Differential effects of age and type 2 diabetes on dynamic vs. peak response of pulmonary oxygen uptake during exercise

Eamonn O’Connor,1 Simon Green,3 Catherine Kiely,1 Donal O’Shea,2 and Mikel Egaña1

1Department of Physiology, School of Medicine, Trinity College Dublin, Dublin, Ireland; 2Endocrinology, St. Columcille’s and St. Vincent’s Hospitals, Dublin, Ireland; and 3School of Science and Health and School of Medicine, University of Western Sydney, Sydney, New South Wales, Australia

Submitted 20 November 2014; accepted in final form 18 February 2015

THE RATE OF ADJUSTMENT of oxygen uptake ($\dot{V}O_2$ kinetics) to steady-state exercise is slowed in younger and middle-aged subjects with type 2 diabetes (T2D) compared with nondiabetic counterparts of similar age, weight, and activity levels (4, 9, 42, 55, 64). The slowing of the $\dot{V}O_2$ kinetic response is associated with a greater reliance on anaerobic metabolism (74) and more rapid fatigue (31) and might help explain the lower exercise tolerance in individuals with T2D (3, 42, 55, 64). An important consequence of this exercise intolerance observed in individuals with T2D is that they perceive even light to moderate exercise as more difficult than healthy peers (30), and this might contribute to their relatively lower levels of physical activity (34, 55) and increased risk of cardiovascular outcomes and all-cause mortality in later life (8, 76).

Similarly, aging and the accompanying reduction in physical activity as individuals age have been shown to slow the kinetic response of $\dot{V}O_2$ at the onset of constant-load exercise (2, 7, 13, 26, 71), and the slowing of $\dot{V}O_2$ kinetics possibly compromise exercise tolerance in these people (24).

Although the underlying mechanisms of these impaired $\dot{V}O_2$ responses are not known, they should relate to $O_2$ delivery to, and/or $O_2$-dependent metabolism within, contracting myocytes. In healthy individuals, during light-to-cadence cycling exercise, it appears that $\dot{V}O_2$ kinetics are limited by the oxidative capacity of skeletal muscle rather than $O_2$ delivery per se (59). However, most, but not all, previous data suggest that $\dot{V}O_2$ kinetics in T2D are impaired, at least in part, due to a defect in $O_2$ delivery/supply to the contracting muscles (4, 34, 35, 39, 44, 57), as is the case in aging (11, 27, 40, 60-62, 70, 75), although defects in $O_2$ extraction have also been reported in participants with T2D (33, 67) and in aging individuals (11, 47).

In contrast to previous investigations showing T2D-associated abnormalities in $\dot{V}O_2$ kinetics in younger and middle-aged individuals, Wilkerson et al. (79) reported that $\dot{V}O_2$ and near-infrared spectroscopy derived deoxygenated hemoglobin concentration kinetics to submaximal (50% peak $\dot{V}O_2$) exercise were not altered in older men with T2D compared with healthy age-matched controls, despite the group of individuals with T2D showing a significant reduction in peak $\dot{V}O_2$ (79). However, it is noteworthy that the disease duration of the participants with T2D investigated by Wilkerson et al. (79) was substantially longer (mean disease duration = ~9 yr) than the disease duration of participants investigated in previous studies that showed reductions in $\dot{V}O_2$ kinetics in younger and middle-aged subjects with T2D (mean disease duration = 2-5 yr) (4, 42, 55, 64). Wilkerson and colleagues suggested that the longer disease duration may have resulted in adaptations in the $O_2$ extraction capabilities of their participants with T2D, thus mitigating the expected age-related reductions of $\dot{V}O_2$ kinetics. This was supported by the significantly larger change in $\Delta$ deoxygenated hemoglobin concentration/$\Delta\dot{V}O_2$ shown by individuals with T2D than controls, which could be interpreted as greater $O_2$ extraction during exercise due to a compromised muscle blood flow. Wilkerson et al. (79) were unable to determine whether age and/or disease duration was the main contributing factor for the lack of differences reported in $\dot{V}O_2$ kinetics among older men with and without T2D.

To explore the age-dependent influence on the T2D-induced impairments on peak exercise performance and $\dot{V}O_2$ kinetics, we compared these responses in middle-aged and older men with and without T2D with similar body mass index (BMI) and activity levels. In addition, participants with T2D were care-
fully matched by disease duration. We studied a cohort of patients who were relatively newly diagnosed (mean disease duration = ~4 yr) and had a similar disease duration as participants assessed in previous studies that showed impaired VO$_2$ kinetic responses in younger and middle aged individuals (4, 42, 55, 64). Assuming that the main contributing factor for the lack of impairments in VO$_2$ kinetics in the older participants with T2D in the present study by Wilkerson et al. (79) was their longer disease duration, we hypothesized that both middle-aged and older participants with T2D in the present study would have a lower peak VO$_2$ and peak workload responses during a graded cycling exercise and slower VO$_2$ kinetics during submaximal cycling compared with nondiabetic age-, activity level-, and BMI-matched counterparts. To explore the mechanistic basis of any aging-specific effects in VO$_2$ kinetics, the rates of adjustment of cardiac output (CO), heart rate (HR), and mean arterial pressure (MAP) during submaximal cycling exercise were also assessed.

**MATERIALS AND METHODS**

**Subjects.** Fifty-four men aged 31–59 yr (“middle-aged”) and 60–69 yr (“older”) took part in this study. Thirty-three of the participants were being treated for T2D (15 middle-aged, 18 older), and 21 were sex- and BMI-matched healthy controls (11 middle-aged, 10 older) (Table 1). The duration of diabetes (mean ± SD) for middle-aged participants was 3.8 ± 2.4 yr, and for older participants 4.1 ± 2.7 yr. Subjects with T2D were recruited from the Diabetes Day Care centers at St. Columcille’s and St. Vincent’s University Hospitals, Dublin, following a chart review. Subjects with T2D were treated by diet (n = 11) or oral hypoglycemic agents (metformin monotherapy, n = 14; metformin and sulphonylurea, n = 7; metformin and glucagon-like peptide-1 receptor agonist, n = 1) and at the start of this study displayed no clinical evidence of ischemic heart disease (normal ECG during treadmill stress test), peripheral arterial disease (0.9 < ankle-brachial index < 1.3), kidney dysfunction (consistent urinary protein > 200 mg/dl), or liver dysfunction (urinary creatinine levels > 2.2 mg/dl). Controlled hypertensive subjects were admitted to the study was approved by the Faculty of Health Science Research Ethics Committee and conducted in accordance with the Declaration of Helsinki (2008).

**Study protocol.** The full study protocol mirrored that previously performed and fully described elsewhere (55). Briefly, each subject was tested on two occasions, separated by 72 h, and at the same time of day. Subjects refrained from consuming caffeine and alcohol in the 24 h before testing and limited their exercise to normal activities of daily living. All exercise for the laboratory testing was performed on an electrically braked cycle ergometer (Excalibur Sport, Lode, Groningen, Netherlands).

On testing day 1, subjects completed a graded cycling exercise test to failure to determine ventilatory threshold (VT) and peak VO$_2$. After a 3-min period of seated rest, all subjects began the graded test by cycling at an initial power output of 40 W for 3 min using a fixed cadence (60 rpm). Thereafter, the power output was increased by 30 W every 3 min until the required cadence could not be maintained (i.e., task failure) (22). The VT was determined using the V-slope method (5), peak VO$_2$ was the highest 30-s mean VO$_2$ value recorded before the subject’s volitional termination of the test, and peak workload was the highest workload sustained for at least 1 min. On testing day 2, subjects performed six 6-min bouts of cycling at 80% VT, with each bout separated by 12 min of rest and preceded by a 3-min cycling period at 10 W (unloaded” cycling). VO$_2$ and HR were recorded during the first four bouts, and CO was measured during the last two bouts. The resting periods applied between bouts were sufficient for HR (n = 54) and blood lactate (measured in a subgroup of n = 25) to return to baseline levels, and this is consistent with previous reports (74, 77).

**Measurements.** During exercise, VO$_2$ was measured breath by breath (Innokor, Innovision A/S, Odense, Denmark); CO was measured using the same system by the inert-gas rebreathing technique at rest and during exercise (30, 240 s); HR was recorded every 5 s (S610i, Polar Electro Oy, Finland); and stroke volume (SV = CO/HR) and arteriovenous O$_2$ difference (a-vDO$_2$) were estimated from these measurements. MAP (0.33 systolic + 0.66 diastolic blood pressure) was measured at rest and during exercise (30 and 240 s) using manual sphygmomanometry, and total peripheral resistance.

**Table 1. Physical characteristics and activity levels**

<table>
<thead>
<tr>
<th></th>
<th>Middle-aged</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Type 2 diabetes</td>
<td>Controls</td>
<td>Type 2 diabetes</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>11</td>
<td>15</td>
<td>10</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Physical characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>48 ± 10</td>
<td>52 ± 7</td>
<td>64 ± 3*</td>
<td>64 ± 3*</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>28.8 ± 3.8</td>
<td>29.3 ± 2.3</td>
<td>28.2 ± 2.9</td>
<td>30.3 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>4.6 ± 0.6†</td>
<td>7.0 ± 1.4</td>
<td>4.9 ± 0.7†</td>
<td>7.5 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>HbaA$_1c$,%</td>
<td>5.4 ± 0.4†</td>
<td>6.7 ± 0.8</td>
<td>5.6 ± 0.4†</td>
<td>7.0 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Duration of disease, yr</td>
<td>3.8 ± 2.4</td>
<td>12.6 ± 5.1</td>
<td>4.1 ± 2.7</td>
<td>12.5 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>Homocysteine, µmol/l</td>
<td>4.8 ± 0.8</td>
<td>4.5 ± 1.2</td>
<td>4.6 ± 0.7</td>
<td>4.1 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>1.3 ± 0.4</td>
<td>1.5 ± 0.6</td>
<td>1.2 ± 0.2</td>
<td>1.2 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>HDL-C, mmol/l</td>
<td>3.2 ± 0.9</td>
<td>2.9 ± 0.8</td>
<td>3.2 ± 0.6</td>
<td>2.7 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>1.6 ± 0.9</td>
<td>1.8 ± 0.8</td>
<td>1.6 ± 0.9</td>
<td>2.0 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>Habitual physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive, h/day</td>
<td>17.5 ± 1.6</td>
<td>18.2 ± 1.6</td>
<td>17.5 ± 1.2</td>
<td>18.3 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>Light, h/day</td>
<td>5.1 ± 1.4</td>
<td>4.7 ± 1.4</td>
<td>5.1 ± 1.1</td>
<td>4.6 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Moderate, h/day</td>
<td>1.1 ± 0.6</td>
<td>0.9 ± 0.5</td>
<td>1.1 ± 0.3</td>
<td>0.9 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Vigorous, h/day</td>
<td>0.5 ± 0.3</td>
<td>0.2 ± 0.1</td>
<td>0.3 ± 0.2</td>
<td>0.2 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of men. BMI, body mass index; HbA$_1c$, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. *P < 0.05 vs. middle-aged within same diabetes status group (i.e., within controls or within Type 2 diabetes). †P < 0.05 vs. subjects with type 2 diabetes within same age group (i.e., within middle-aged or within older).
(TPR = MAP/CO) and systemic vascular conductance (SVC = CO/MAP) were calculated. Final values for all variables were averaged from responses during the final two submaximal exercise bouts.

**Data analysis.** To determine the kinetic parameters of $V_{O2}$ at 80% VT, $V_{O2}$ responses during the first four bouts were linearly interpolated to 1-s intervals, time aligned, and averaged (42), and finally smoothed using a 5-s moving average filter. The $V_{O2}$ responses of 12 subjects revealed a small third phase (i.e., a $V_{O2}$ slow component), suggesting that the VT was overestimated in these participants. Thus, these data were fitted to either a biexponential function (Eq. 1) or triexponential function (Eq. 2) as follows:

$$V_{O2}(t) = \text{baseline } V_{O2} + A_1 \left[ 1 - e^{-\left(\frac{t}{\tau_c}\right)} \right] U_c + A_2 \left[ 1 - e^{-\left(\frac{t}{\tau_p}\right)} \right] U_p \quad (1)$$

$$V_{O2}(t) = \text{baseline } V_{O2} + A_1 \left[ 1 - e^{-\left(\frac{t}{\tau_c}\right)} \right] U_c + A_2 \left[ 1 - e^{-\left(\frac{t}{\tau_p}\right)} \right] U_p \quad (2)$$

Either one or the other function was selected for fitting on the basis of comparing the goodness-of-fit of these functions (50), and only parameter estimates representing the first two phases ("cardiodynamic" and "primary" phase) are presented. The presence of a third phase in 12 subjects (middle-aged ND, $n = 3$; older ND, $n = 1$; middle-aged with T2D, $n = 4$; older with T2D, $n = 4$) has minimal impact on the interpretation of our data, since parameters related to the primary phase are unaffected by the presence of the third phase (78), and the outcomes of statistical analyses were unaffected by excluding these subjects. In both equations, baseline $V_{O2}$ is $V_{O2}$ during unloaded cycling, and $A_1$ and $A_2$, $\tau_c$ and $\tau_p$, and $TD_c$ and $TD_p$ are the amplitudes, time constants, and time delays of the cardiodynamic and primary phases, respectively. The conditional expressions ($U_c$ and $U_p$) limit the fitting of a particular phase to the period at and beyond the time delay associated with that phase. Fitting the cardiodynamic phase allowed us to visually determine the transition between the cardiodynamic and primary phase, given that, when this transition is determined using a set value (i.e., 20 s), the $\tau_p$ can be overestimated (48). However, the cardiodynamic phase cannot always be described by an exponential term (38), and thus only its amplitude and duration ($TD_c$ and $TD_p$) are presented (see Table 3).

The $V_{O2}$ data were fitted to either function (Eqs. 1 or 2) using a weighted least-squares nonlinear regression procedure (TableCurve 2D, Systat). Data points lying outside the 95% prediction interval during the initial fit of a model were excluded. The steady-state $V_{O2}$ response, referred to as End A, was calculated using the following formula:

$$\text{End A} = \text{baseline } V_{O2} + A_1 \left[ 1 - e^{-\left(\frac{360 - TD_c}{\tau_c}\right)} \right] + A_2 \left[ 1 - e^{-\left(\frac{360 - TD_p}{\tau_p}\right)} \right] \quad (3)$$

$V_{O2}$ gain was calculated as shown in Eq. 4:

$$V_{O2} \text{gain} = \left( \text{End A} - \text{Baseline } V_{O2} \right) / \left( \text{Workload @ 80% VT - 10 W} \right) \quad (4)$$

HR responses from the four bouts were averaged to yield a single time series of HR data for each subject and were then fitted using a monoexponential function (see Eq. 5).

$$\text{Heart rate} = \text{baseline HR} + A \left[ 1 - e^{-\left(\frac{t}{\tau}\right)} \right] \quad (5)$$

where baseline HR is the average HR during the 3-min cycling at 10 W, $A$ is the amplitude of the exercise response, $TD$ is the delay in rise of HR after exercise onset at 80% VT, and $\tau$ is the time constant of the response. Fitting procedures were identical to that described for $V_{O2}$.

To assess the dynamic response of CO, the rate of increase of CO over the initial period compared with steady-state period of exercise was estimated as the relative or percent change in CO from baseline (%ΔCO) at 30 s compared with 240 s (%ΔCO = ΔCO/CO0 × 100) (55). Peak oxygen pulse was calculated by dividing peak $V_{O2}$ by HR at the time peak $V_{O2}$ was achieved.

**Statistical analysis.** Physical characteristics and activity levels, peak physiological responses, and kinetic parameters were compared using a two-way (diabetic status vs. age) ANOVA (PRISM, version 5.03, GraphPad Software). Cardiovascular responses were assessed using a three-way (diabetic status vs. age vs. time of measurement) repeated-measures ANOVA (Datadesk version 6.2.1 OS X, Data Description). Differences between groups were detected using Bonferroni’s post hoc test. Significance was set at $P < 0.05$. All values are expressed as means ± SD.

**RESULTS**

**Physical characteristics and activity levels.** There were no significant differences in BMI, lipid levels, or activity levels between groups, although participants with T2D tended to spend more hours inactive than controls (main effect, diabetes status, $P = 0.1$). The disease duration, HbA1c, fasting glucose, and homocysteine levels were similar between the two groups with T2D.

**Graded test.** Peak $V_{O2}$ (l/min) was significantly ($P < 0.05$) lower in middle-aged and older participants with T2D compared with their respective nondiabetic counterparts, but the magnitude of this reduction, although not significantly different, tended to be larger among middle-aged participants (diabetes status × age interaction, $P < 0.1$) (Table 2). Peak $V_{O2}$ (ml·kg$^{-1}$·min$^{-1}$), peak workload, time to failure, and workload at VT during the graded test were also significantly lower in both middle-aged and older people with T2D compared with their nondiabetic counterparts, and the magnitude of these differences were greater in middle-aged compared with older participants within same diabetes status group (i.e., within controls or within Type 2 diabetes). +$P < 0.05$ vs. subjects with Type 2 diabetes within same age group (i.e., within middle-aged or within older).

**Table 2. Peak physiological responses during incremental cycling exercise**

<table>
<thead>
<tr>
<th></th>
<th>Middle-aged</th>
<th></th>
<th></th>
<th>Older</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>15</td>
<td>Type 2 diabetes</td>
<td>Controls</td>
<td>18</td>
</tr>
<tr>
<td>Peak $V_{O2}$, l/min</td>
<td>3.2 ± 0.5†</td>
<td>2.5 ± 0.3</td>
<td>2.7 ± 0.4*</td>
<td>2.4 ± 0.4*</td>
<td></td>
</tr>
<tr>
<td>Peak $V_{O2}$, ml·kg$^{-1}$·min$^{-1}$</td>
<td>35.5 ± 6.9†</td>
<td>28.4 ± 4.0</td>
<td>29.5 ± 5.2*</td>
<td>25.3 ± 4.6*</td>
<td></td>
</tr>
<tr>
<td>Peak $V_{E}$, l/min</td>
<td>96.8 ± 9.3†</td>
<td>93.9 ± 12.3</td>
<td>97.4 ± 9.5†</td>
<td>84.3 ± 16.5</td>
<td></td>
</tr>
<tr>
<td>Peak HR, beats/min</td>
<td>160 ± 11</td>
<td>160 ± 11</td>
<td>156 ± 13*</td>
<td>154 ± 14*</td>
<td></td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.10 ± 0.04</td>
<td>1.11 ± 0.06</td>
<td>1.10 ± 0.05</td>
<td>1.12 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>Peak workload, W</td>
<td>212 ± 27†</td>
<td>168 ± 21</td>
<td>184 ± 24†*</td>
<td>162 ± 23*</td>
<td></td>
</tr>
<tr>
<td>Workload at VT, W</td>
<td>174 ± 28†</td>
<td>132 ± 18</td>
<td>151 ± 25†*</td>
<td>127 ± 25*</td>
<td></td>
</tr>
<tr>
<td>Peak $O_{2}$ pulse, ml·kg$^{-1}$·beats$^{-1}$</td>
<td>0.21 ± 0.04†</td>
<td>0.18 ± 0.03</td>
<td>0.19 ± 0.04†</td>
<td>0.16 ± 0.02</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of men. $V_{O2}$, oxygen consumption; $V_{E}$, minute ventilation; HR, heart rate; RER, respiratory exchange ratio; VT, ventilatory threshold. +$P < 0.05$ vs. middle-aged within same diabetes status group (i.e., within controls or within Type 2 diabetes). †$P < 0.05$ vs. subjects with Type 2 diabetes within same age group (i.e., within middle-aged or within older).
impairments was not different between middle-aged and older participants.

\( \dot{V}O_2 \) and HR kinetics. \( \dot{V}O_2 \) responses during moderate exercise for representative individuals are presented in Fig. 1. Compared with control subjects, the total steady-state amplitude of \( \dot{V}O_2 \), as well as amplitudes of phase I and II (cardiovascular and primary), were significantly \( (P < 0.05) \) lower in T2D, irrespective of age, which was a function of subjects with T2D exercising at a lower absolute power output (Table 3). However, the \( \tau_p \) was only significantly \( (P < 0.05) \) slowed in middle-aged men with T2D compared with healthy counterparts, while \( \tau_p \) was similar among older men with and without T2D (Table 3). In addition, aging slowed \( \tau_p \) only in nondiabetic participants. The “gain” of the \( \dot{V}O_2 \) responses was not different between any of the groups. HR kinetics were significantly slowed in subjects with T2D \((i.e.,\ higher \tau \ values; \ Table \ 3)\), but the extent of slowing was similar for middle-aged and older subjects.

Cardiovascular responses. Cardiovascular responses at rest and during cycling exercise are shown in Fig. 2 (HR, SV, TPR are not shown), and their “gains” relative to workload at 30 and 240 s are shown in Table 4. Absolute CO, SV, and SVC responses during exercise were significantly \( (P < 0.05) \) lower among middle-aged men with T2D than controls, but they were similar between the older groups (Fig. 2). When the change in absolute workload was taken into account, the gains in CO and SV were not affected by T2D (Table 4). In addition, both groups with T2D displayed significantly higher absolute MAP \((P < 0.05) \) and TPR \((P < 0.05) \) responses compared with their respective counterparts. The gains in MAP, although also significantly \( (P < 0.05) \) higher in both groups with T2D (Table 4), tended to be larger between middle-aged individuals with and without T2D than between older participant groups (diabetes status \( \times \) age interaction, \( P < 0.06 \) for MAP gain at 30 s; \( P = 0.16 \) for MAP gain at 240 s). The slope of the relationship between CO and MAP responses, which is the equivalent of the “gain” in SVC, was significantly \( (P < 0.05) \) lower among middle-aged men with T2D than controls \((0.25 \pm 0.08 \) vs. \( 0.57 \pm 0.22 \)) but it was not significantly different between the older patients with T2D and controls \((0.30 \pm 0.18 \) vs. \( 0.40 \pm 0.21 \)). No differences were detected in HR or estimated \( a-\dot{V}O_2 \) during submaximal exercise due to diabetes status; however, the gains in \( a-\dot{V}O_2 \) at 240 s were significantly larger in both middle-aged and older individuals with T2D than controls (Table 4). The relative \%\Delta CO \((\text{see MATERIALS AND METHODS})\) was not significantly affected by diabetes (data not shown).

**DISCUSSION**

The main finding of the present study was the differential effect of T2D on peak \( \dot{V}O_2 \) and \( \dot{V}O_2 \) kinetics between middle-aged and older individuals. On one hand, peak \( \dot{V}O_2 \) and peak power output were significantly reduced both in middle-aged and older men with T2D compared with their respective healthy counterparts and that the magnitude of these impairments was not affected by age. On the other hand, the \( \tau_p \) of the \( \dot{V}O_2 \) response during submaximal exercise was only slowed in middle-aged men with T2D compared with healthy peers, while it was similar between older men with and without T2D. Regarding the cardiovascular responses, the principal findings were that the absolute SVC response and its “gain” \((\text{i.e., the slope of the relationship between CO and MAP})\) during submaximal exercise were significantly blunted in middle-aged men with T2D than controls, while they were similar between the older men with and without T2D. Thus the present study suggests that the impaired SVC responses observed in middle-aged people with T2D contributed, at least in part, to their slower \( \dot{V}O_2 \) kinetics.

Recently, Wilkerson et al. (79) showed similar \( \dot{V}O_2 \) kinetics responses in older men with T2D compared with healthy age-matched men of similar age as the older participants of the present study \((\text{mean age } = \sim 64 \text{ yr})\) and attributed this to the long duration of diabetes and its adaptive response in skeletal muscle.
muscle O2 extraction capacity. These findings are consistent with our observations of similar \( \dot{V}_O_2 \) kinetics among older participants. However, the duration of diabetes of the participants investigated by Wilkerson et al. (−9 yr) was longer than that of the participants in the present study (−4 yr), and it was also longer than the disease duration of the patients in previous studies that found slowed \( \dot{V}_O_2 \) kinetic responses in T2D (range 2–5 yr). Thus the present study clarifies that the effect of T2D on \( \dot{V}_O_2 \) kinetic responses during moderate submaximal exercise depends on age rather than disease duration. This suggests that the effects of diabetes on \( \dot{V}_O_2 \) kinetics are masked by the equally powerful effects of aging between 60 and 70 yr of age, at least in sedentary participants in whom activity levels were similar between individuals with T2D and nondiabetic controls.

Peak exercise performance. Maximum or “peak” \( \dot{V}_O_2 \), which is an independent risk factor for all-cause and cardiovascular disease mortality (58), has been consistently reported to be reduced in individuals with T2D of all ages compared with nondiabetic counterparts of similar age, BMI, and activity levels (3, 37, 44, 55, 63, 64). However, our present findings are consistent with these observations; however, we emphasize that the effect of T2D on peak \( \dot{V}_O_2 \) (l/min) was marginally more blunted in older than younger subjects (11 vs. 22% reduction, diabetes status x age interaction, \( P \leq 0.1 \)). These observations suggest that the differential effect of age on peak and dynamic responses of \( \dot{V}_O_2 \) relates more to the extent than type of effect. In healthy men, the age-related reduction in peak or maximum \( \dot{V}_O_2 \) (l/min) for men over 40 yr is estimated to be −0.7%/yr (72), and one-half of this effect is attributed to the decline in maximum HR (73) and CO. Similarly, in the present control subjects, peak \( \dot{V}_O_2 \) was 16% lower in older than middle-aged individuals (loss of 1%/yr), and one-half (−8%) of this difference can be attributed to the reduction in peak HR. In T2D, a smaller age-related reduction in peak \( \dot{V}_O_2 \) was associated with a smaller but similar reduction in peak HR, suggesting that this aging effect in T2D can be explained entirely by the fall in peak HR and does not involve reductions in peak a-vDo2 (a-vDo2) or SV. Mechanisms underlying this effect might include a decline in maximum pacemaker rate (12, 32) or, more likely, factors that contribute to the reduction in peak workload (given its close coupling with peak HR), which might exert their effects during submaximal stages.

\( \dot{V}_O_2 \) kinetics during moderate exercise. Our data regarding significantly slower \( \tau_p \) responses in middle-aged men with T2D compared with healthy controls are consistent with previous reports that included men and women with T2D of similar age and disease duration (4, 9, 42, 55, 64). In addition, the fact that \( \tau_p \) responses were significantly slower in older compared with middle-aged nondiabetic healthy individuals (27 vs. 43 s) is consistent with other evidence of aging-related slowing of \( \dot{V}_O_2 \) kinetics in healthy individuals [range of \( \tau_p \) = 40–45 vs. 20–30 s; (2, 13, 16, 26, 51, 71)]. On the other hand, in the present study, the similar \( \tau_p \) responses (40–45 s) in both middle-aged and older individuals with T2D were similar to other values of \( \tau_p \) reported for adults with T2D (4, 9, 42, 43, 55, 63, 64). Thus, as suggested by Wilkerson et al. (79), the T2D-induced slowing of \( \dot{V}_O_2 \) kinetics might plateau after 2–3 yr following the onset of the disease, and aging does not appear to further slow this response, at least in uncomplicated T2D.

The large effect of T2D on \( \dot{V}_O_2\tau_p \) in middle-aged subjects (52% increase) lies in sharp contrast to the absence of this effect in older subjects. Middle-aged and older men with T2D exercised at significantly lower power outputs than their healthy counterparts, and the increases in \( \dot{V}_O_2 \) and CO, albeit the latter only in middle-aged participants, were also lower but resulted in similar “gains” of these responses when normalized to the change in power output. By contrast, the absolute rise in pulmonary a-vDo2 was similar between subjects with T2D and controls, and thus the gain of this response was higher at the 4th min of exercise (Table 4). Importantly, the gain of a-vDo2 at the onset of exercise (i.e., at 30 s), although not significantly different, was −30% larger in middle-aged participants with T2D compared with controls, whereas it was identical among the two older groups. These observations are consistent with near-infrared spectroscopy-derived evidence of greater O2 extraction during moderate-intensity submaximal cycling (calculated at the 6th min of exercise) in older men with T2D than controls (see Introduction) (72).

A greater increase in pulmonary a-vDo2 relative to \( \dot{V}_O_2 \) and CO reflects a lower mixed-venous O2 concentration ([O2]) and points to greater degree of perfusion-limited O2 exchange in...
contracting muscles (41). There is substantial evidence of prediabetes and diabetes-induced impairment of vascular control in contracting skeletal muscle from human (34, 35, 39, 44) and nonhuman studies (53, 54, 56, 57). As O2 consumption in mitochondria begins to rise in contracting myocytes, slower blood flow and vasodilation mean that O2 flux between capillary blood and these myocytes becomes more “flow limited” (41), capillary PO2 will fall to a greater extent (6), and mixed-venous [O2] will be lower. Under such conditions, the control of the rise in muscle and pulmonary V˙O2 depends more heavily on perfusive (“O2 delivery”) as opposed to diffusive (“O2 utilization”) processes. We have shown that T2D blunts the initial, rapid vasodilation and slows the second phase of vasodilation (i.e., increases its τ) during intermittent contractions of the human calf muscle (34, 44). Although this effect has not been established during submaximal “whole body” exercise, its existence would help explain the slowed primary phase of V˙O2 observed only in middle-aged subjects with T2D. In older subjects, the balance of pulmonary a-vDo2, CO, and V˙O2 were less affected by T2D, particularly at the onset of exercise, and this is consistent with the lack of effect of T2D on V˙O2p and might reflect the converging effects of T2D and aging (10, 36, 46) on dynamic responses of muscle hyperemia.

The pressor response during exercise might provide insight into the influence of muscle perfusion on V˙O2p in T2D. T2D was associated with a greater rise in MAP during submaximal

![Graphs showing data](image-url)
cycling, but the increase at 30 s was substantially larger in middle-aged than in older-aged subjects (Fig. 2, Table 4). Assuming that this greater pressor response is not due entirely to increased arterial stiffness (52), then the larger increase in MAP, despite a smaller rise in CO, implies a more blunted rise in SVC in T2D. The rise in SVC during cycle exercise is dominated by the rise in vascular conductance and blood flow in contracting skeletal muscle (49). These findings support the idea that T2D slows the rise in muscle vascular conductance and SVC during the transient period of exercise and, in the presence of a normal rise in CO, contributes to an exaggerated pressor response and slowing of the dynamic response of pulmonary VO₂. The fact that no such effects of T2D on vascular conductance were seen during the first 30 s of exercise in older subjects provides further support to this view.

**Perspective.** The age-related reduction in effects of T2D on VO₂ τp and peak VO₂ raises a question about the causal connection between these variables. In middle-aged subjects, the larger effect of T2D on peak VO₂ compared with older subjects could not be entirely explained by a fall in HR and thus can be partly attributed to a reduction in peak pulmonary a-vDO₂ (3) and/or SV (65). How might a relatively large effect of T2D on VO₂ τp translate to a smaller effect on these latter responses during peak exercise?

One possibility articulated in a contemporaneous review (25) relates to the powerful and reversible effects of perfusion on muscle contractility (23, 28, 29) at higher, submaximal workloads. Acute reductions in muscle perfusion pressure during exercise induced by changes in body position slow the rise in muscle blood flow, VO₂, and reduce fatigue resistance during submaximal contractions of isolated lower limb muscles (18, 19, 45). Similar postural maneuvers during cycle ergometer exercise result in a greater EMG in thigh and leg muscles at higher submaximal intensities (>VT) and reduce peak HR, power output, and VO₂ during graded exercise by 10–20% (14, 15, 17, 20, 21). These findings raise the possibility that slowed muscle hyperemic responses during more intense bouts of submaximal exercise (>80% VT) reduce muscle contractility, necessitate an increased motor drive during submaximal exercise, and ultimately diminish the peak workload achieved during a graded test.

The widening of pulmonary a-vDO₂ during graded exercise is mainly a function of a decreasing mixed-venous [O₂], which, in turn, is influenced by the blood flows returning from inactive and active tissues and their respective [O₂] concentrations. Reduced perfusion of contracting muscle in the presence of elevated MAP is predicted to have three main consequences: it decreases the contribution of venous blood with lower [O₂] from contracting muscles to mixed-venous blood entering the lungs; increases the contribution of venous blood with higher [O₂] from inactive tissues to this venous blood; and it reduces venous "return", ventricular filling volume, and SV because the increase of total venous blood flow ("venous return") during exercise is influenced by the pumping power of skeletal muscle and the blood flow through it (68). Consequently, lower muscle perfusion during submaximal stages of graded exercise in T2D might eventually result in an altered balance of vascular resistances and blood flows in contracting (lower flow, lower venous O₂) and noncontracting tissue (higher flow, higher venous O₂) at higher arterial blood pressures, which, collectively, result in lower peak responses of a-vDO₂ and SV.

**Limitations.** Due to the limited temporal resolution of the inert-gas rebreathing technique, CO was not assessed continuously, and, as a result, we were only able to estimate the %ΔCO from rest at 30 s compared with 240 s. Even if this relative %ΔCO from baseline was not significantly affected by diabetes, we cannot exclude the possibility that the dynamic response of CO in T2D is slowed and/or affected in an age-dependent manner. Further work examining CO responses more frequently is warranted to better elucidate the contrasting age-dependent effects of T2D on VO₂ and HR kinetics on the one hand and CO responses on the other.

**Conclusions.** The results of the present study suggest that middle-aged and older men with T2D exhibit a similar degree of impairment in peak exercise capacity compared with age-similar nondiabetic men. However, during submaximal exercise, middle-aged individuals with T2D demonstrate significantly slowed VO₂ kinetics accompanied with blunted SVC.

---

**Table 4. Gains of cardiac output and related variables during cycling at 80% VT**

<table>
<thead>
<tr>
<th></th>
<th>Middle-aged</th>
<th>Type 2 diabetes</th>
<th>Older</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>11</td>
<td>15</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td><strong>Gains at 30 s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO, ml·min⁻¹·W⁻¹</td>
<td>45 ± 13</td>
<td>42 ± 11</td>
<td>41 ± 12</td>
<td>45 ± 12</td>
</tr>
<tr>
<td>HR, beats·min⁻¹·W⁻¹</td>
<td>0.20 ± 0.08</td>
<td>0.21 ± 0.12</td>
<td>0.16 ± 0.06</td>
<td>0.20 ± 0.07</td>
</tr>
<tr>
<td>SV, ml/W</td>
<td>0.29 ± 0.12</td>
<td>0.28 ± 0.12</td>
<td>0.30 ± 0.13</td>
<td>0.32 ± 0.10</td>
</tr>
<tr>
<td>a-vDO₂, ml·min⁻¹·W⁻¹</td>
<td>0.028 ± 0.019</td>
<td>0.038 ± 0.021</td>
<td>0.041 ± 0.027</td>
<td>0.042 ± 0.022</td>
</tr>
<tr>
<td>VO₂, ml·min⁻¹·W⁻¹</td>
<td>6.2 ± 1.5</td>
<td>6.3 ± 1.4</td>
<td>6.6 ± 1.5</td>
<td>7.0 ± 2.2</td>
</tr>
<tr>
<td>MAP, mmHg/W</td>
<td>0.079 ± 0.036†</td>
<td>0.170 ± 0.042</td>
<td>0.157 ± 0.101†</td>
<td>0.162 ± 0.087</td>
</tr>
<tr>
<td><strong>Gains at 240 s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO, ml·min⁻¹·W⁻¹</td>
<td>62 ± 12</td>
<td>60 ± 08</td>
<td>63 ± 11</td>
<td>66 ± 12</td>
</tr>
<tr>
<td>HR, beats·min⁻¹·W⁻¹</td>
<td>0.39 ± 0.13</td>
<td>0.43 ± 0.08</td>
<td>0.34 ± 0.08</td>
<td>0.39 ± 0.09</td>
</tr>
<tr>
<td>SV, ml/W</td>
<td>0.26 ± 0.13</td>
<td>0.25 ± 0.09</td>
<td>0.33 ± 0.09†</td>
<td>0.33 ± 0.09*</td>
</tr>
<tr>
<td>a-vDO₂, ml·min⁻¹·W⁻¹</td>
<td>0.066 ± 0.018†</td>
<td>0.084 ± 0.024</td>
<td>0.074 ± 0.020†</td>
<td>0.087 ± 0.024</td>
</tr>
<tr>
<td>VO₂, ml·min⁻¹·W⁻¹</td>
<td>13.5 ± 1.80</td>
<td>13.4 ± 2.10</td>
<td>13.5 ± 0.80</td>
<td>14.3 ± 2.9</td>
</tr>
<tr>
<td>MAP, mmHg/W</td>
<td>0.106 ± 0.028†</td>
<td>0.245 ± 0.065</td>
<td>0.180 ± 0.113†</td>
<td>0.241 ± 0.100</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of men. CO, cardiac output; HR, heart rate; SV, stroke volume; a-vDO₂, arterial-venous oxygen difference; MAP, mean arterial pressure. *P < 0.05 vs. middle-aged within same diabetes status group (i.e., within controls or within Type 2 diabetes). †P < 0.05 vs. subjects with type 2 diabetes within same age group (i.e., within middle-aged or within older).
responses by the initial 30 s of exercise compared with their middle-aged healthy peers, while in older individuals with T2D, $\dot{V}O_2$ kinetics and SVC responses are similar compared with those of healthy older controls. It is possible that the T2D-induced slowing in $\dot{V}O_2$ kinetics and reductions in SVC responses during moderate exercise might reach a plateau after the initial years following the onset of the disease. Thus aging (between 60 and 70 yr of age) does not appear to affect these responses in a synergistic manner with T2D, at least in a cohort of male patients with recently diagnosed diabetes. Further studies are needed to elucidate if these responses are also apparent in women.

**GRANTS**

This publication has emanated from research conducted with the financial support of Science Foundation Ireland under Grant 08/RFP/BMT1342.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**

Author contributions: E.O., S.G., C.K., D.O., and M.E. conception and design of research; E.O. performed experiments; E.O., S.G., C.K., D.O., and M.E. interpreted results of experiments; E.O., S.G., C.K., D.O., and M.E. edited and revised manuscript; E.O., S.G., C.K., D.O., and M.E. approved final version of manuscript; M.E. prepared figures; M.E. drafted manuscript.

**REFERENCES**

43. Macananey O, O'Shea D, Warmington SA, Green S, Egaña M. MacAnaney O, Reilly H, O'Shea D, Egaña M, Green S.

Levick JR.


Murias JM, Kowalchuk JM, Paterson DH.

51. 50. 49. 48. 47.

Nichols WW, O'Rourke MF. MacDonald MJ, Shoemaker JK, Tschakovsky ME, Hughson RL. MacDonald MJ, Shoemaker JK, Tschakovsky ME, Hughson RL.

55. 54. 53. 52. 51.


