Older Type 2 diabetic males do not exhibit abnormal pulmonary oxygen uptake and muscle oxygen utilization dynamics during submaximal cycling exercise

D. P. Wilkerson, D. C. Poole, A. M. Jones, J. Fulford, D. M. Mawson, C. I. Ball, and A. C. Shore

1School of Sport and Health Sciences, St. Luke’s Campus, University of Exeter, Exeter, Devon, United Kingdom; 2Departments of Kinesiology, Anatomy and Physiology, Kansas State University, Manhattan, Kansas; and 3Diabetes and Vascular Medicine, Institute of Biomedical and Clinical Science, Peninsula Medical School, University of Exeter, and Peninsula National Institute for Health Research, Clinical Research Facility, Devon, United Kingdom

Address for reprint requests and other correspondence: D. P Wilkerson, 1 D. C. Poole, 1 A. M. Jones, 1 J. Fulford, 3 D. M. Mawson, 3 C. I. Ball, 3 and A. C. Shore 3

Submitted 22 July 2010; accepted in final form 21 December 2010

THE EXERCISE INTOLERANCE CHARACTERISTIC of patients with Type 2 diabetes has been attributed substantially to dysfunction at multiple steps of the O2 transport pathway. Thus, Type 2 diabetes impairs cardiac function (16, 38, 46) reducing maximal O2 transport which, combined with peripheral dysfunction, decreases total and fractional O2 extraction (3) and maximal pulmonary O2 uptake (V\text{O2\text{max}}, 3, 39, 40). Sentinel changes in vascular function and skeletal muscle include blunted endothelium-dependent vasodilation and blood flow increases (22, 24, 31, 32, 50), elevated plasma concentrations of endothelin-1 (45), reduced capillary density (27, 28), and dysfunctional capillary hemodynamics (34, 47), as well as decreased mitochondrial volume density (41) and function (21, 26). There may also be a relative propensity for a greater fraction of Type IIb (highly glycolytic) muscle fibers in these patients (27, but see also Ref. 1).

A key determinant of exercise intolerance is the rate at which oxygen uptake (V\text{O2}) rises to meet the ATP turnover requirements of the exercise (i.e., V\text{O2 kinetics}). V\text{O2} kinetics are usually determined via pulmonary measurements of V\text{O2}, which has been shown to be indicative of muscle V\text{O2} kinetics once the transit delay from muscle to lung has been accounted for (15, 23). Faster V\text{O2} kinetics are beneficial because this increases the contribution of oxidative relative to nonoxidative metabolism to energy turnover and helps minimize intracellular perturbations (i.e., Δ[phosphocreatine], Δ[ADP]free, Δ[H+] and Δ[ lactate]) that are associated with exercise intolerance (see Ref. 20 for a review). There are several reports of slower V\text{O2} kinetics in Type 2 diabetic patients compared with healthy age-matched controls (4, 8, 39, 40). In healthy humans, during moderate or heavy intensity cycling, V\text{O2} kinetics is thought to be limited by intramuscular energetics rather than O2 delivery per se (see Ref. 36 for a review). In contrast, Padilla at al. (35; electrically stimulated rat spinotrapezius muscle, phosphorescence quenching) and Bauer et al. (4; human quadriceps during cycling) recently reported a transiently increased skeletal muscle deoxygenation (as assessed using near-infrared spectroscopy, NIRS) following the onset of contractions in Type 2 diabetic vs. healthy control individuals. These results were interpreted as evidence for a relative mismatch in muscle O2 delivery-to-V\text{O2} during the early stages of exercise, such that, in the diabetic condition, as opposed to the healthy condition, the V\text{O2} kinetics limitation might be related in part to a compromised O2 delivery.

Previous work examining V\text{O2} kinetics in Type 2 diabetic individuals has focused predominantly on premenopausal females under 50 years of age (disease duration <5 years; 8, 39, 40), which may have been inspired by the observation that this disease has a more profound impact on the V\text{O2max} of females compared with males (39). Considering that the prevalence of Type 2 diabetes is approximately equal between sexes (53), it is important to examine the V\text{O2} kinetic responses of Type 2 diabetic males, as it is currently unknown whether their response is similar to that found in females. In addition, as the prevalence of Type 2 diabetes increases substantially with age, it is also important to resolve whether similarly impaired V\text{O2} kinetics and muscle deoxygenation profiles are found in older individuals in whom the disease duration may have been far longer. It would seem reasonable to predict that extended...
disease duration may lead to greater disruption in the individual’s ability to transport and/or utilize O₂.

Our hypotheses were that older Type 2 diabetic males would have 1) a significantly lower VO₂max and maximal work rate, 2) slower pulmonary VO₂ kinetics, and 3) an abnormal muscle deoxygenation profile compared with healthy age-matched control participants. Further, as the patients with Type 2 diabetes that were the focus of this investigation were older and were >5 years from presentation of diabetes, we also hypothesized that the difference in the VO₂ kinetic responses between the diabetic and control groups would be greater compared with previous studies (8, 39, 40).

METHODS

Participants. Twelve male participants with Type 2 diabetes and 12 healthy control subjects volunteered to participate in this study (Table 1). All participants provided their written informed consent to take part in this research, which had been approved by the Exeter and North Devon Local Medical Research Ethics Committee. All participants were sedentary, which was defined as participating in low-to-moderate intensity exercise less than 2 days/wk in the preceding 3 mo. The inclusion criteria for the patient group were as follows: those who had Type 2 diabetes diagnosed at least 5 years prior to the commencement of the study at 33 years of age or older, those with no ketones at time of diagnosis, and those treated with diet alone or oral hypoglycemic agents. The healthy control participants were defined as taking no medication, having no immediate family member with Type 2 diabetes, and being confirmed as glucose tolerant via an oral glucose tolerance test. Participants were excluded from the study if they had suffered a stroke or myocardial infarction, systemic vasculitis, uncontrolled hypertension (>160/90 mmHg), unstable angina, a pacemaker, or an abnormal ECG.

Blood samples. Glycated hemoglobin (HbA1c), glucose, and insulin were measured following an overnight fast. HbA1c was measured using HPLC ( Tosoh G7 HPLC System; Tosoh Bioscience, Redditch, UK). Plasma glucose was measured using a Roche modular analyzer (Roche Diagnostics, Lewes, UK), and insulin was measured using an immunoenzymometric assay (Appligene Oncor/Lifescreeen, Uxbridge, UK) calibrated against IRP66/304 with no detectable cross-reactivity with proinsulin.

Experimental overview. Following a screening session (conducted on a different day), participants completed three bouts of exercise on a cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands) at a cadence of 60–65 rpm. Participants were asked to arrive at the laboratory rested and fully hydrated, having avoided the consumption of food and caffeine in the preceding 2 h. The first bout of exercise was a ramp incremental test (15 W/min), which resulted in volitional exhaustion within 8–12 min. The participants then rested for a minimum of 45 min. It has been shown that 45 min is a sufficient rest period to allow the restoration of a “normal” VO₂ response following prior high-intensity exercise in young healthy participants (9). In the present study, we were careful to ensure that sufficient recovery time was allowed such that VO₂ during the “unloaded” cycling baseline, which preceded subsequent exercise bouts, was restored. The second and third tests were identical and consisted of cycling at the lowest available power output on the ergometer (20 W) for 3 min, followed by an immediate “step” increment in power output to a power that was 50% of the maximum achieved in the ramp incremental test for 6 min. Participants rested for 10 min before completing the second of the “step” tests. Two-step exercise tests were completed to improve the signal-to-noise ratio and enhance the underlying response characteristics of the VO₂ response (25). It was decided a priori to compare the groups at the same relative as opposed to absolute exercise intensity. As mentioned previously, it is widely reported that individuals with Type 2 diabetes have a lower VO₂max than age-matched healthy control participants (e.g., 39); thus, exercise conducted at the same absolute work rate would not provide a fair comparison between the groups (i.e., the groups would likely be in different exercise-intensity domains, known to elicit distinctly different metabolic and pulmonary gas exchange responses; see Ref. 20 for a review).

Measurements. Pulmonary gas exchange was measured breath by breath throughout all exercise tests (Jaeger Oxycon Alpha, Hoechberg, Germany). The volume transducer was calibrated before each test with a 3-liter calibration syringe, and the analyzers were calibrated with gases of known concentration. Heart rate (HR) was recorded every 5 s using short-range telemetry (Polar PE 4000, Kempele, Finland).

The oxygenation status of the *musculus vastus lateralis* of the right leg was monitored using a commercially available NIRS system (model no. NIRO 300, Hamamatsu Photonics KK, Hiuggashi-ku, Japan). The system consists of an emission probe that irradiates laser beams and a detection probe, which is positioned several centimeters from the emission probe in an optically dense rubber holder. Four different wavelength laser diodes provided the light source (776, 826, 845, and 905 nm), and the light returning from the tissue was detected by a photomultiplier tube in the spectrometer. The intensity of incident and transmitted light were recorded continuously at 2 Hz and used to estimate concentration changes from the resting baseline for oxygenated, deoxygenated, and total tissue hemoglobin. The device was secured to the skin with adhesive at 20 cm above the fibular head. The validity and utility of the use of NIRS during exercise have been reviewed (7).

Data analysis procedures. The breath-by-breath data were linearly interpolated to provide second-by-second values and, for each individual, the two bouts were time-aligned to the start of exercise and ensemble-averaged. The first 20 s of data after the onset of exercise (i.e., the phase I response) were deleted and a nonlinear least-squares algorithm was used to fit the data. The data were adequately fit with a monoexponential model (Eq. 1) in most cases, although there were four subjects in each group for whom a biexponential model was necessary (Eq. 2). Conducted above the exercise gas exchange threshold (GET), a biexponential model is required to account for the presence of the VO₂ slow component. That four subjects in each group were likely above their GET has minimal impact on the interpretation of our data as the “fundamental phase” VO₂ kinetics is not different between moderate (<GET) and heavy (GET) intensity exercise (51). When statistical analyses were carried out with these subjects removed from each group, respectively, it made no difference to the

### Table 1. Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Type 2 Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62 ± 6</td>
<td>65 ± 5</td>
</tr>
<tr>
<td>Duration of disease, yr</td>
<td>9.3 ± 3.8*</td>
<td></td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>87.2 ± 5.5</td>
<td>87.3 ± 8.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.4 ± 1.2</td>
<td>29.2 ± 2.5</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>5.6 ± 0.9</td>
<td>7.3 ± 0.7*</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>135 ± 9</td>
<td>142 ± 11</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>84 ± 9</td>
<td>81 ± 8</td>
</tr>
<tr>
<td>Fasting insulin, pmol/l</td>
<td>51 ± 21</td>
<td>100 ± 39*</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.1 ± 0.6</td>
<td>8.3 ± 1.1*</td>
</tr>
<tr>
<td>Insulin sensitivity, %, HOMA</td>
<td>100 ± 39</td>
<td>49 ± 24*</td>
</tr>
<tr>
<td>Baseline VO₂, ramp test: l/min</td>
<td>0.96 ± 0.07</td>
<td>0.96 ± 0.07</td>
</tr>
<tr>
<td>Baseline heart rate, ramp test: bpm</td>
<td>98 ± 10</td>
<td>102 ± 11</td>
</tr>
<tr>
<td>VO₂max, l/min</td>
<td>2.72 ± 0.40</td>
<td>1.98 ± 0.43*</td>
</tr>
<tr>
<td>∆VO₂/∆WR slope, ml·W⁻¹·min⁻¹</td>
<td>10.8 ± 0.50</td>
<td>10.5 ± 1.69</td>
</tr>
<tr>
<td>Time to exhaustion during ramp test, min</td>
<td>12.5 ± 2.5</td>
<td>8.1 ± 2.2*</td>
</tr>
<tr>
<td>Work rate for step tests, W</td>
<td>102 ± 19.5</td>
<td>71 ± 16.3*</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD. HbA1c, glycated haemoglobin; HOMA, homeostatic model assessment; bpm, beats per minute; WR, work rate. ∗P < 0.05; †P < 0.01; Type 2 diabetic vs. control participants.
principal findings, and thus all 12 subjects in each group were included in the analyses presented.

\[
\dot{V}_{\text{O}2}(t) = \dot{V}_{\text{O}2\text{ baseline}} + A_P(1 - e^{-(t - T_D_P)/\tau_P})
\]

(1)

\[
\dot{V}_{\text{O}2}(t) = \dot{V}_{\text{O}2\text{ baseline}} + A_P(1 - e^{-(t - T_D_P)/\tau_P}) + A_S(1 - e^{-(t - T_D_S)/\tau_S})
\]

(2)

where \(\dot{V}_{O2}(t)\) represents the absolute \(\dot{V}_{O2}\) at a given time \(t\); \(\dot{V}_{O2\text{baseline}}\) represents the mean \(\dot{V}_{O2}\) in the baseline period; \(A_P\), \(T_D_P\), and \(\tau_P\) represent the amplitude, time delay, and time constant, respectively, describing the increase in \(\dot{V}_{O2}\) above baseline. \(A_S\), \(T_D_S\), and \(\tau_S\) represent the amplitude, time delay before the onset of, and time constant describing the development of the \(\dot{V}_{O2}\) slow component, respectively. The end-exercise \(\dot{V}_{O2}\) was defined as the mean \(\dot{V}_{O2}\) measured over the final 30 s of exercise. The absolute fundamental component amplitude (absolute \(A_P\)) was defined as the sum of \(\dot{V}_{O2\text{baseline}}\) and \(A_P\). In addition, the functional “gain” of the fundamental \(\dot{V}_{O2}\) response was computed by dividing \(A_P\) by the \(\Delta\) work rate.

To provide information on muscle oxygenation, we also modeled the [HHb] response to exercise. A monoeponential model similar to that described in Eq. 1 above was used, with the exception that the fitting window commenced at the onset of exercise (i.e., at \(t = 0\)). In addition to the [HHb] \(\tau\) and \(T_D\) derived from the monoeponential fit, we also used the [HHb] amplitude to determine the \(\Delta\)[HHb]/\(\Delta\dot{V}_{O2}\) during this phase of the response. This ratio indicates the degree of O2 extraction required for a given increment in \(\dot{V}_{O2}\) and can, therefore, provide insight into the dynamic balance between O2 delivery and utilization. Finally, the “gain” of the [HHb] response was calculated by dividing the steady-state amplitude by the \(\Delta\) work rate.

HR responses were modeled using a nonlinear least-squares monoeponential model without time delay, with the fitting window commencing at \(t = 0\).

**RESULTS**

The participants’ demographic data are presented in Table 1, along with information regarding disease status and responses to the ramp incremental test. Note that the subjects were well matched for age and body mass index. As expected, the Type 2 diabetic patients had a significantly elevated fasting glucose and HbA1c levels compared with the healthy controls. The diabetic patients exhibited a significantly lower \(\dot{V}_{O2\max}\), which was attained at a significantly lower power output than their healthy counterparts (i.e., time to exhaustion during the ramp incremental test was significantly reduced). The \(\Delta\dot{V}_{O2}/\Delta\text{WR}\) slope was not significantly different between the groups.

There were no significant differences between the groups for the time course of the \(\dot{V}_{O2}\) response during the transition from unloaded to submaximal exercise (Fig. 1 and Table 2). There was a significant difference between the two groups for the steady state \(\dot{V}_{O2}\) amplitude, which was elevated in the control subjects as a function of this group exercising at a higher absolute power output. The “gain” of the \(\dot{V}_{O2}\) response was not different between the groups.

There were no significant differences between the groups for the time course of the [HHb] response (\(\tau\), or \(T_D\); Table 3). An “overshoot” in [HHb] was not a consistent feature of the response in the diabetic patients. Indeed, this behavior ([HHb] “overshoot,” i.e., an initial excursion of [HHb] above the level attained during the steady state within the first 60–100 s of exercise) was observed in only four individuals, two of whom were in the healthy control group (Fig. 2). Despite the lack of any difference between groups with respect to an overshoot of [HHb], there was a markedly higher [HHb] gain, which was ~50% greater in Type 2 diabetic patients, such that \(\Delta\text{[HHb]}/\Delta\dot{V}_{O2}\) was significantly elevated compared with healthy controls. The time constant of the heart rate kinetics was not different between Type 2 diabetic patients and healthy control participants (61 ± 15 vs. 59 ± 21 s, respectively) and was, in both instances, slower than \(\dot{V}_{O2}\) kinetics.

**DISCUSSION**

To our knowledge, this is the first investigation to examine the pulmonary \(\dot{V}_{O2}\) kinetics and muscle deoxygenation dynamics of older males with long-standing Type 2 diabetes (i.e., disease duration exceeding 5 yr). The main findings were that 1) Type 2 diabetic individuals had a significantly reduced \(\dot{V}_{O2\max}\) and maximal work rate compared with healthy controls (consistent with our first hypothesis and previous reports); 2) the time constant of the pulmonary \(\dot{V}_{O2}\) kinetics was not different between Type 2 diabetic patients and healthy controls (inconsistent with our second hypothesis), such that there was a dissociation between \(\dot{V}_{O2\max}\) and \(\dot{V}_{O2}\) kinetics; and 3) the pattern of skeletal muscle deoxygenation was not different between patients and controls (i.e., no consistent [HHb] overshoot in the patients—in disagreement with our third hypothesis). However, [HHb] increased more per unit work and \(\dot{V}_{O2}\) in the Type 2 diabetic patients, suggesting a greater relative mismatch in muscle O2 delivery-to-\(\dot{V}_{O2}\) in this population.

These results are surprising from several perspectives. Specifically, the \(\dot{V}_{O2}\) kinetics and skeletal muscle HHb dynamics in these patients were not different from healthy age-matched controls despite the patients reduced \(\dot{V}_{O2\max}\) and maximal work rate, and the extended duration of disease (>5 years). Putative explanations for the variance from previous research include sex differences, older age, and duration of disease. Accordingly, these current data indicate that either males have a fundamentally different response compared with females, or that the perturbations to \(\dot{V}_{O2}\) and [HHb] dynamics seen in younger patients with Type 2 diabetes do not worsen (\(\dot{V}_{O2}\) kinetics), and indeed may even normalize ([HHb] dynamics), with aging.

\(\dot{V}_{O2\max}\). The aging associated reduction in \(\dot{V}_{O2\max}\) is well documented and is presumably associated with reduced muscle O2 supply [blood flow] (37, 49), capillarity (12, 42; but see also 18, 29), endothelial function (10, 33), O2 diffusing capacity (17), fractional O2 extraction (30), and mitochondrial enzyme activity (12, 48). However, in the current study, despite similar ages, the control participants had a significantly higher \(\dot{V}_{O2\max}\) than the Type 2 diabetic participants (consistent with previous studies, which examined younger participants; 3, 39, 40), despite no differences in the submaximal \(\dot{V}_{O2}\) kinetic response. It is difficult to explain how such a profound reduction in \(\dot{V}_{O2\max}\) does not also result in significantly slower \(\dot{V}_{O2}\) kinetics in the Type 2 diabetic group, but it is presumably related to the pernicious effects of the disease on skeletal muscle structure and function. Individuals with Type 2 diabetes have been shown to have a reduced mitochondrial volume density (41)
and function (21, 26) compared with healthy control participants. Our data suggest that the influence of Type 2 diabetes on skeletal muscle structure and function has a greater impact (over and above the deleterious impact of aging/detraining) on the \( \dot{V}O_2 \)max than on the submaximal \( \dot{V}O_2 \) kinetic response.

Sex differences in \( \dot{V}O_2 \) kinetics. It has been previously noted that Type 2 diabetes has a greater impact upon the \( \dot{V}O_2 \)max of females compared with males (unpublished observations noted in Ref. 39). In contrast to the notion that males might be less or even minimally impacted by this disease, the present results demonstrate a substantial lowering of \( \dot{V}O_2 \)max (27%), and maximal work rate and time-to-exhaustion (35%) on the incremental exercise test compared with healthy control participants. In addition, Bauer et al. (4) found that \( \dot{V}O_2 \) kinetics was slowed in both male and female Type 2 diabetic patients (average age 47 years, disease duration not reported) with no sexual dimorphism noted. In addition, to our knowledge, and equating aerobic fitness (\( \dot{V}O_2 \)max) across sexes, there is no a priori reason to support the concept that those elements of the \( O_2 \) transport system that are affected by Type 2 diabetes should be differently impacted in males compared with females (20).

### Table 2. \( O_2 \) uptake kinetics during exercise

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Type 2 Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ( \dot{V}O_2 ), l/min</td>
<td>0.97 ± 0.06</td>
<td>0.91 ± 0.12</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) ( \tau ), s</td>
<td>41 ± 12</td>
<td>43 ± 17</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) time delay, s</td>
<td>4 ± 11</td>
<td>4 ± 11</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) amplitude, l/min</td>
<td>0.91 ± 0.19</td>
<td>0.57 ± 0.17*</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) gain, ml\cdot min(^{-1})\cdot W(^{-1})</td>
<td>11.2 ± 1.2</td>
<td>11.6 ± 2.8</td>
</tr>
<tr>
<td>End-exercise ( \dot{V}O_2 ), l/min</td>
<td>1.94 ± 0.14</td>
<td>1.52 ± 0.29*</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD. *\( P = <0.05 \), Type 2 diabetic vs. control participants. For more information on modeling procedures, please see text.
Although the current study demonstrates that older male diabetic individuals do not have abnormally slow VO₂ kinetics compared with their healthy counterparts, it is currently unknown whether the same is true for younger Type 2 diabetic males.

Age-related effects and duration of Type 2 diabetes and VO₂ kinetics. It is well known that aging and the accompanying reduction in physical activity manifested as individuals approach senescence result in slowed VO₂ kinetics at exercise onset (2, 6, 11, 44). In this regard, it is noteworthy that the mean VO₂ of 41 s for our healthy controls herein was substantially slower than that found in younger populations (i.e., 20–24 s; see Ref. 43 for a review). This slowing of VO₂ kinetics in aged individuals has been attributed to a reduced muscle O₂ supply (37, 49), capillarity (12, 42), endothelial function (10, 33), O₂ diffusing capacity (17), fractional O₂ extraction (30), and VO₂max (possibly linked to reduced mitochondrial enzyme activity; Refs. 12, 48). In addition, in aged rodent muscles, a transient O₂ delivery-to-VO₂ mismatch following the onset of contractions causes muscle microvascular PO₂ to fall below the subsequent steady-state values (5). Thus, Type 2 diabetes (see introduction) and aging have substantial commonality with respect to their impact on multiple elements of the O₂ transport and utilization pathway.

One important consideration is whether the effects of Type 2 diabetes and aging (and possibly duration of disease) are additive. The results of the present investigation provide evidence to support the suggestion that, at least in males, this is not the case. Rather, whereas Type 2 diabetes slows VO₂ kinetics in comparatively younger individuals (40- to 50-yr-olds; see Refs. 4, 8, 39, 40), the subsequent age-related slowing of VO₂ kinetics to the seventh decade appears to be either reduced or curtailed. This was counter to our hypothesis that older individuals who have had Type 2 diabetes for ~9 years, on average, would have had an exaggerated perturbation of O₂ delivery and utilization capabilities, translating into appreciably slower VO₂ kinetics than have previously been reported for younger patients with disease durations <5 years. It is possible that the slowing seen in the VO₂ kinetics of individuals with Type 2 diabetes reaches a plateau within 2–3 yr subsequent to disease onset, after which little or no further slowing occurs. In individuals with Type 2 diabetes, further slowing associated with aging/detraining may not accentuate the slow VO₂ kinetics already incurred by their disease. Thus, the similarity in the VO₂ dynamics between groups may be explained by the notion that the healthy controls in the present investigation (who were matched for activity levels with the diabetic patients and who were recruited from the same community) may have experienced an aging/detraining-related slowing of their VO₂ kinetics, while the Type 2 diabetic group did not. Consistent with this hypothesis and regardless of sex, VO₂ kinetics in the
delivery-to-VO₂ mismatch following the onset of contractions causes muscle microvascular PO₂ to fall below the subsequent steady-state values (5). Thus, Type 2 diabetes (see introduction) and aging have substantial commonality with respect to their impact on multiple elements of the O₂ transport and utilization pathway.

Table 3. Heart rate and deoxyhemoglobin kinetics during exercise

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Type 2 Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline heart rate, bpm</td>
<td>100 ± 10</td>
<td>105 ± 15</td>
</tr>
<tr>
<td>End-exercise heart rate, bpm</td>
<td>136 ± 15</td>
<td>129 ± 18</td>
</tr>
<tr>
<td>Heart rate τ, s</td>
<td>14 ± 3</td>
<td>17 ± 8</td>
</tr>
<tr>
<td>[HHb] time delay, s</td>
<td>8 ± 2</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>[HHb] mean response time, s</td>
<td>22 ± 6</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>Δ[HHb]/ΔVO₂, AU·min⁻¹</td>
<td>135 ± 33</td>
<td>235 ± 99*</td>
</tr>
<tr>
<td>[HHb] gain, AU/W</td>
<td>1.54 ± 0.4</td>
<td>2.39 ± 0.9*</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD. *P = <0.05, Type 2 diabetic vs. control participants. For more information on modeling procedures, please see text.

![Fig. 2](http://ajpregu.physiology.org/)

Fig. 2. Representative examples of the [HHb] response during exercise for two healthy control subjects (A) and two patients with Type 2 diabetes (B) who either did (A: ×; B: +) or did not (A: ○; B: ♦) exhibit an [HHb] "overshoot". The data are scaled such that the end-exercise values equate to 100%. The majority of subjects demonstrated no overshoot in [HHb], with an overshoot only being noted in 2/12 healthy control subjects and 2/12 patients with Type 2 diabetes; see text for more details.
diabetic patients in the present investigation (mean phase II \( \tau \) 43 s) was not different from that reported previously in younger Type 2 diabetic patients (i.e., 40- to 50-yr olds; 4, 8, 39). Rather, it was the healthy control group that evidenced a slowing of \( \dot{V}_{O_2} \) kinetics compared with previous findings in young healthy individuals (i.e., \( \sim 41 \) s vs. \( <30 \) s; 4, 8, 39). Thus, it appears that the impact of aging/detraining on the \( \dot{V}_{O_2} \) kinetic responses of the aged control participants in the current study may explain why no difference was observed between the groups in the dynamic \( \dot{V}_{O_2} \) response at the onset of exercise. Whether there is some minimal speed of \( \dot{V}_{O_2} \) kinetics that is defended in aged individuals, possibly related to the slowest value consistent with some level of ambulation, is not known at this time. This consideration is particularly interesting in light of the substantial impairment of O\(_2\) transport and utilization during maximal exercise (decreased \( \dot{V}_{O_{2\max}} \) and work rate) in the present population of older Type 2 diabetic patients.

Profile of muscle deoxygenation. That we did not consistently observe an “overshoot” in the \([HHb]\) response in our patient group is perhaps surprising considering recent reports of this phenomenon in the Type 2 diabetic human (4) and rodent (35). The overshoot noted in Type 2 diabetics has been taken as evidence of an impaired increase of muscle blood flow relative to muscle \( \dot{V}_{O_2} \). There is evidence that Type 2 diabetic individuals have both macrovascular (22) and microvascular (34) disturbances, which might be expected to result in a greater reliance on oxygen extraction during the early stages of exercise. In the present investigation, an \([HHb]\) overshoot was observed in four participants only (two individuals from each group; Fig. 2). Thus, the \([HHb]\) responses noted herein indicates that either 1) the overshoot in \([HHb]\) is not an obligatory consequence of Type 2 diabetes; or 2) the overshoot is something that occurs predominantly during the early stages of the disease, and those that have had the disease for longer (perhaps irrespective of age) experience an adaptation in O\(_2\) delivery/ extraction capabilities to compensate for this perturbation. The \([HHb]\) overshoot noted in the individuals from the control group is presumably related to disruption in muscle blood flow relative to muscle \( \dot{V}_{O_2} \), perhaps as a consequence of aging/ detraining (14). It is noteworthy that a recent report (52) demonstrated that skeletal muscle blood flow was well preserved in patients with well-controlled uncomplicated Type 2 diabetes during forearm flexor muscle exercise, but an abnormal blood flow response was noted in those with Type 2 diabetes and associated microvascular complications. Although the data of Womack et al. (52) are not directly comparable with those of the present study due to differences in exercise modality, the possibility remains that the patients in the present study were devoid of microvascular complications that may be necessary to elicit a detrimental impact upon skeletal muscle blood flow.

An interesting finding regarding \([HHb]\) was the 55% elevation in the gain of the response (i.e., increase in \([HHb]\) per unit increase in WR) in the Type 2 diabetic individuals compared with the control participants, a corollary of this being a significantly elevated \( \Delta[H\text{Hb}] / \Delta \dot{V}_{O_2} \) in this group. An elevated \( \Delta[H\text{Hb}] / \Delta \dot{V}_{O_2} \) is indicative of a greater proportional contribution of \( O_2 \) extraction to satisfy a given increase in \( \dot{V}_{O_2} \) (13). On first inspection, it appears that the Type 2 diabetic patients have enhanced capabilities compared with the control individual to support aerobic metabolism by \( O_2 \) extraction. A possible explanation for the higher gain of \([HHb]\) would be that it is a necessary adaptation to a compromised skeletal muscle blood flow in the diabetic individual, as has previously been reported (22), resulting in a greater fractional \( O_2 \) extraction from the “available” blood. This may indicate that the Type 2 diabetic individuals who have had the disease for an extended period has an improved \( O_2 \) extraction capability, something that may not be evident in shorter-disease-term Type 2 diabetics that have been studied previously (4, 8, 39, 40). It is noteworthy in this regard that individuals who have had Type 2 diabetes for shorter periods of time (with similar characteristics in terms of treatment, ethnicity, or complications to the patients studied in the present study) exhibit altered \([HHb]\) dynamics (i.e., an overshoot; Ref. 4), but with a similar gain to age-matched control subjects. This \([HHb]\) profile may be characteristic of shorter-term Type 2 diabetic individuals who have not yet “adapted” to the disease. This may go some way toward explaining why a slower \( \dot{V}_{O_2} \) response is evident in those who have had the disease for shorter periods of time, but not in those with longer disease durations.

With respect to the limitation(s) to \( \dot{V}_{O_2} \) kinetics during conventional ambulatory activities (i.e., cycling, running/walking), it is likely that healthy individuals become increasingly \( O_2 \) delivery limited with advancing age (36, 43). This would act to slow \( \dot{V}_{O_2} \) kinetics at exercise onset, irrespective of mitochondrial oxidative capacity. This notion has been conceptualized as a “tipping point” for muscle \( O_2 \) delivery below which \( \dot{V}_{O_2} \) kinetics are no longer constrained by mitochondrial energetics alone but are additionally slowed by inadequate \( O_2 \) delivery (19). Given this logic, the increased \( \Delta[H\text{Hb}] / \Delta \dot{V}_{O_2} \) ratio in the diabetic patients would imply that, all else being equal, \( O_2 \) delivery, and thus \( \dot{V}_{O_2} \) kinetics, should be more compromised than in the healthy control participants. That this did not occur is important and suggests that other adaptations within the exercising muscles may have facilitated faster \( \dot{V}_{O_2} \) kinetics than would have been expected in this population. Candidate mechanisms deserving future investigation include altered capillary hemodynamics and improved muscle \( O_2 \) diffusing capacity.

Exercise tolerance. One interpretation of the above data is that, at least at similar relative exercise intensities, older Type 2 diabetic individuals, who have had Type 2 diabetes for more than several years, will not have any \( \dot{V}_{O_2} \) kinetics-related compromise of their exercise tolerance compared with healthy age-matched individuals. This is a potentially important observation and one that has implications for our understanding of the exercise capabilities of older diabetic patients. However, it should be pointed out that the significantly lower \( \dot{V}_{O_{2\max}} \) of Type 2 diabetic individuals compared with control participants mandates that any absolute work-rate or exercise intensity will prove more challenging for the Type 2 diabetic patient than their age-matched healthy counterpart.

For practical reasons, the diabetic and control participants in the present study completed the ramp incremental test and the submaximal step tests within the same session (separated by \( \sim 45 \) min). This might be considered a limitation. While there is evidence that a period of 45 min following high-intensity exercise is sufficient for complete recovery to occur in young healthy individuals (i.e., to have no effect on \( \dot{V}_{O_2} \) kinetics during subsequent exercise; Ref. 9), we cannot rule out the
possibility that completion of the initial ramp incremental test had an impact upon the physiological responses to subsequent step exercise in our study participants. However, this concern may be mitigated by evidence that baseline HR and VO2 were not different within groups between the ramp incremental test and the subsequent submaximal step tests (Tables 1–3).

Perspectives and Significance

In the face of decreased VO2max and maximal work capacity, VO2 kinetics following the onset of cycle exercise is not different in older Type 2 diabetic patients compared with healthy age-matched control participants. These similar VO2 kinetic responses may be related to the healthy individuals experiencing an aging/detraining-related slowing of VO2 kinetics, whereas the patients do not. The elevated Δ[HHb]/ΔVO2 in the Type 2 diabetic individuals possibly indicates a compromised muscle blood flow that mandates a greater O2 extraction during exercise. Interestingly, any limitations in blood flow in the transition to a higher exercise intensity did not translate into any limitations in VO2 uptake kinetics in Type 2 diabetic individuals. It is possible that those who have had Type 2 diabetes for an extended period have experienced adaptations in their O2 extraction capabilities to account for any blood flow perturbations, and these adaptations mitigate the expected age-related slowing of VO2 kinetics. These data enhance our understanding of exercise tolerance in older Type 2 diabetic patients by indicating that the response of these individuals to submaximal exercise may be less impacted by the disease than might be predicted. Future work should investigate the temporal relationships among disease duration, VO2 and [HHb] kinetics, and exercise performance in Type 2 diabetic individuals, as well as muscle-specific adaptations in the O2 transport pathway. Such information would be important in resolving the mechanistic bases for the impact of Type 2 diabetes (and aging) on exercise function in this burgeoning population.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


