.61	1.93 ± 0.50	2.41 ± 0.66	1.95 ± 0.50
$\dot{V}O_2$ MRT, s	73 ± 15†	94 ± 31	57 ± 17*	59 ± 22*
CI$_{95}$ $\dot{V}O_2$ MRT, s	7.4 ± 2.3	7.9 ± 1.4	7.1 ± 2.1	7.1 ± 2.5
End-exercise $\dot{V}O_2$ gain, mL.min^{-1}.W^{-1}	11.2 ± 1.6	10.3 ± 1.7	11.0 ± 1.9	10.2 ± 1.7

Values are means ± SD; *n* = no. of participants. A, amplitude; τ, time constant; end A, steady-state oxygen uptake ($\dot{V}O_2$) response; CI$_{95}$ 95% confidence interval; G, oxygen uptake ($\dot{V}O_2$) gain; TD, time delay; p, primary phase; s slow component phase.

* $P < 0.05$ vs. unprimed within same diabetes status group (i.e. within controls or within Type 2 diabetes). † $P < 0.05$ vs. participants with type 2 diabetes within same condition (i.e. within unprimed or primed).

Table 3

Table 3 Dynamic response characteristics of Δ[HHb+Mb] during moderate-intensity and high-intensity cycling exercise of the work-to-work transitions

	Unprimed		Primed	
	Controls	Type 2 diabetes	Controls	Type 2 diabetes
n	9	9	9	9
Moderate-intensity				
Δ[HHb+Mb] A, μM*cm	77.1 ± 74.7	101.4 ± 87.4	77.5 ± 72.7	110.4 ± 77.9
Δ[HHb+Mb] τ', s	29.4 ± 10.4	31.5 ± 4.8	30.7 ± 6.9	32.7 ± 5.8
Baseline TOI, %	75.4 ± 4.6	69.5 ± 4.5	79.0 ± 5.4*	72.9 ± 4.6*
TOI A, %	2.2 ± 4.7	4.1.8 ± 3.9	3.1 ± 4.8*	6.4 ± 5.1*
High-intensity				
Δ[HHb+Mb] A_p, μM*cm	34.4 ± 35.7	41.6 ± 24.6	31.4 ± 34.3*	29.9 ± 12.1*
Δ[HHb+Mb] τ', s	31.0 ± 20.5	31.8 ± 17.2	29.1 ±11.3	29.1 ± 7.2
Δ[HHb+Mb] A_s, μM*cm	11.7 ± 14.4	6.4 ± 3.7	5.2 ± 6.8	4.5 ± 5.7
Baseline TOI, %	73.3 ± 8.2	65.7 ± 5.9	76.0 ± 9.0*	66.6 ± 7.3*
TOI A, %	2.4 ± 1.9	3.5 ± 1.9	2.4 ± 1.1	2.5 ± 0.7

Values are means ± SD; n = no. of participants. A, amplitude; τ, time constant; p, primary phase; s slow component phase; τ', effective response time (τ + TD); TOI, tissue oxygenation index; [HHb+Mb], deoxygenated haemoglobin and myoglobin concentration.

* $P < 0.05$ vs. unprimed within same diabetes status group (i.e. within controls or within Type 2 diabetes).

DECLARATIONS

Funding

This publication has emanated from research conducted with the financial support of the Health Research Board (Grant No HRA_POR/2073/274).

Conflict of interest

Authors declare that they have no conflict of interest, financial or otherwise.

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Faculty of Health Sciences' Research Ethics Committee, Trinity College Dublin, and St Vincent's Healthcare Ethics and Medical Research Committee

Informed consent

Consent to participate

Written informed consent was obtained from all individual participants included in the study.

Consent to publish

Patients signed informed consent regarding publishing their data

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions

N.G., J.R., M.E., D.O'S. and S.G. contributed to the study conception and design. N.G. and J.R. performed data collection. N.G., and M.E. analysed data. N.G. and M.E. drafted the manuscript. S.G., D.O'S and J.R. contributed to critically revising of this manuscript. All authors approved the final version.