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Gymnasium-Based Unsupervised Exercise Maintains Benefits in Oxygen Uptake Kinetics Obtained Following Supervised Training in Type 2 Diabetes

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Gymnasium-based unsupervised exercise maintains benefits in oxygen uptake kinetics obtained following supervised training in type 2 diabetes

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Abstract: Supervised exercise (SE) in patients with type 2 diabetes improves oxygen uptake kinetics at the onset of exercise. Maintenance of these improvements, however, has not been examined when supervision is removed. We explored if potential improvements in oxygen uptake kinetics following a 12-week SE that combined aerobic and resistance training were maintained after a subsequent 12-week unsupervised exercise (UE). The involvement of cardiac output (CO) in these improvements was also tested. Nineteen volunteers with type 2 diabetes were recruited. Oxygen uptake kinetics and CO (inert gas rebreathing) responses to constant-load cycling at 50% ventilatory threshold (V_T), 80% V_T , and mid-point between V_T and peak workload (50% Δ) were examined at baseline (on 2 occasions) and following each 12-week training period. Participants decided to exercise at a local gymnasium during the UE. Thirteen subjects completed all the interventions. The time constant of phase 2 of oxygen uptake was significantly faster ($p < 0.05$) post-SE and post-UE compared with baseline at 50% V_T (17.3 ± 10.7 s and 17.5 ± 5.9 s vs. 29.9 ± 10.7 s), 80% V_T (18.9 ± 4.7 and 20.9 ± 8.4 vs. 34.3 ± 12.7 s), and 50% Δ (20.4 ± 8.2 s and 20.2 ± 6.0 s vs. 27.6 ± 3.7 s). SE also induced faster heart rate kinetics at all 3 intensities and a larger increase in CO at 30 s in relation to 240 s at 80% V_T ; and these responses were maintained post-UE. Unsupervised exercise maintained benefits in oxygen uptake kinetics obtained during a supervised exercise in subjects with diabetes, and these benefits were associated with a faster dynamic response of heart rate after training.

Key words: cardiac output, gymnasium-based, home-based, cycling, type 2 diabetes, resistance, aerobic.

Résumé : Des exercices physiques supervisés (SE) chez des diabétiques de type 2 améliorent la cinétique de la consommation d'oxygène au début de l'exercice. Néanmoins, on ne sait pas si ces améliorations sont maintenues lorsque cesse la supervision. On explore si les améliorations de la cinétique de la consommation d'oxygène suscitées par 12 semaines d'entraînement aérobie et contre résistance sont maintenues au cours des 12 semaines suivantes sans supervision (UE). On vérifie en outre l'implication du débit cardiaque (CO) dans ces améliorations. On sollicite 19 volontaires présentant un diabète de type 2. On analyse la cinétique de la consommation d'oxygène et du CO (réinspiration d'un gaz inerte) au cours d'un exercice sur vélo aux intensités suivantes : 50 % du seuil ventilatoire (V_T), 80 % du V_T et à mi-chemin entre le V_T et le pic de travail (50 % Δ), et ce, au début (en deux occasions) et après chaque programme de 12 semaines d'entraînement. Les participants décident de s'entraîner au gymnase local en période UE. Treize sujets se rendent jusqu'à la fin. La constante de temps de la phase 2 de la consommation d'oxygène est significativement plus petite ($p < 0,05$) post-SE et post-UE comparativement au départ à 50 % V_T ($17,3 \pm 10,7$ et $17,5 \pm 5,9$ vs. $29,9 \pm 10,7$ s), 80 % V_T ($18,9 \pm 4,7$ et $20,9 \pm 8,4$ vs. $34,3 \pm 12,7$ s) et 50 % Δ ($20,4 \pm 8,2$ et $20,2 \pm 6,0$ vs. $27,6 \pm 3,7$ s). SE améliore la cinétique du rythme cardiaque (HR) aux trois intensités et suscite une plus grande augmentation du CO à la 30^e seconde comparativement à la 240^e seconde à 80 % V_T ; ces ajustements sont maintenus post-UE. Le programme non supervisé d'exercices maintient les gains observés sur le plan de la cinétique de la consommation d'oxygène au cours du programme supervisé d'exercices chez des diabétiques; ces gains sont associés à une réponse dynamique plus rapide du HR à la suite du programme d'entraînement.

Mots-clés : débit cardiaque, exercice en gymnase, exercice à domicile, vélo, diabète de type 2, résistance, aérobie.

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Introduction

The rate at which pulmonary oxygen uptake increases during the initial period of exercise ($\dot{V}O_2$ kinetics) is slower in young and middle-aged subjects with type 2 diabetes compared with nondiabetic controls (Regensteiner et al. 1998; Brandenburg et al. 1999; Bauer et al. 2007; MacAnaney et al. 2011a), although recent data suggests that $\dot{V}O_2$ kinetics are not impaired in older men with type 2 diabetes compared with aged-matched healthy controls (Wilkerson et al. 2011). There is some debate as to whether the source of the slower $\dot{V}O_2$ kinetic responses observed in young and middle-aged diabetics is due to reduced O_2 delivery and (or) due to lower levels of O_2 extraction. In healthy individuals during cycling exercise it appears that $\dot{V}O_2$ kinetics are limited by the oxidative machinery rather than O_2 delivery per se (reviewed by Poole et al. (2008)). However, in type 2 diabetes $\dot{V}O_2$ kinetics are impaired, at least in part, due to a reduced O_2 delivery to the contracting muscles. Support for reduced O_2 delivery as the source of the impairment can be found in the fact that in the rat spinotrapezius muscle capillary haemodynamics are reduced at rest (Padilla et al. 2006), and when this muscle is electrically stimulated the microvascular partial pressure of oxygen response is also impaired in diabetics compared with nondiabetics (Padilla et al. 2007). Similarly, in humans with type 2 diabetes the microvascular blood flow responses, estimated from simultaneously measured near-infrared spectroscopy-derived concentration of deoxygenated haemoglobin of the thigh and pulmonary $\dot{V}O_2$ responses, were significantly slower during moderate cycling compared with healthy controls (Bauer et al. 2007), suggesting, together with the findings by Padilla et al. (2007), a limitation in oxygen transport relative to oxygen usage in diabetes. In addition, we have recently shown that the dynamic response of vascular conductance in the contracting calf muscle is slowed in females with type 2 diabetes (MacAnaney et al. 2011b), and others reported reduced steady-state measurements of leg blood flow during cycling (Kingwell et al. 2003; Lalonde et al. 2008) in diabetic humans. However, the role of the skeletal muscle in the impaired submaximal exercise responses observed in type 2 diabetes cannot be excluded given the evidence of a lower mitochondrial content (Ritov et al. 2005) and abnormal mitochondrial function (Kelley et al. 2002; Ritov et al. 2005).

Regardless of the mechanism, the slowing of the $\dot{V}O_2$ kinetic response is associated with a greater reliance on anaerobic metabolism (Timmons et al. 1996), more rapid fatigue, and a lower exercise tolerance (Hughson and Tschakovsky 1999). This might help explain the lower exercise tolerance in individuals with type 2 diabetes (Kjaer et al. 1990; Regensteiner et al. 1995, 1998, 2009; Baldi et al. 2003; MacAnaney et al. 2011a) and their perception that routine daily activities are more difficult to perform when compared with healthy controls (Huebschmann et al. 2009). Therefore, interventions aimed at accelerating the $\dot{V}O_2$ kinetic response might be important to improve exercise tolerance in diabetic individuals and reduce the associated risk of mortality (Wei et al. 2000).

Short-term, supervised exercise training accelerates the kinetic response of $\dot{V}O_2$ during submaximal exercise (Brandenburg et al. 1999) and increases exercise tolerance in type 2

diabetes (reviewed by Zanuso et al. (2010)). At present the physiological mechanisms underlying these exercise adaptations are not known, although they might include mechanisms that enhance O_2 delivery to (i.e., cardiac output, muscle blood flow) — and (or) O_2 -dependent metabolism within — contracting myocytes. In addition, relatively little is known about the period over which these short-term improvements are maintained after supervision has been removed. An important objective of exercise training is to help individuals create and maintain their own self-controlled programme of physical activity once the supervision has ceased. However, home-based unsupervised exercise has been shown insufficient to maintain benefits in glycaemic control and body composition obtained following a supervised exercise mainly because of reductions in exercise adherence in type 2 diabetes (Dunstan et al. 2005). To our knowledge, the effectiveness of such a programme in maintaining improvements in $\dot{V}O_2$ kinetics and exercise tolerance is not known.

To explore the mechanistic basis of the training-induced improvement in $\dot{V}O_2$ kinetics, the present study tested the hypothesis that supervised exercise training increases the rate of adjustment of heart rate, cardiac output (CO), and $\dot{V}O_2$ during submaximal exercise. Whether or not such improvements could be maintained with a subsequent period (12 weeks) of unsupervised training was also tested.

Materials and methods

Subjects

Nineteen volunteers (12 men and 7 women) with type 2 diabetes (mean \pm SD; age, 50 ± 6 years; HbA_{1c} , $7.3\% \pm 1.2\%$; fasting glucose, 8.4 ± 1.7 mmol·L⁻¹) were recruited from the Diabetes Unit at St Columcille's Hospital, Dublin, Ireland. Participants were excluded if diagnosed with peripheral arterial disease, hypertension, coronary heart disease, neuropathy, or retinopathy, or had smoked during the 12 months preceding the study. Subjects were taking metformin ($n = 7$) or thiazolidinedione ($n = 1$) mono-therapy or were undergoing dietary control ($n = 11$) of their diabetes. All subjects had a clinical history of diabetes ranging between 1 and 4 years, but immediately prior to the study did not have clinical evidence of ischaemic heart disease (normal electrocardiogram during treadmill stress test), kidney dysfunction (consistent urinary protein < 200 mg·dL⁻¹), or liver dysfunction (urinary creatinine levels < 2.2 mg·dL⁻¹).

Female participants were both premenopausal ($n = 3$) and postmenopausal ($n = 4$). Subjects were classified as inactive (<1 h·week⁻¹ of moderate intensity exercise in the preceding 3 months), which was confirmed using the Low Level Physical Activity Recall (LOPAR) questionnaire (Kriska et al. 2006). All subjects provided written informed consent prior to participation, and the study was approved by the Faculty of Health Science Research Ethics Committee, Trinity College Dublin, and conducted in accordance with the Declaration of Helsinki.

Overview of experimental protocol

Subjects were requested to participate in a 12-week supervised exercise training programme (SE) immediately followed by a 12-week unsupervised exercise training programme (UE). Baseline laboratory testing occurred twice (BS1 and

BS2) separated by 12 weeks. This control period aimed to examine stability of measurements prior to entering the training programme, during which subjects did not perform any regular physical exercise apart from their customary recreational physical activities (i.e., walking). Laboratory testing was then repeated post-SE and post-UE.

Subject attrition

All 19 subjects completed laboratory testing at BS1. Of these, 15 completed laboratory testing at BS2. All 19 participants entered the 12-week SE, during which 4 were withdrawn from the study because of poor adherence to the exercise training. As such, 15 subjects entered the 12-week UE. Early in the UE an additional 2 subjects withdrew from the study for personal reasons, and so 13 subjects completed the laboratory testing post-UE.

The analysis for the control phase (BS1 vs. BS2) included data from 15 subjects (10 men, 5 women; 2 postmenopausal). The analysis for the exercise intervention phase (baseline vs. post-SE vs. post-UE) included responses from the 13 participants (8 men, 5 women; 3 postmenopausal) that completed the 2 training phases. For the training related effects, “baseline” data were calculated as the average of BS1 and BS2 when the physiological responses were not significantly different between the 2 baselines (the majority of the cases, see Results section) as this approach would yield a value closer to the true baseline value. Instead, BS2 measurements were used when a significant difference between the 2 baselines was observed and for subjects’ physical characteristics. BS1 data were used for subjects that entered the training program without completing laboratory testing at BS2 ($n = 2$).

Laboratory testing

All laboratory testing utilised identical protocols to those described previously (MacAnaney et al. 2011a). At each laboratory testing phase (BS1, BS2, post-SE, post-UE) subjects attended the human laboratory of the Department of Physiology, Trinity College Dublin, for 3 visits over 8 days. For premenopausal subjects this was aligned with the mid-follicular phase of the menstrual cycle (days 5–12). Each visit was separated by 36–72 h. Before each visit subjects were asked to refrain from consuming caffeine and alcohol in the 24 h prior to testing, in addition to limiting exercise to activities of daily living. All exercise for the laboratory testing was performed on an electrically braked cycle ergometer (Excalibur Sport, Lode, Groningen, Netherlands).

During visit 1, subjects performed a graded cycling exercise test to failure to determine the ventilatory threshold (V_T) and peak $\dot{V}O_2$. Following 3 min of rest, subjects cycled at an initial workload of 40 W, which was increased by 20 W every 3 min until the required cadence (60 repetitions per minute) could not be maintained (i.e., task failure). The peak workload achieved was defined as the highest workload able to be maintained for at least 1 min. From this test, the workload at which the V_T occurred was determined using the V-slope method (Beaver et al. 1986; Amann et al. 2004).

On each remaining testing day (2 and 3), subjects were required to complete exercise bouts at 3 different workloads, 50% V_T , 80% V_T , and 50% Δ (midpoint between V_T and peak workload) according to the following sequence: 3 min rest, 7 min cycling (50% V_T), 10 min rest, 7 min cycling

(80% V_T), 15 min rest, 7 min cycling (50% Δ). Subjects then rested for 45 min before repeating the exercise sequence. Previous data suggest that the rest periods used were sufficient for heart rate (HR) and blood lactate to return to resting levels (Barstow et al. 1996; Burnley et al. 2006). The first three 7-min bouts at each intensity were used to determine $\dot{V}O_2$ and HR kinetics, and the fourth bout at each intensity was used for determination of CO responses. Exercise intensities at BS1, BS2, post-SE, and post-UE were all calculated from the graded cycling test performed at BS1 (i.e., exercise workloads were not recalculated).

Measurements

Throughout rest and during exercise HR was recorded every 5 s (S725x, Polar Electro Oy, Kempele, Finland). In addition, subjects wore a facemask to collect expired air and determine $\dot{V}O_2$ on a breath-by-breath basis using an online metabolic system (Innocor, Innovision A/S, Odense, Denmark). This system was also used to measure CO during the final 7 min of exercise at each intensity on testing day 3, but at 2 time-points only (30 s and 240 s). CO was measured using an inert gas rebreathing technique as previously used during similar exercise testing procedures (Jakovljevic et al. 2008; MacAnaney et al. 2011a). Stroke volume was calculated as CO/HR. The rate of increase of CO relative to its steady-state level was estimated by $(CO \text{ at } 30s - \text{resting CO}) / (CO \text{ at } 240s - \text{resting CO}) \cdot 100$.

Data analysis

To determine the kinetic parameters of $\dot{V}O_2$ for each subject, at each exercise intensity, the 7-min data sets were analysed according to previously published methods (MacAnaney et al. 2011a). Briefly, data sets were linearly interpolated to provide values at 1-s intervals, then time aligned and averaged. Data were then smoothed using a 5-s moving average filter. Kinetic parameters at each intensity were determined by fitting a multiphasic exponential curve to the results (see eq. [1] below). For exercise at 50% V_T and 80% V_T a biphasic exponential curve model was used (i.e., utilizing only the first 2 exponential component terms in eq. [1]), while for the 50% Δ , the full triphasic function was used.

$$[1] \quad \dot{V}O_2(t) = \text{baseline } \dot{V}O_2 + A_1 [1 - e^{-(t-TD_1)/\tau_1}] U_1 \\ + A_2 [1 - e^{-(t-TD_2)/\tau_2}] U_2 + A_3 [1 - e^{-(t-TD_3)/\tau_3}] U_3$$

The 3 exponential terms represent the “cardiodynamic”, “fast”, and “slow” components of the $\dot{V}O_2$ response to exercise. Baseline $\dot{V}O_2$ represents oxygen uptake during the initial 3-min rest period of each exercise sequence; and for each exponential term A is the amplitude; τ is the time constant; and TD is the time delay. The parameter U is a conditional expression that limits the fitting of a particular phase to the period at and beyond the time delay associated with that phase. The models were fitted using a weighted least-squares nonlinear regression procedure (TableCurve 2D, Systat, USA).

The mean response time (MRT) represents the time to reach ~63% of the difference between baseline and the exercise plateau (MacDonald et al. 1998) and was calculated as a weighted sum of the time delay and time constant of each

phase according to eq. [2] (using the first 2 components for 50% V_T and 80% V_T and all 3 components for 50% Δ):

$$[2] \quad \text{MRT} = [A_1/(A_1 + A_2 + A_3)(\text{TD}_1 + \tau_1)] \\ + [A_2/(A_1 + A_2 + A_3)(\text{TD}_2 + \tau_2)] \\ + [A_3/(A_1 + A_2 + A_3)(\text{TD}_3 + \tau_3)]$$

Heart rate responses were averaged to yield a single time-series of heart rate data for each subject at each intensity. Heart rate responses at 50% and 80% V_T intensities were fitted using a monophasic (instead of biphasic) function according to eq. [3], as this was the model that best fitted the responses for the majority of subjects on the basis of comparing the goodness-of-fit of these 2 (monophasic and biphasic) functions (Motulsky and Ransnas 1987).

$$[3] \quad \text{Heart rate} = a + A[1 - e^{-(t-\text{TD})/\tau}]$$

where a is the initial resting heart rate, A the amplitude of the exercise response, TD the delay in rise of heart rate after exercise onset, and τ is the time constant of the response. Fitting procedures were identical to that described for $\dot{V}O_2$.

For 50% Δ intensities heart rate responses were fitted using a biphasic function (as described in eq. [1]) as this model was best fitted for the majority of the responses compared with a monophasic or triphasic functions (Motulsky and Ransnas 1987). The MRT for heart rate responses at 50% Δ were calculated according to eq. [2] (using the first 2 components).

SE programme

Each subject was required to train 3 times per week normally in nonconsecutive days during the 12-week programme. Sessions were supervised by one of the study researchers. Exercise intensities were personalised according to the incremental cycling test at BS1. Warm-up comprised 10 min of stationary cycling at 60% heart rate reserve (HRR) and static stretching of major muscle groups. Aerobic exercise comprised 35–40 min at 70%–75% HRR (weeks 1–6), progressing to 75%–80% HRR (weeks 7–12). Subjects were allowed to choose among stationary bikes, treadmills, elliptical trainers, rowers, and stair masters for aerobic exercise. Resistance training included 6 resistance exercises, 5 of which were compound exercises incorporating major muscle groups (bench press, pull down, leg press, leg extension, and squats), plus calf raises that were performed on a step whilst holding a weight. Subjects completed 1 set of 12 repetitions (weeks 1–6) at 60% of 1 repetition concentric maximum (1RM), and progressed to 2 sets of 12 repetitions (weeks 7–12) at 70% 1RM. 1RM was determined at week 0 and reassessed every 4 weeks during the programme with training loads adjusted accordingly. Cool-down comprised 5 min of treadmill walking and the stretching routine.

UE programme

Subjects were encouraged to train at home, at local leisure centres, or nearby facilities (parks, sports fields, etc.). A 3-month subscription in the same leisure centre where the SE was conducted was offered. All participants decided to perform all of the UE training sessions in this leisure centre. Subjects were again requested to train 3 times per week for

12 weeks and were informed of their graded test performance post-SE to assist them in personalizing the aerobic exercise component. Similar to the SE, participants were requested to begin at 30–40 min at 75%–80% HRR for aerobic exercise, and 1–2 sets of 12 repetitions at 70% 1RM for the same 6 resistance exercises. The study investigators maintained weekly contact with subjects via phone calls and gave advice when required.

Maximum strength

Upper body (bench press) and lower body (leg extension) maximum strength were assessed (1RM) before and after the SE and the UE.

Statistical analyses

Physiological responses during the control period (between BS1 and BS2) were compared using a paired t test. The training-related resting and peak physiological effects (between baseline, post-SE, and post-UE) were tested using 1-way repeated measures ANOVA. Cardiac responses during the constant load cycling bouts during both the control and the training period were compared using a 2-way repeated measures ANOVA (time \times group). Differences were located using Tukey's post hoc test. Data that were not normally distributed were analysed using Kruskal–Wallis test and multiple comparisons were then performed using Dunn's method. The level of significance was set as $p \leq 0.05$. All values are expressed as means \pm SD.

Results

Training adherence

Adherence to the supervised exercise program was $92\% \pm 8\%$ (81%–100%) and adherence to the unsupervised training program was $90\% \pm 10\%$ (72%–100%). The adherence between the 2 training programmes was not significantly different.

Maximum strength (resistance training)

Compared with baseline (i.e., pre-training), 1RM outcomes for the upper and lower body resistance exercises were significantly higher both post-SE and post-UE (bench press: 39 ± 25 kg, 46 ± 30 kg, 46 ± 30 kg, respectively; leg extension: 45 ± 27 kg, 58 ± 31 kg, 59 ± 30 kg, respectively), and not different between post-SE and post-UE.

Physical characteristics and activity levels

Exercise training induced significantly higher physical activity scores post-SE and post-UE compared with baseline (Table 1). There was a main significant effect on body mass (kg) following exercise training (main effect = time, $p = 0.048$), although post hoc tests did not reveal significant differences between baseline and post-SE and (or) post-UE. Body mass index did not change significantly ($p = 0.41$) following SE and UE compared with baseline.

Graded test

During the control phase, peak heart rate (beats·min⁻¹) was significantly lower at BS2 compared with BS1 but the rest of the variables remained unaltered (Table 2). Following the training intervention, peak $\dot{V}O_2$ (mL·kg⁻¹·min⁻¹) and peak

Table 1. Physical characteristics and activity levels.

	BS1 (n = 15)	BS2 (n = 15)	Baseline (n = 13)	Post-SE (n = 13)	Post-UE (n = 13)
Age (y)	50±6		51±7		
HbA _{1c} (%)	7.3±1.2		7.1±1.2		
FPG (mmol·L ⁻¹)	8.4±1.7		8.4±1.6		
Body mass (kg)	96.9±17.1	97.2±17.5	93.1±18.3	91.3±18.3	91.6±18.1
BMI (kg·m ⁻²)	32.8±5.8	32.9±5.8	31.2±3.8	30.6±4.0	30.6±3.9
Activity (METs; h·week ⁻¹)	160±13	160±12	164±13	176±12 [†]	173±13 [†]

Note: Values are means ± SD for physical and haematological characteristics and activity levels. BS1 and BS2, baseline laboratory testing; SE, supervised exercise; UE, unsupervised exercise; FPG, fasting blood glucose; BMI, body mass index.

[†]Significantly different ($p < 0.05$) than baseline.

Table 2. Peak physiological responses.

	BS1 (n = 15)	BS2 (n = 15)	Baseline (n = 13)	Post-SE (n = 13)	Post-UE (n = 13)
Peak $\dot{V}O_2$ (mL·min ⁻¹ ·kg ⁻¹)	19.6±5.5	20.1±4.6	20.5±5.7	24.9±7.4 [†]	24.8±8.1 [†]
Peak workload (W)	128±41	127±45	131±45	162±61 [†]	165±62 [†]
Peak HR (beats·min ⁻¹)	160±16	152±14*	151±13	153±14	158±16
Time to failure (min)	15.4±6.1	14.9±6.3	15.9±6.8	20.2±8.7 [†]	20.8±9.3 [†]
Workload at V_T (W)	86±34	86±38	89±37	115±65 [†]	132±66 [†]
$\dot{V}O_2$ at V_T (mL·min ⁻¹ ·kg ⁻¹)	15.5±4.0	16.1±4.5	16.5±4.5	19.0±6.8 [†]	19.5±6.6 [†]

Note: Values are means ± SD for peak physiological responses following the graded test. BS1 and BS2, baseline laboratory testing; SE, supervised exercise; UE, unsupervised exercise; HR, heart rate; V_T , ventilatory threshold.

*Significantly different ($p < 0.05$) than BS1

[†]Significantly different ($p < 0.05$) than baseline.

workload (W) were significantly larger post-SE and post-UE compared with baseline. Workload (W) and $\dot{V}O_2$ (mL·kg⁻¹·min⁻¹) at V_T were also significantly larger post-SE and post-UE compared with baseline. Exercise training did not affect peak HR responses. None of the physiological responses was different between post-SE and post-UE.

CO responses

Following the training intervention, absolute values of CO (L·min⁻¹) were not different from baseline at any intensity (Fig. 1). However, the relative or percentage change in CO from rest at 30 s compared with 240 s was larger post-SE (78% ± 15%) and post-UE (80% ± 16%) compared with baseline (64% ± 16%) at 80% V_T ; and tended to be larger at 50% V_T ($p = 0.06$) and 50% Δ ($p = 0.14$). HR responses at 240 s during all 3 cycle intensities were lower both post-SE and post-UE compared with baseline, and at 30 s they were reduced post-UE compared with baseline. Only at 50% Δ was HR at 30 s lower post-SE compared with baseline. Stroke volume responses were significantly larger both at 30 s and 240 s, post-SE and post-UE compared with baseline at 50% V_T , and although not significantly different, stroke volume responses tended to be larger at 80% V_T ($p = 0.08$) but not at 50% Δ ($p = 0.41$).

$\dot{V}O_2$ and HR kinetic responses

The mean kinetic parameter estimates defining the biphasic (50% V_T and 80% V_T) and triphasic (50% Δ) response of $\dot{V}O_2$, as well as kinetic parameters defining the monophasic (50% V_T and 80% V_T) and biphasic (50% Δ) response of HR during constant load cycling can be seen in Table 3. $\dot{V}O_2$

responses during exercise at 50% V_T in a representative individual at baseline, post-SE, and post-UE are shown in Fig. 2. Following the training intervention, the time constant of the second phase (τ_2) and MRT were significantly lower at all 3 intensities post-SE and post-UE compared with baseline. In addition, at the highest intensity the time constant of the third phase (τ_3) and A_3 were lower post-SE and post-UE compared with baseline. For the HR kinetic responses, the time constants at 50% V_T and 80% V_T were significantly lower post-SE and post-UE compared with baseline. At 50% Δ , the mean response time of HR was lower post-SE and post-UE compared with baseline. Also, at 80% V_T and 50% Δ , the amplitude of the HR response (A_1) was lower post-SE and post-UE compared with baseline.

Discussion

In the present study, 12 weeks of supervised exercise training significantly increased the rate of adjustment of pulmonary $\dot{V}O_2$ (i.e., mean response time) during 3 levels of submaximal exercise. This effect was associated with a significant and consistent reduction in the time constant of phase 2 of the $\dot{V}O_2$ response, as well as a significant reduction in the amplitude and time constant of phase 3 at the highest intensity. Training resulted in a faster adjustment in heart rate during exercise combined with a larger relative change in CO over 30 s, as well as a larger increase in stroke volume during exercise at the lowest intensity. These improvements in dynamic responses coexisted with significant increases in exercise tolerance and peak $\dot{V}O_2$, all of which were maintained during a subsequent period of unsupervised training.

Fig. 1. Mean (\pm SD) cardiac output (CO), stroke volume (SV), and heart rate (HR) during cycling exercise at 50% ventilatory threshold (V_T), 80% V_T and 50% Δ for subjects who completed the control phase (baseline 1 (white square) and baseline 2 (black circle), $n = 15$) and the exercise intervention phases (baseline (white triangle), post-supervised exercise (SE) (black square) and post-unsupervised exercise (UE) (white circle), $n = 13$). *, Significantly different ($p < 0.05$) than BS1; †, post-SE significantly different ($p < 0.05$) than baseline; ‡, post-UE significantly different ($p < 0.05$) than baseline; §, post-UE significantly different ($p < 0.05$) than post-SE.

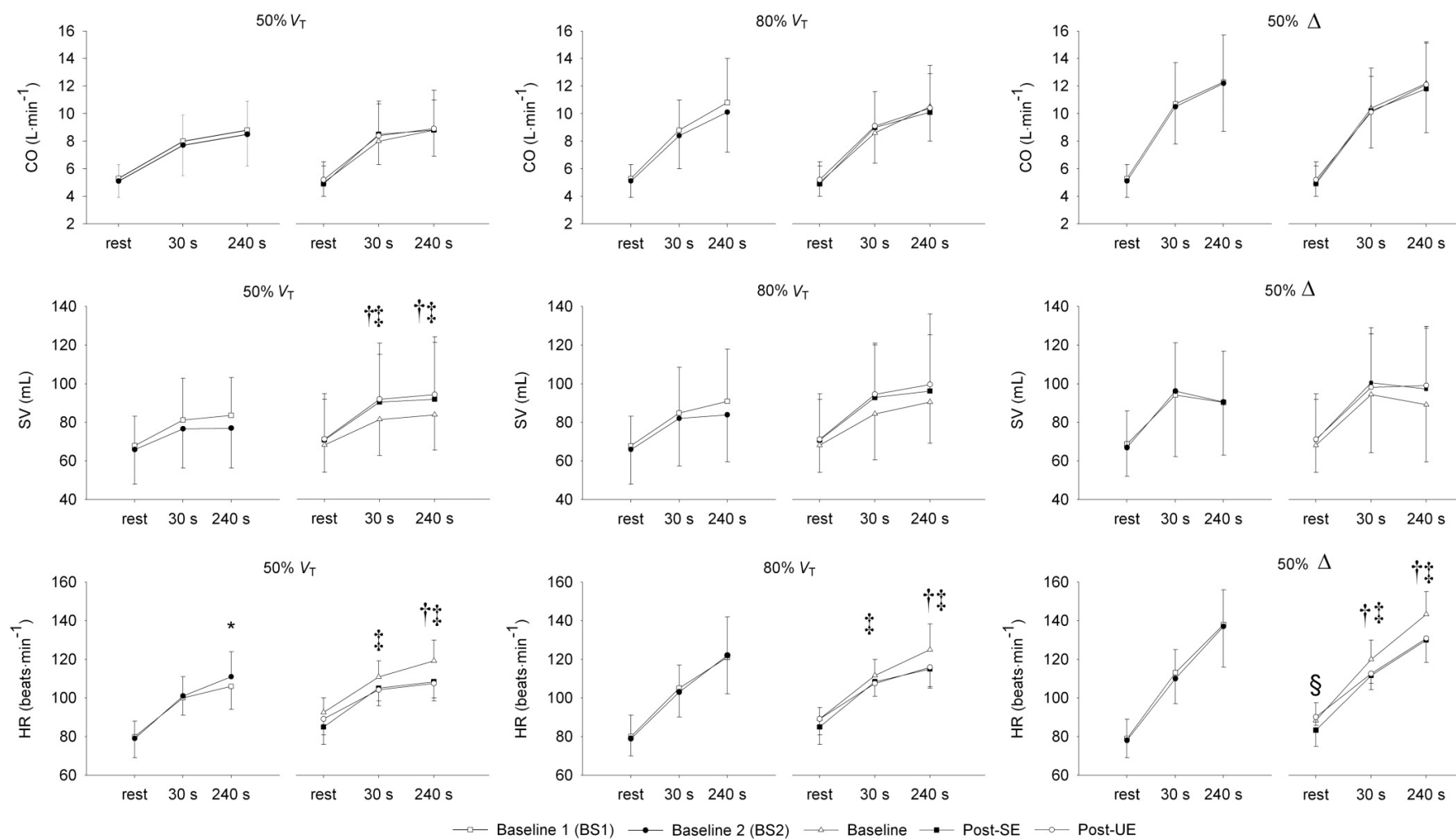


Table 3. Oxygen uptake and heart rate kinetic parameters.

	BS1 (n = 15)	BS2 (n = 15)	Baselines (n = 13)	Post-SE (n = 13)	Post-UE (n = 13)
50% V_T					
$\dot{V}O_2 A_1$ (L·min ⁻¹)	0.35±0.11	0.37±0.10	0.36±0.13	0.41±0.20	0.43±0.13
$\dot{V}O_2 \tau_1$ (s)	4.5±2.4	5.6±2.3	4.9±2.3	5.3±1.7	5.0±2.0
$\dot{V}O_2 A_2$ (L·min ⁻¹)	0.35±0.16	0.42±0.18*	0.43±0.19	0.32±0.11 [†]	0.35±0.16
$\dot{V}O_2 \tau_2$ (s)	29.2±14.0	31.7±8.4	29.9±10.7	17.3±10.7 [†]	17.5±5.9 [†]
$\dot{V}O_2$ MRT (s)	31.8±10.9	37.4±8.4	34.4±8.3	29.7±7.4 [†]	25.2±4.7 ^{†,‡}
HR A_1 (beats·min ⁻¹)	28±10	23±6	24±6	23±3	22±8
HR τ_1 (s)	44.6±29.6	33.0±25.0	32.0±21.6	10.5±4.8 [†]	19.3±12.1 [†]
80% V_T					
$\dot{V}O_2 A_1$ (L·min ⁻¹)	0.37±0.12	0.46±0.19*	0.46±0.21	0.48±0.18	0.54±0.21
$\dot{V}O_2 \tau_1$ (s)	4.7±3.0	5.4±3.1	4.8±2.9	4.2±2.5	5.4±2.0
$\dot{V}O_2 A_2$ (L·min ⁻¹)	0.56±0.26	0.61±0.19	0.61±0.23	0.53±0.18	0.51±0.19 [†]
$\dot{V}O_2 \tau_2$ (s)	32.4±7.9	35.2±9.7	34.3±12.7	18.9±4.7 [†]	20.9±8.4 [†]
$\dot{V}O_2$ MRT (s)	38.2±6.6	40.5±10.1	41.1±12.3	33.4±6.1 [†]	32.1±6.1 [†]
HR A_1 (beats·min ⁻¹)	39±17	37±14	38±11	33±6 [†]	33±11 [†]
HR τ_1 (s)	47.6±19.5	40.8±13.7	39.6±14.1	19.3±7.1 [†]	20.7±11.2 [†]
50% Δ					
$\dot{V}O_2 A_1$ (L·min ⁻¹)	0.56±0.24	0.57±0.25	0.54±0.25	0.58±0.22	0.61±0.24
$\dot{V}O_2 \tau_1$ (s)	6.0±3.9	6.3±2.9	5.6±2.4	5.0±2.5	4.3±2.5
$\dot{V}O_2 A_2$ (L·min ⁻¹)	0.70±0.25	0.80±0.33*	0.81±0.30	0.82±0.32	0.80±0.35
$\dot{V}O_2 \tau_2$ (s)	25.6±5.7	27.7±4.4	27.6±3.7	20.4±8.2 [†]	20.2±6.0 [†]
$\dot{V}O_2 A_3$ (L·min ⁻¹)	0.15±0.06	0.14±0.07	0.16±0.06	0.07±0.04 [†]	0.09±0.05 [†]
$\dot{V}O_2 \tau_3$ (s)	107.1±49.8	101.4±41.6	115.4±46.1	63.1±22.8 [†]	80.9±27.5 [†]
$\dot{V}O_2$ MRT (s)	58.9±13.2	58.6±11.5	66.0±24.7	48.8±15.1 [†]	48.5±15.2 [†]
HR A_1 (beats·min ⁻¹)	48±13	46±12	51±12	41±12 [†]	41±10 [†]
HR τ_1 (s)	35.7±10.9	37.9±8.4	37.6±9.1	24.5±15.5 [†]	34.0±22.6
HR A_2 (beats·min ⁻¹)	24±11	16±12*	16±12	11±8 [†]	12±8 [†]
HR τ_2 (s)	330.2±129.2	256.1±159.4	258.6±117.3	116.1±146.3 [†]	151.2±160
HR MRT (s)	185.7±72.2	133.4±22.4	143.3±54.8	74.4±55.6 [†]	92.7±57.9 [†]

Note: Values are means ± SD for $\dot{V}O_2$ and HR kinetic parameters at 3 exercise intensities (50% V_T , 80% V_T , and 50% Δ) for subjects who completed the control phase (BS1 and BS2) and the exercise intervention phases (baseline, post-SE, and post-UE). SE, supervised exercise; UE, unsupervised exercise; V_T , ventilatory threshold; $\dot{V}O_2$, oxygen uptake; A_1 , A_2 , A_3 , amplitude of the exercise response for each exponential phase; τ_1 , τ_2 , τ_3 , time constant for each exponential phase; HR, heart rate; MRT, mean response time.

*Significantly different ($p < 0.05$) than BS1.

[†]Significantly different ($p < 0.05$) than baseline.

[‡]Significantly different ($p < 0.05$) than post-SE.

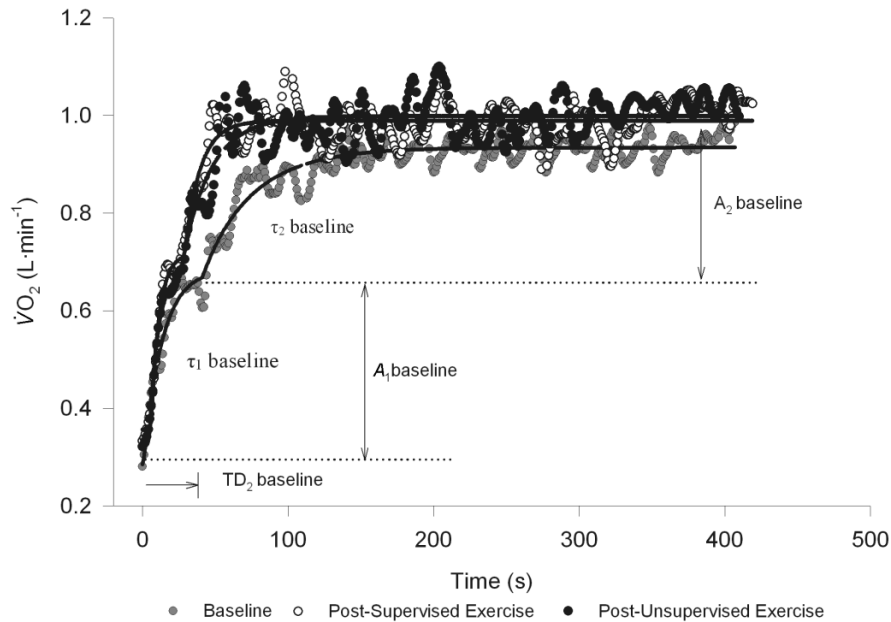
Training and $\dot{V}O_2$ kinetics

In type 2 diabetes, exercise training is an important therapeutic modality because it improves exercise tolerance and peak $\dot{V}O_2$ (Zanuso et al. 2010), both of which are strongly associated with cardiovascular and all-cause mortality (Wei et al. 2000; Myers et al. 2002). Although the physiological basis of these training adaptations is not clear, it might be related to an increased fatigue resistance and faster adjustment of $\dot{V}O_2$ during submaximal exercise. The present findings reveal consistently faster $\dot{V}O_2$ kinetics (i.e., lower MRT) across a wide range of submaximal intensities after training. These data confirm a previous report of a training-induced reduction in the time constant of pulmonary $\dot{V}O_2$ during exercise, when the $\dot{V}O_2$ response was assumed to be mono-exponential (Brandenburg et al. 1999). However, we used a biphasic or triphasic function to characterise this response (Whipp 2009) and showed that the improved mean response time of $\dot{V}O_2$, analogous to the finding by Brandenburg et al. (1999), was associated with a significant reduction in

the time constant of phase 2, as well as a significant reduction in the time constant and amplitude of phase 3 at the highest intensity. Since these phases of the pulmonary $\dot{V}O_2$ response have been linked to mitochondrial control in contracting muscles (Grassi et al. 1996; Krstrup et al. 2004), then the present study suggests that exercise training in type 2 diabetes influences those O_2 -dependent processes that underlie phase 2 and, when it occurs at higher intensities, phase 3 of this response.

The control of $\dot{V}O_2$ during the initial period of an acute exercise depends on the control of muscle blood flow (O_2 delivery) and $a\text{-}vO_2$. Oxygen delivery could be linked by poor pumping capacity and (or) impaired vasodilation; whereas $a\text{-}vO_2$ reflects an interaction between blood flow and oxidative metabolism. The slowed $\dot{V}O_2$ kinetic responses in uncomplicated diabetes do not seem to be related to CO as its responses during submaximal cycling exercise are not slower or smaller than in nondiabetic controls (Baldi et al. 2003; MacAnaney et al. 2011a). The role of the skeletal

Fig. 2. Representative oxygen uptake ($\dot{V}O_2$) responses during cycling exercise at intensities equivalent to 50% V_T in an individual at baseline, post-supervised exercise, and post-unsupervised exercise. Note that at baseline, the time constant for phase 2 (τ_2) and the mean response time are slower compared with post-supervised exercise and post-unsupervised exercise. A_1 , A_2 , amplitude for phases 1 and 2, respectively; τ_1 , τ_2 , time constant for phases 1 and 2, respectively; TD_2 , time delay for training phase 2.



muscle is not to be excluded given the observations of a lower mitochondrial content (Ritov et al. 2005) and abnormal mitochondrial function (Kelley et al. 2002; Ritov et al. 2005; Phielix et al. 2008) in muscles of diabetics compared with healthy controls. However, $a\text{-}\dot{V}O_2$ responses during submaximal cycling adjust at a similar rate and to a similar level in type 2 diabetes compared with healthy controls (Baldi et al. 2003; MacAnaney et al. 2011a), suggesting that the capacity of O_2 extraction by the diabetic skeletal muscle might not be altered *during* exercise. There is more evidence suggesting that the slowing of the $\dot{V}O_2$ kinetic response in uncomplicated type 2 diabetes is linked to a maldistribution and (or) slowing of the blood flow kinetic response to the active muscle. The latter is directly supported by recent evidence of slower vascular conductance kinetic responses in diabetes than in nondiabetic controls during static calf plantar-flexion exercise (MacAnaney et al. 2011b); and similarly, the estimated microvascular blood flow responses of the quadriceps muscle has been shown to be slower during moderate cycling in subjects with type 2 diabetes compared with healthy controls (Bauer et al. 2007).

In the present study we focused on O_2 delivery and, specifically, measured the relative change in CO over the early period of exercise ($t = 30$ s) relative to its total adjustment to more stable (steady-state) levels later during submaximal exercise ($t = 240$ s). Steady-state ($t = 240$ s) responses of CO were not affected by training (Fig. 1), consistent with responses in healthy individuals (Saltin et al. 1968). Similarly, the CO achieved at 30 s was not affected by training. By contrast, the relative change in CO from rest to 30 s relative to 240 s was larger following training compared with baseline, demonstrating an important and novel effect of training suggestive of an enhanced dynamic response of CO that is independent of any effect on its amplitude.

This training induced increase in the ratio of the CO response at 30 s relative to 240 s coincided with a significant acceleration of the HR kinetic response (i.e., smaller τ), a significant reduction in HR during exercise, and a larger change in stroke volume by 30 s of exercise. Thus, training induced a significant change in the control of both HR and stroke volume that is reasonable to assume contributed to the improved relative change in CO from rest at 30 s compared with 240 s. Although the mechanistic basis of these cardiac effects are not clear, it is probable that underlying mechanisms relate independently to HR (e.g., vagal withdrawal) and stroke volume (e.g., increased diastolic relaxation), involve an interaction between inotropic and chronotropic mechanisms (Bolter and Wilson 1999), and (or) are influenced by the dynamic response of blood flow returning to the heart from the contracting muscles.

An implication of these findings is that the training-induced increase in $\dot{V}O_2$ kinetics is linked causally to an increased blood flow and rate of O_2 delivery to the contracting muscles. Although the training-induced increase in the ratio of the change of CO response from rest at 30 s relative to 240 s was manifest during exercise before a significant effect on $\dot{V}O_2$ occurred (TD of phase 2 $\cong 30$ s), a closer temporal alignment between these responses at the level of contracting muscles would be expected given the delay between them of $\sim 10\text{--}20$ s that is associated with the transit of blood returning to the lungs. Consequently, even though the CO kinetic responses were not measured in the present study, it is tempting to suggest that the training improvement in $\dot{V}O_2$ kinetics might be causally linked to an improved control of the dynamic response of cardiac output in type 2 diabetes.

Others have also shown significant improvements in resting left ventricular diastolic function in uncomplicated type 2 diabetes following 12 weeks of supervised aerobic exercise

(Brassard et al. 2007); although longer training interventions seem to be required for potential alterations in left ventricular diastolic function in subjects with more advanced diabetes ($\text{HbA}_{1c} > 8\%$, Loimaala et al. (2007)). Apart from the benefits observed in cardiac (and possibly blood flow) adjustments, the improvements in $\dot{V}\text{O}_2$ kinetic responses observed in the present study following supervised training are also likely to be mediated by adaptations in O_2 extraction capacity of the active muscle. The latter is evidenced by recent work of Phielix et al. (2010), which reported increases in mitochondrial content and improvements in intrinsic mitochondrial function following 12 weeks of combined aerobic and resistance supervised training (Phielix et al. 2010). In the present study, the functional gain (i.e., the ratio between the amplitude of the $\dot{V}\text{O}_2$ and work load obtained under different intensities) was not affected after training (results not shown) most likely because $\dot{V}\text{O}_2$ amplitudes were not altered. On the other hand, endothelial vasodilator function has also been reported to be improved in diabetes after 8 weeks of combined aerobic and resistance supervised training (Maiorana et al. 2001); effects that could contribute to the speeding of O_2 delivery to active muscle. To elucidate this, however, direct measurements of the dynamic responses of blood flow are required.

Unsupervised training

To our knowledge this is the first study to report that improvements in exercise tolerance, peak $\dot{V}\text{O}_2$, and $\dot{V}\text{O}_2$ kinetics in type 2 diabetes can be maintained through a programme of “unsupervised” exercise. Given the association between exercise tolerance and all-cause mortality (Myers et al. 2002), these findings support the efficacy of unsupervised exercise training in the treatment of type 2 diabetes and its complications, at least in the short-term. Participants in the present study chose to perform unsupervised exercise in a “leisure centre”, and although the level of support and supervision was much less than that which was part of supervised training, we acknowledge that some level of “supervision” and support from centre staff would have occurred. Nevertheless, the incorporation of less supervised training in such environments into a programme with an initial phase of intense supervision represents a potentially effective way of educating and motivating participants to exercise on their own and ensure long-term exercise adherence. In the present study, adherence to the unsupervised training was high and similar to that for supervised training, and this good outcome of unsupervised exercise might be related to exercise being conducted in the same health centre previously used for the supervised training, and participants being familiar with the training routines and equipment used.

Limitations

Despite the lack of a control group, the design of the present study included 2 complete and identical baseline measurements separated by a long baseline period (12 weeks) and demonstrated stability in measurements before the training period. In addition, the effect of supervised training persisted when this training was changed to what might be argued to be a less effective training. The stability in measurements within the baseline period was evident by the similar peak physiological responses during the graded test, and

similar $\dot{V}\text{O}_2$ and HR kinetic response time constants and time delays at the 3 submaximal cycling intensities. The study design was required because it was very difficult to recruit more than 19 normotensive patients with recently diagnosed type 2 diabetes who were willing to take part in this long intervention study. Due to the limited temporal resolution of the inert gas rebreathing technique, CO was not assessed continuously, and as discussed, we were only able to estimate the training-induced percentage change in CO from rest at 30 s compared with 240 s. Further work examining CO responses more frequently is warranted to better elucidate if training effects the dynamic response of CO in type 2 diabetes.

In conclusion, type 2 diabetes slows the adjustment of $\dot{V}\text{O}_2$ at the beginning of light to moderate exercise, and as a consequence, uncomplicated diabetic subjects perceive daily light routine activities as being more difficult (Huebschmann et al. 2009). The present findings confirm that a supervised exercise programme results in the speeding of the $\dot{V}\text{O}_2$ kinetic responses and that these benefits can be maintained with a follow-up gymnasium-based unsupervised programme. Faster adjustments in $\dot{V}\text{O}_2$ are related to improvements in exercise tolerance that might help to increase the willingness to adopt a more active lifestyle and increase the quality of life in subjects with diabetes.

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