Cardiac Output is not Related to the Slowed O2 Uptake Kinetics in Type 2 Diabetes

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Cardiac Output Is Not Related to the Slowed $O_2$ Uptake Kinetics in Type 2 Diabetes

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$^1$Department of Physiology, Trinity College Dublin, Dublin, IRELAND; $^2$Centre for Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, Victoria, AUSTRALIA; $^3$Endocrinology, St. Columcilles and St. Vincent’s Hospitals Co., Dublin, IRELAND; and $^4$Department of Physiology, University of Otago, Dunedin, NEW ZEALAND

ABSTRACT

MAC ANANEY, O., J. MALONE, S. WARMINGTON, D. O’SHEA, S. GREEN, and M. EGAÑA. Cardiac Output Is Not Related to the Slowed $O_2$ Uptake Kinetics in Type 2 Diabetes. Med. Sci. Sports Exerc., Vol. 43, No. 6, pp. 935–942, 2011. Purpose: This study aimed to investigate whether cardiac output (CO) responses were related to $V_O_2$ kinetics during cycling in type 2 diabetes. Methods: A total of 9 middle-aged women with uncomplicated type 2 diabetes, 9 nondiabetic overweight women, and 11 nondiabetic lean women were recruited. Initially, the ventilatory threshold (VT) and peak $V_O_2$ were determined during a maximal graded test. Then, on two separate days, subjects completed three 7-min bouts of constant-load cycling at each of three intensities: 50% VT, 80% VT, and midpoint between VT and peak $V_O_2$ (50% Δ). CO (inert gas rebreathing) was recorded at 30 and 240 s of an additional bout at each intensity. $V_O_2$ kinetic parameters were determined by fitting a biexponential (50% VT and 80% VT) or triexponential (50% Δ) function to the $V_O_2$ data. Results: Peak $V_O_2$ was significantly lower in type 2 diabetes compared with the two nondiabetic groups ($P < 0.05$). The time constant of phase 2 was significantly greater ($P < 0.05$) in type 2 diabetes compared with the nondiabetic heavy and lean groups at 50% VT (34.2 ± 15.7 vs 15.4 ± 7.3 and 20.2 ± 9.7 s) and 80% VT (39.1 ± 9.0 vs 24.8 ± 8.8 and 36.8 ± 7.9 s), but none of the $V_O_2$ kinetic parameters were different at 50% Δ. CO responses during exercise were not different among the three groups, and at 80% VT, the change in CO from 30 to 240 s was significantly larger in type 2 diabetes compared with the two nondiabetic groups. Conclusions: The results confirm that type 2 diabetes slows the dynamic response of $V_O_2$ during light and moderate relative intensity exercise in females but that this occurs in the absence of any slowing of the CO response during the initial period of exercise. Key Words: CARDIAC OUTPUT, $O_2$ UPTAKE KINETICS, TYPE 2 DIABETES, WOMEN, CYCLING

Subjects with type 2 diabetes exhibit exercise intolerance (2,20,23,25) that is associated with an increased risk of mortality (30). The cause of exercise intolerance in diabetes is not well understood, but peak oxygen uptake ($V_O_2$) has consistently been shown to be reduced in type 2 diabetic subjects compared with healthy control subjects matched for age, weight, and activity levels (2,18,23–25,28). In addition, pulmonary $V_O_2$ has been reported to adjust more slowly during the early period of exercise (i.e., slower $V_O_2$ kinetics) in type 2 diabetes compared with nondiabetic controls during submaximal cycling exercise (4,7,23).

Slowing of the dynamic response of $V_O_2$ during submaximal exercise might increase fatigue and contribute to exercise intolerance (13). The control of $V_O_2$ during the initial period of exercise depends on the control of blood flow ($O_2$ delivery) to, and control of $O_2$ consumption by, the contracting muscles. To our knowledge, there are no data on the dynamic response of either cardiac output (CO) or muscle blood flow during exercise in humans with type 2 diabetes. In streptozotocin-induced rats (a type 2 diabetes model), the decline in muscle microvascular $P_O_2$ observed during the first 60 s of intermittent contractions (1 Hz) was more rapid than in control animals (6). Similarly, the near-infrared spectroscopy (NIRS)–measured concentrations of oxygenated and deoxygenated hemoglobin/myoglobin ([HHb]) of the thigh muscle showed a transient “overshoot” at the onset of moderate cycling exercise above the level achieved for steady state in humans with type 2 diabetes but not in healthy controls (4). In the same study, the microvascular blood flow...
responses, estimated from simultaneously measured NIRS-derived [HHb] signals and pulmonary VO$_2$ responses, were significantly slower in subjects with type 2 diabetes compared with healthy controls (4). Both of these observations (4,6) suggest that the rate of O$_2$ delivery is slowed relative to the rate of O$_2$ consumption by contracting muscle in type 2 diabetes.

Steady-state measurements provide a more conflicting picture of this problem. Lower limb blood flow measured after several minutes of submaximal cycling was blunted in subjects with type 2 diabetes (17). In contrast, both CO and arteriovenous O$_2$ difference (a-v O$_2$) measured after 5 min of submaximal cycling were similar between diabetic subjects and healthy controls (2). However, none of these findings shed light on the rate of cardiovascular adjustments before the achievement of a steady state. To explore this further, the aim of the present study was to test the hypothesis that the dynamic responses of CO and oxygen uptake are slowed in type 2 diabetes. Because the effect of type 2 diabetes on VO$_2$ kinetics might depend on the intensity of exercise (4,7,23), this hypothesis was tested at three submaximal workloads.

**METHODS**

**Subjects.** Unless otherwise stated, all experimental procedures were completed within the Department of Physiology, Trinity College Dublin, after approval by the Faculty of Health Sciences Research Ethics Committee in accordance with the Declaration of Helsinki. After providing written informed consent, 29 female subjects were recruited into the following three groups according to specific inclusion/exclusion criteria: patients being treated for type 2 diabetes mellitus (n = 9); overweight but otherwise healthy controls (“heavy controls,” n = 9); and lean and healthy controls (“lean controls,” n = 11; Table 1).

Subjects with type 2 diabetes were recruited in consultation with, and were all receiving treatment for diabetes at, St. Columcilles Hospital, Dublin. Healthy subjects were recruited from Trinity College Dublin. All subjects were free of signs, symptoms, and clinical evidence of coronary or peripheral arterial disease, neuropathy, or retinopathy. They were nonsmokers and had not smoked during the 12-month period preceding the study. None of the subjects were taking insulin, β-blockers, calcium channel blockers, or any other antihypertensive drugs. None of the control subjects were on prescriptive medication. However, diabetic subjects were taking oral hypoglycemic prescription drugs (metformin, n = 5; rosiglitazone, n = 1), statins (n = 3), and an angiotensin-converting enzyme inhibitor (n = 1) and/or were undergoing dietary control of their diabetes. All diabetic subjects had a clinical history of diabetes of 1–5 yr. They were prescreened by the treating physicians to confirm that blood pressure was normal and that there was no kidney dysfunction (consistent urinary protein < 200 mg.dL$^{-1}$) or liver dysfunction (urinary creatinine levels < 2.2 mg.dL$^{-1}$). In addition, there was no clinical evidence of ischemic heart disease based on a 12-lead EKG response during a standard treadmill stress test.

All subjects were sedentary (<1 h.wk$^{-1}$ of moderate-intensity exercise) for at least 3 months before the study, and this was confirmed after completion of the Low-Level Physical Activity Recall questionnaire (19,26). Subjects were required to refrain from taking alcohol, caffeine, and exercise in the 12 h preceding each testing session (see below).

**Experimental protocol.** Each subject attended the laboratory on three separate days for testing. Given that some subjects were premenopausal (n = 11: 4 diabetic, 4 heavy controls, and 3 lean controls), testing sessions for all subjects were separated by between 48 and 72 h to complete all testing within 8 d, and this was aligned with the midfollicular phase of the menstrual cycle (days 5–12) for the premenopausal subjects. None of the subjects were taking contraceptive drugs or receiving hormone replacement therapy during or 6 months before the testing period.

On all testing days, exercise was performed on an electrically braked cycle ergometer (Excalibur Sport; Lode, Groningen, The Netherlands). Subjects wore an HR monitor (S725x; Polar Electro Oy, Kempele, Finland) to continuously record HR every 5 s at rest and during exercise. In addition, subjects wore a silicon facemask (7900 series; Hans Rudolph, Kansas City, MO) for continuous analysis of expired gases on a breath-by-breath basis using an online metabolic system (Innoci; Innovision A/S, Odense, Denmark). Analysis of expired air allowed determination of oxygen uptake (VO$_2$), carbon dioxide production (VCO$_2$), minute ventilation (V$_{E}$), and the RER during all rest and exercise periods. This system also enabled the measurement of CO at specific time points via a rebreathing technique (see below for description).

On testing day 1, subjects completed a graded cycle test to fatigue. After 3 min of rest, subjects cycled at an initial workload of 40 W for 3 min before the workload was increased by 20 W every 3 min until a cadence of 60 rpm 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 ventilatory threshold (VT) occurred was determined using the V slope method by identifying the power output at which a clear steeper increase of VCO$_2$ as compared with VO$_2$ occurs (1,5).

On testing days 2 and 3, subjects were required to complete six 7-min exercise bouts on each day, so that during the

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TABLE 1. Mean ($\pm$SD) physical and hematological characteristics for the three groups of subjects.

<table>
<thead>
<tr>
<th></th>
<th>Type 2 Diabetes</th>
<th>Heavy Controls</th>
<th>Lean Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.1 $\pm$ 5.7</td>
<td>42.5 $\pm$ 12.6</td>
<td>44.1 $\pm$ 8.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 $\pm$ 7</td>
<td>162 $\pm$ 8</td>
<td>165 $\pm$ 10</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>94.0 $\pm$ 22.8*</td>
<td>77.4 $\pm$ 8.7*</td>
<td>63.6 $\pm$ 16.7</td>
</tr>
<tr>
<td>BMI (kg.m$^{-2}$)</td>
<td>34.4 $\pm$ 7.4*</td>
<td>29.0 $\pm$ 8.7*</td>
<td>22.7 $\pm$ 1.2</td>
</tr>
<tr>
<td>Glucose (mmol.L$^{-1}$)</td>
<td>8.1 $\pm$ 1.7***</td>
<td>5.5 $\pm$ 0.4</td>
<td>4.6 $\pm$ 0.5</td>
</tr>
<tr>
<td>HbA$_1c$ (%)</td>
<td>6.8 $\pm$ 1.0***</td>
<td>5.1 $\pm$ 0.4</td>
<td>5.3 $\pm$ 0.3</td>
</tr>
<tr>
<td>Insulin (mU.L$^{-1}$)</td>
<td>12.3 $\pm$ 4.8*</td>
<td>8.3 $\pm$ 1.0</td>
<td>6.8 $\pm$ 1.5</td>
</tr>
</tbody>
</table>

* Significantly different ($P < 0.05$) from the lean group.
** Significantly different ($P < 0.05$) from the heavy group.
2 d, each subject completed four exercise bouts at each of the following three intensities relative to the workloads achieved at VT and peak VO₂ as defined by the graded test performed on day 1: 50% VT, 80% VT, and midpoint between VT and peak workload (50% ∆). Exercise bouts were completed in a sequence of three, beginning with 3-min rest followed by 7-min cycling at 50% VT, then 10-min rest followed by 7-min cycling at 80% VT, then 15-min rest followed by 7-min cycling at 50% ∆. Subjects then rested for 45 min, after which the exercise sequence was repeated. The entire session (i.e., six bouts) was then replicated on testing day 3. Previous data suggest the rest periods used are sufficient for HR and blood lactate to return to resting levels (3,8,31).

The initial three bouts at each of the three intensities were used to determine oxygen uptake kinetics, and the fourth bout at each intensity was used for determination of CO responses (see below).

**Oxygen uptake and HR kinetics.** Kinetics of oxygen uptake were determined for each constant-load exercise intensity using the breath-by-breath VO₂ data collected during the first three 7-min exercising periods at each intensity. Data were linearly interpolated to 1-s intervals, time aligned to the onset of exercise, and then an average data set determined for each subject at each intensity. The data set was then smoothed using a 5-s moving average filter. Kinetic parameters were determined by fitting a two-component exponential curve to the results for the exercise intensities below the ventilatory threshold (50% VT and 80% VT; see equation 1) while fitting a three-component exponential curve to the results for the exercise intensity above the ventilatory threshold (50% ∆; see equation 2).

\[
\frac{d}{dt}VO_2(t) = baseline \cdot VO_2 + A_1 \left(1 - e^{-(t/TD_1)/\eta_1}\right)U_1 \\
+ A_2 \left(1 - e^{-(t/TD_2)/\eta_1}\right)U_2
\]  
\[1\]

\[
\frac{d}{dt}\tilde{VO}_2(t) = baseline \cdot \tilde{VO}_2 + A_1 \left(1 - e^{-(t/TD_1)/\eta_1}\right)U_1 \\
+ A_2 \left(1 - e^{-(t/TD_2)/\eta_1}\right)U_2 + A_3 \left(1 - e^{-(t/TD_3)/\eta_3}\right)U_3
\]  
\[2\]

The three exponential terms represent the “cardiodynamic,” “fast,” and “slow” components of the VO₂ response to exercise. Baseline VO₂ represents oxygen uptake during the initial 3-min rest period of each exercise bout; and for each exponential term, A₁, A₂, and A₃ are the asymptotic amplitudes; τ₁, τ₂, and τ₃ are the time constants; and TD₁, TD₂, and TD₃ are the time delays. The parameters U₁, U₂, and U₃ are conditional expressions that limit the fitting of a particular phase to the period at and beyond the time delay associated with that phase. The models were fitted to the data using a weighted least-squares nonlinear regression procedure (TableCurve 2D; Systat, Chicago, IL). Data that exceeded the 95% prediction intervals during an initial fit of a model were excluded. The investigator who performed the curve fitting procedure was blinded with respect to patient identification.

The mean response time (MRT) that represents the time to reach 63% of the overall amplitude of the response from baseline was calculated as a weighted sum of the time delay and time constant of each phase. The equation used for 50% VT and 80% VT can be seen below (equation 3):

\[
MRT = \frac{A_1/\left(A_1 + A_2\right)(TD_1 + \tau_1)}{\left[A_1/\left(A_1 + A_2\right)\right](TD_2 + \tau_2)} + \frac{A_2/\left(A_1 + A_2\right)\left(TD_2 + \tau_2\right)}{\left[A_1/\left(A_1 + A_2\right)\right]\left(TD_3 + \tau_3\right)}
\]  
\[3\]

For 50% ∆ MRT was calculated as follows (equation 4):

\[
MRT = \frac{A_1/\left(A_1 + A_2\right)(TD_1 + \tau_1)}{\left[A_1/\left(A_1 + A_2\right)\right](TD_2 + \tau_2)} + \frac{A_2/\left(A_1 + A_2\right)\left(TD_2 + \tau_2\right)}{\left[A_1/\left(A_1 + A_2\right)\right]\left(TD_3 + \tau_3\right)}
\]  
\[4\]

HR was measured at rest and every 5 s during each of the three constant-load cycling exercise trials at each intensity and averaged to yield a single time series of HR data for each subject at each intensity. The dynamic structures of the HR responses were not as consistent between subjects as the oxygen uptake responses, so a relatively simpler, monoeponential function was chosen to fit HR responses (equation 5),

\[
heart \ rate = a + A\left(1 - e^{-(t/TD)/\tau}\right)
\]  
\[5\]

where a is the baseline HR, A is the amplitude of the exercise response, TD is the delay in rise of HR after exercise onset, and τ is the time constant of the response. The fitting procedures were identical with that described for oxygen uptake.

**CO.** CO was measured using an inert gas (sulfur hexafluoride (SF₆)) and nitrous oxide (N₂O) rebreathing technique based on the Fick principle, as previously described (14). This was performed during the final exercise bout only on testing day 3, but at two time points (at 30 and 240 s) during each 7-min exercise period at each intensity. In brief, subjects were required to initially inspire an entire bolus volume (40% predicted vital capacity) of the test gas mixture contained within a rubber bag connected to the Innocor respiratory valve assembly. A preset respiratory rate (20 breaths per minute) was required to be maintained in synchrony with the visual display on the Innocor screen during continuous re-breathing with the rubber bag until equilibration of gas concentrations was apparent. This usually occurred within four to five breaths (approximately 15–20 s). From each maneuver, pulmonary blood flow (CO) was determined, and in conjunction with the continuous HR record, stroke volume (SV) was calculated (CO/HR). The a-v O₂ difference was calculated as VO₂/CO. Recent unpublished data from our laboratory revealed that the device provides highly reproducible responses when the same subjects (both subjects with diabetes n = 7 and subjects without diabetes n = 10) perform the same CO measurements at 30 and 240 s during three exercise bouts (at 50% VT, 80% VT, and 50% ∆) completed on two to three occasions (coefficient of variation ~5%).

Before the exercise on testing day 3, subjects were familiarized with the rebreathing technique by completing the maneuver up to 5 times in “demo” mode, which simulates the rebreathing technique without utilizing the test gas. Subjects then completed a further two “live” maneuver to determine resting CO before beginning the exercise bouts. Technical difficulties precluded the recording of CO in two diabetic participants.
Statistical analyses. Peak physiological responses and kinetic parameters were compared at rest and during exercise among the three groups using a one-way ANOVA (Sigma Stat, Systat). A two-way repeated-measures ANOVA (group × time) was used to compare cardiac responses during constant-load cycle exercise bouts. Differences were located using Tukey post hoc test. Data that were not normally distributed were analyzed using Kruskal–Wallis test, and multiple comparisons were then performed using Dunn method. The level of significance was set as $P \leq 0.05$. All values are expressed as mean ± SD.

RESULTS

Graded test. Exercise times and peak physiological responses for the three groups during the graded test are shown in Table 2. Peak VO$_2$ (L·min$^{-1}$; mL·kg$^{-1}$·min$^{-1}$) and the workload at VT were lower in the group with type 2 diabetes compared with the control groups ($P < 0.05$). The workload at VT relative to peak workload and peak VO$_2$ was not different among groups (68% ± 13% and 78% ± 6% type 2 diabetes, 72% ± 10% and 77% ± 7% heavy controls, and 73% ± 10% and 77% ± 8% lean controls). In addition, peak VO$_2$ (mL·kg$^{-1}$·min$^{-1}$) was lower in the heavy control group compared with the lean control group ($P < 0.05$). Peak HR and peak workload were lower in the group with type 2 diabetes compared with the lean group but not different compared with the heavy group ($P < 0.05$). No differences in peak RER were observed among the three groups.

Cardiac responses to constant-load exercise. Cardiac responses obtained at rest and during constant-load exercise (30 and 240 s) for the three groups and three intensities can be seen in Figure 1. At rest and during exercise intensities equivalent to 50% VT, cardiac responses were not different among the groups. At 80% VT, SV was higher in subjects with type 2 diabetes at 240 s compared with the lean and heavy controls ($P < 0.05$), and the changes of CO and SV index from 30 to 240 s of exercise were significantly larger in the group with type 2 diabetes than the lean and heavy control groups. In addition, the changes of CI and SV were also larger from 30 to 240 s in the diabetic compared with the heavy control group. When cycling at heavy exercise intensities, HR was higher in the lean group at 240 s compared with both the group with type 2 diabetes and heavy control group ($P < 0.05$).

Oxygen uptake and HR kinetic responses to constant-load exercise. Parameters describing O$_2$ kinetics during the three workloads are shown in Table 3. VO$_2$ responses during exercise at 50% VT in a diabetic, heavy control, and lean control subject are shown in Figure 2. The time constant for the second phase ($\tau_2$) of the VO$_2$ response was slower in type 2 diabetes compared with the control groups at intensities relative to 50% VT and 80% VT. The MRT for VO$_2$ was slower in type 2 diabetes compared with the heavy and lean control groups at 50% VT. MRT was also slower in type 2 diabetes compared with the heavy control group, but not the lean control group, at 80% VT. The time delay for phase 1 (TD$_1$) at 50% VT was greater for the heavy and lean control groups compared with the group with type 2 diabetes.

There were no significant differences in parameters that describe the dynamics of the HR response among these three groups (type 2 diabetes vs heavy vs lean), at any of the three intensities, including the time constant ($\tau_2$; 50% VT = 37.9 ± 20.1 vs 25.7 ± 11.5 vs 31.2 ± 18.5 s; 80% VT = 55.1 ± 22.1 vs 36.4 ± 17.1 vs 60.3 ± 40.1 s; 50% Δ = 65.0 ± 20.5 vs 68.1 ± 15.3 vs 71.0 ± 31.5 s).

DISCUSSION

There were two important findings in this study. First, VO$_2$ kinetic responses were slowed during constant-load cycling exercise at light and moderate exercise intensities in females with uncomplicated type 2 diabetes compared with nondiabetic lean and heavy controls, confirming previous findings (4,7,23). Second, simultaneous measurements of CO responses at the three constant-load cycling exercise intensities were similar among the three groups, whereas the change in CO during the period of the fast phase of VO$_2$ was manifest as greater, rather than smaller, in type 2 diabetes at the moderate intensity. These findings suggest that the slowing of VO$_2$ kinetics in type 2 diabetes is not due to an impaired response of CO.

Peak oxygen uptake. Subjects with type 2 diabetes exhibit exercise intolerance (2,20,23,25) that is associated with an ~20% reduction in peak VO$_2$ compared with healthy subjects of similar age, weight, and activity levels (2,18,23–25,28). The present findings of a 20% lower peak VO$_2$ in the presence of slowed VO$_2$ kinetics are in agreement with other data.

Oxygen uptake kinetics. Understanding the control of the dynamic response of VO$_2$ in diabetes is important as slowing of this response might be linked to increased fatigue during exercise and exercise intolerance (13). This VO$_2$ response consists of at least two to three phases (22). At light to moderate intensities (<VT), two phases are observed, whereas at higher intensities above VT and below peak VO$_2$, an additional “slow” phase is manifest (10). The second and third of these phases are particularly relevant

<table>
<thead>
<tr>
<th>TABLE 2. Mean (±SD) peak physiological responses from the graded test for the three groups of subjects.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameters</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Peak VO$_2$ (L·min$^{-1}$)</td>
</tr>
<tr>
<td>Peak VO$_2$ (mL·min$^{-1}$·kg$^{-1}$)</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
</tr>
<tr>
<td>Peak W$_{max}$ (W)</td>
</tr>
<tr>
<td>W$_{peak}$ at VT (W)</td>
</tr>
<tr>
<td>VO$_2$ at VT (mL·min$^{-1}$·kg$^{-1}$)</td>
</tr>
<tr>
<td>Peak RER</td>
</tr>
</tbody>
</table>

* Significantly different ($P < 0.05$) from the lean group.
** Significantly different ($P < 0.05$) from the heavy group.
FIGURE 1—CO, cardiac index, SV, stroke volume index, and a–v $\text{O}_2$ difference during cycling exercise at 50% VT, 80% VT, and 50% $\Delta$ in type 2 diabetes, heavy controls, and lean controls. *Significantly different ($P < 0.05$) from the lean group. †Significantly different ($P < 0.05$) from the heavy group.
TABLE 3. Mean (±SD) dynamic response characteristics of oxygen uptake during cycling exercise at 50% VT, 80% VT, and 50% Δ in type 2 diabetes, heavy controls, and lean controls.

<table>
<thead>
<tr>
<th></th>
<th>Type 2 Diabetes</th>
<th>Heavy Controls</th>
<th>Lean Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% VT Baseline VO2 (L min⁻¹)</td>
<td>0.34 ± 0.09</td>
<td>0.29 ± 0.06</td>
<td>0.28 ± 0.10</td>
</tr>
<tr>
<td>A1 (L min⁻¹)</td>
<td>0.30 ± 0.12</td>
<td>0.29 ± 0.16</td>
<td>0.33 ± 0.11</td>
</tr>
<tr>
<td>TD1 (s)</td>
<td>3.7 ± 3.3</td>
<td>4.7 ± 4.5</td>
<td>5.1 ± 3.9</td>
</tr>
<tr>
<td>τ1 (s)</td>
<td>5.9 ± 3.4</td>
<td>5.0 ± 4.7</td>
<td>5.5 ± 3.8</td>
</tr>
<tr>
<td>A2 (L min⁻¹)</td>
<td>0.34 ± 0.12</td>
<td>0.30 ± 0.11</td>
<td>0.34 ± 0.10</td>
</tr>
<tr>
<td>TD2 (s)</td>
<td>36.0 ± 12.4</td>
<td>27.4 ± 11.1</td>
<td>32.5 ± 8.7</td>
</tr>
<tr>
<td>τ2 (s)</td>
<td>15.4 ± 15.7***</td>
<td>15.4 ± 7.3</td>
<td>20.2 ± 9.7</td>
</tr>
<tr>
<td>A20 (L min⁻¹)</td>
<td>0.98 ± 0.22</td>
<td>0.88 ± 0.16</td>
<td>0.95 ± 0.24</td>
</tr>
<tr>
<td>MRT (s)</td>
<td>40.7 ± 9.2***</td>
<td>25.6 ± 6.6</td>
<td>32.1 ± 5.2</td>
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<tr>
<td>80% VT Baseline VO2 (L min⁻¹)</td>
<td>0.33 ± 0.09</td>
<td>0.31 ± 0.08</td>
<td>0.31 ± 0.11</td>
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<tr>
<td>A1 (L min⁻¹)</td>
<td>0.31 ± 0.12</td>
<td>0.41 ± 0.12</td>
<td>0.44 ± 0.15</td>
</tr>
<tr>
<td>TD1 (s)</td>
<td>1.4 ± 2.1*</td>
<td>5.0 ± 3.5</td>
<td>6.0 ± 4.6</td>
</tr>
<tr>
<td>τ1 (s)</td>
<td>5.0 ± 5.4</td>
<td>3.5 ± 1.7</td>
<td>6.6 ± 2.6</td>
</tr>
<tr>
<td>A2 (L min⁻¹)</td>
<td>0.51 ± 0.15</td>
<td>0.47 ± 0.20</td>
<td>0.49 ± 0.22</td>
</tr>
<tr>
<td>TD2 (s)</td>
<td>29.8 ± 8.8</td>
<td>30.8 ± 8.9</td>
<td>32.5 ± 10.6</td>
</tr>
<tr>
<td>τ2 (s)</td>
<td>39.1 ± 9.0***</td>
<td>24.8 ± 8.8</td>
<td>26.8 ± 10.4</td>
</tr>
<tr>
<td>A20 (L min⁻¹)</td>
<td>1.16 ± 0.19</td>
<td>1.19 ± 0.22</td>
<td>1.24 ± 0.32</td>
</tr>
<tr>
<td>MRT (s)</td>
<td>41.1 ± 5.9**</td>
<td>33.2 ± 4.5</td>
<td>36.8 ± 7.9</td>
</tr>
<tr>
<td>50% Δ Baseline VO2 (L min⁻¹)</td>
<td>0.33 ± 0.08</td>
<td>0.32 ± 0.05</td>
<td>0.35 ± 0.13</td>
</tr>
<tr>
<td>A1 (L min⁻¹)</td>
<td>0.42 ± 0.15</td>
<td>0.49 ± 0.11</td>
<td>0.47 ± 0.09</td>
</tr>
<tr>
<td>TD1 (s)</td>
<td>4.8 ± 6.2</td>
<td>7.0 ± 5.4</td>
<td>5.0 ± 4.0</td>
</tr>
<tr>
<td>τ1 (s)</td>
<td>6.5 ± 5.0</td>
<td>5.5 ± 4.6</td>
<td>8.5 ± 6.2</td>
</tr>
<tr>
<td>A2 (L min⁻¹)</td>
<td>0.56 ± 0.32</td>
<td>0.65 ± 0.24</td>
<td>0.84 ± 0.27</td>
</tr>
<tr>
<td>TD2 (s)</td>
<td>33.4 ± 10.0</td>
<td>32.0 ± 8.7</td>
<td>26.8 ± 14.0</td>
</tr>
<tr>
<td>τ2 (s)</td>
<td>22.1 ± 12.2</td>
<td>21.1 ± 6.2</td>
<td>24.1 ± 10.2</td>
</tr>
<tr>
<td>A20 (L min⁻¹)</td>
<td>0.14 ± 0.05</td>
<td>0.14 ± 0.06</td>
<td>0.19 ± 0.09</td>
</tr>
<tr>
<td>MRT (s)</td>
<td>139.9 ± 167.8</td>
<td>83.2 ± 65.0</td>
<td>84.6 ± 45.0</td>
</tr>
</tbody>
</table>

See Methods for further description.
* Significantly different (P < 0.05) from the lean group.
* Significantly different (P < 0.05) from the heavy group.

because they reflect oxygen consumption by active muscle (11). Accurate interpretation of the effect of type 2 diabetes on the dynamic response of VO2 depends on an accurate description of these phases. Inaccurate description of the structure of a dynamic response (e.g., the number of phases) leads to large errors in estimating time constants and erroneous conclusions about the “kinetics” of the response (21). A limitation with two of the three previous studies of VO2 kinetics in type 2 diabetes (7,23) is the assumption that the VO2 response during a 3- to 6-min bout of submaximal exercise was monophasic. Although a larger time constant of this single-phase response was observed at low and moderate intensities in type 2 diabetes (7,23), suggesting that the overall VO2 response is slowed, the real response is at least biphasic, and so it is not clear which of these two phases is slowed.

In the present study, biphasic and triphasic functions were fitted to responses at low to moderate and high intensities, respectively. At the low and moderate intensity, a larger time constant for phase 2 of the VO2 response in type 2 diabetes clearly demonstrates a slowing of the “kinetic” response of this phase. This is consistent with more recent evidence of a slowing of phase 2 at an intensity below the “lactate threshold” (4). Collectively, these data show that the slowed ad-

justment of VO2 during the early period of exercise in type 2 diabetes, represented by a larger mean response time, is focused on phase 2. Because this phase is attributed almost entirely to O2 consumption by contracting muscle (11), these data confirm that type 2 diabetes results in a slowing of the initial adjustment of muscle VO2 during exercise.

However, at the highest intensity, the time constant of phase 2 was similar among the three groups. This is also consistent with earlier evidence of no slowing of the overall VO2 response (monophasic) in type 2 diabetes at a relatively high intensity (23). In the absence of other physiological data, this intensity-dependent effect of type 2 diabetes on VO2 kinetics is difficult to explain.

Mechanisms for the slowed oxygen uptake kinetics. On the basis of the Fick equation for VO2, the control of VO2 depends on the control of blood flow and a-v O2. Blood flow could be limited by poor pumping capacity and/or impaired vasodilation, whereas a-v O2 reflects an interaction between blood flow and myocyte VO2, where the latter can be impaired by metabolic inertia (16).

CO responses in diabetic subjects have been shown to be similar to nondiabetic subjects after 5 min of submaximal cycling (2). However, before the present study, no data describing the rate of adjustment of CO before these responses plateauing during steady-state exercise were available. In addition, this is the first time where VO2 kinetics and CO responses have been measured simultaneously in the same subjects during the same exercise protocols. The present findings found no differences in CO between groups at any time point during exercise, and HR kinetics were also similar. In addition, the change in CO from the onset (30 s) to 240 s of exercise was significantly greater, and not lower, at moderate intensities in the group with type 2 diabetes compared with the two nondiabetic control groups. Because this period is closely associated with phase 2 of the VO2 response, these findings suggest that the slowed VO2 response is not due to a slow adjustment of CO.

The dynamic response of VO2 might be impaired by a slowing of the rise in O2 consumption by contracting muscle, resulting in a slower increase in a-v O2. In support of this is evidence of a lower mitochondrial content (27) and abnormal mitochondrial function (15,27) in skeletal muscle of subjects with type 2 diabetes compared with healthy controls. However, in the present study, the a-v O2 was not different during any of the three submaximal exercise intensities investigated between type 2 diabetes and nondiabetic controls. In addition, the changes in a-v O2 difference from rest to the onset of exercise (30 s) and from 30 to 240 s of exercise were not different between groups (Fig. 1). This suggests that the ability of active muscle to extract O2 during exercise might not be impaired in type 2 diabetes. Our findings support the results by Baldi et al. (2), who also reported similar a-v O2 responses after 5 min of submaximal cycling in diabetic and nondiabetic subjects.

In the absence of any apparent cardiac dysfunction and similar a-v O2 responses, it is likely that the slowed VO2...
kinetic responses are, at least in part, linked to a maldistribution and/or slowed dynamic adaptations of blood flow to the active muscles. The latter is supported by observations of significantly lower limb blood flow responses after several minutes of submaximal cycling in uncomplicated type 2 diabetes (17). This would help explain the more rapid decline in muscle microvascular PO$_2$ observed in diabetic rats compared with control rats (6) and the transient “overshoot” in NIRS-measured [HHb] at the onset of cycling exercise above the steady-state levels in humans with uncomplicated type 2 diabetes. (4). Collectively, these findings suggest that the rate of O$_2$ delivery is slowed relative to the rate of O$_2$ consumption by the active muscles in type 2 diabetes. However, steady-state blood flow measurements (17) do not demonstrate the dynamic adaptations before these responses, and thus, further studies are needed to explore if muscle blood flow kinetics are altered in diabetes.

The present findings are clinically important. The slower O$_2$ uptake adaptations to light–moderate exercise intensities in diabetes imply a greater reliance on anaerobic metabolism leading to more rapid fatigue and a lowering of exercise tolerance. These effects might contribute to the perception of daily light routine activities (i.e., climbing stairs, etc.) as being more difficult, as observed in uncomplicated type 2 diabetes (12), and they might reduce the willingness to adopt a more active lifestyle.

**Limitations.** Previous diabetic women studied in regard to VO$_2$ kinetics were premenopausal (4,7,23). In contrast, in the present study, both premenopausal and postmenopausal women were studied and menopause may affect exercise responses by reducing endothelial-dependent vasodilation (29). However, this is unlikely to have introduced bias in the results given that the distribution of premenopausal and postmenopausal women was similar in the three groups. The BMI values were numerically larger (although not significantly different) in subjects with type 2 diabetes compared with heavy controls. It is unlikely that these differences in BMI affected our results given that “obesity” per se did not alter exercise responses among nondiabetic lean and heavy participants. The peak VO$_2$ during the incremental test was numerically lower (but not significantly different) than the VO$_2$ at the end of the high-intensity constant-load test in the diabetic participant. Although others have also reported these responses (23), these data might question whether the incremental test evoked “peak” or maximal responses in diabetic participants. Although only two of the nine diabetic subjects reached their predicted maximum HR, eight of the nine subjects reached peak RER values in excess of 1.1, and their VO$_2$ values increased <2 mL·kg$^{-1}$·min$^{-1}$ with an increase in work rate (i.e., eight of nine diabetic participants reached VO$_{2\text{max}}$ (9)). Thus, we are confident that diabetic participants reached maximal responses.

**CONCLUSIONS**

In summary, these findings confirm that exercise tolerance and the dynamic response of oxygen uptake during low to moderate exercise are impaired in type 2 diabetes. These effects, however, are not related to CO because its response during exercise was not slower or smaller in type 2 diabetes. These findings are limited to females with uncomplicated type 2 diabetes, and further research is required.
to establish the influence of CO on exercise VO2 when comorbidities are present and in male subjects with type 2 diabetes.

REFERENCES


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