Skeletal Muscle Deoxygenation After the Onset of Moderate Exercise Suggests Slowed Microvascular Blood Flow Kinetics in Type 2 Diabetes

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OBJECTIVE — People with type 2 diabetes have impaired exercise responses even in the absence of cardiovascular complications. One key factor associated with the exercise intolerance is abnormally slowed oxygen uptake ($\dot{V}O_2$) kinetics during submaximal exercise. The mechanisms of this delayed adaptation during exercise are unclear but probably relate to impairments in skeletal muscle blood flow. This study was conducted to compare skeletal muscle deoxygenation (deoxygenated hemoglobin/myoglobin [HHb]) responses and estimated microvascular blood flow (Qm) kinetics in type 2 diabetic and healthy subjects after the onset of moderate exercise.

RESEARCH DESIGN AND METHODS — Pulmonary $\dot{V}O_2$ kinetics and [HHb] (using near-infrared spectroscopy) were measured in 11 type 2 diabetic and 11 healthy subjects during exercise transitions from unloaded to moderate cycling exercise. Qm responses were calculated using $\dot{V}O_2$ kinetics and [HHb] responses via rearrangement of the Fick principle.

RESULTS — $\dot{V}O_2$ kinetics were slowed in type 2 diabetic compared with control subjects (43.8 ± 9.6 vs. 34.2 ± 8.2 s, $P < 0.05$), and the initial [HHb] response after the onset of exercise exceeded the steady-state level of oxygen extraction in type 2 diabetic compared with control subjects. The mean response time of the estimated Qm increase was prolonged in type 2 diabetic compared with healthy subjects (47.7 ± 14.3 vs. 35.8 ± 10.7 s, $P < 0.05$).

CONCLUSIONS — Type 2 diabetic skeletal muscle demonstrates a transient imbalance of muscle O_2 delivery relative to O_2 uptake after onset of exercise, suggesting a slowed Qm increase in type 2 diabetic muscle. Impaired vasodilatation due to vascular dysfunction in type 2 diabetes during exercise may contribute to this observation. Further study of the mechanisms leading to impaired muscle oxygen delivery may help explain the abnormal exercise responses in type 2 diabetes.

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Exercise is highly recommended as a cornerstone of treatment for people with type 2 diabetes. However, reduced peak exercise tolerance is common in type 2 diabetes (1–3) and is linked to mortality in individuals with type 2 diabetes as well as healthy individuals (4). Submaximal exercise responses are also affected in individuals with type 2 diabetes, as demonstrated by an abnormally slowed increase of oxygen uptake ($\dot{V}O_2$ kinetics) after the onset of exercise, and seem to possibly be related to abnormal cardiovascular responses (1,2). Clinically, these findings observed during submaximal exercise testing are significant because they indicate a greater perturbation of intramuscular homeostasis in response to any exercise challenge, with the potential to contribute to the premature muscular fatigue (5) and hence the reduced exercise tolerance in type 2 diabetic individuals (1,2). However, the mechanisms of impaired muscle oxygen delivery and/or oxidative metabolism responsible for the abnormal exercise responses in type 2 diabetes remain unclear.

Recent work in rodent models of type 2 diabetes has demonstrated impaired skeletal muscle capillary hemodynamics (6) and abnormal capillary PO_2 responses during exercise (7). These findings demonstrated a transient impairment of oxygen delivery relative to muscle oxygen uptake after the onset of exercise that may limit oxygen transfer and utilization (7,8). It is not known whether a similar defect exists in individuals with type 2 diabetes. Such an impairment of microvascular oxygen delivery and exchange in human skeletal muscle could similarly contribute to the observed limitation of $\dot{V}O_2$ and exercise performance in type 2 diabetes. Indeed, reductions in exercising leg blood flow (9) and baseline metabolic defects (10,11) are known to occur in human type 2 diabetic skeletal muscle. Given that skeletal muscle plays an important role in the pathophysiology of insulin resistance and type 2 diabetes, the investigation of oxygen delivery and blood flow at the level of the exercising skeletal muscle in human type 2 diabetes would provide unique insight into the exercise limitations observed in this patient population.

Near-infrared spectroscopy (NIRS) is a noninvasive technique that offers functional insight into changes in skeletal muscle oxygen status (12). This technique uses the absorption characteristics of near-infrared light directed into tissue to determine the concentration changes

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Abbreviations: CWR, constant work rate; [HHb], deoxygenated hemoglobin/myoglobin; MRT, mean response time; NIRS, near-infrared spectroscopy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Subject characteristics*

	Control	Type 2 diabetic
Age (years)	47 ± 6	47 ± 4
Weight (kg)	81.5 ± 18.5	84.0 ± 8.8
BMI (kg/m^2)	28.0 ± 3.0	30.8 ± 4.3
A1C (%)	5.4 ± 0.2	6.75 ± 1.2*
Fasting insulin (μU/ml)	8.0 ± 3.6	13.6 ± 12.1
Fasting glucose (mg/dl)	96 ± 9	128 ± 42†
Body fat (%)	32.6 ± 7	32.7 ± 7

Data are means ± SD. Body fat was calculated from a dual-energy X-ray absorptiometry scan. *$P < 0.01$; †$P < 0.05$, type 2 diabetic versus control subjects.

of oxygenated and deoxygenated hemoglobin/myoglobin ([HHb]) in the small vessels (arterioles, capillaries, and venules) and skeletal muscle. Thus, similar to capillary P_{O_2}, the time course of muscle [HHb] increase after onset of exercise reflects the local balance of O_2 delivery and O_2 uptake within the muscle region studied. Prior studies have demonstrated NIRS to be highly sensitive to muscle changes due to exercise, hypoxemia, and aging (13–15), and, thus, NIRS [HHb] provides a noninvasive surrogate of muscle oxygen extraction. Moreover, the measurement of [HHb] in parallel with $\dot{V}_{O_2}$ during exercise can provide useful inferences regarding regional blood flow and allows for the estimation of the increase in muscle microvascular blood flow (Qm) via the Fick principle (16,17).

In the present study we examined whether skeletal muscle [HHb] responses and estimated Qm kinetics are altered in individuals with type 2 diabetes compared with sedentary healthy control subjects. We hypothesized that individuals with type 2 diabetes would have altered skeletal muscle oxygen extraction responses and concordantly slowed estimates of Qm kinetics compared with healthy subjects after the onset of moderate-intensity constant work rate exercise. If confirmed, these observations would further explain the potential mechanisms of exercise limitation and intolerance in people with type 2 diabetes as related to changes in skeletal muscle blood flow and oxygen delivery.

RESEARCH DESIGN AND METHODS

Eleven subjects with type 2 diabetes (5 male and 6 female) and 11 healthy control subjects (6 male and 5 female) between the ages of 30 and 55 years volunteered to participate in this study (Table 1). The study was approved by the University of Colorado Multiple Institutional Review Board, and subjects provided informed consent before study participation. Subjects were sedentary, which was defined as participating in low- to moderate-intensity exercise <2 days/week in the preceding 3 months and confirmed using a low-level physical activity recall (1). Healthy control subjects were defined as taking no medications and did not have a direct family member (parent or sibling) with type 2 diabetes. Diabetes was documented in type 2 diabetic subjects by chart review and confirmed using fasting blood glucose and A1C at screening. Subjects were excluded from the study if they demonstrated *1*) a history of stroke, congestive heart failure, hypertension, or cardiopulmonary disease; *2*) current smoking or smoking within the last 12 months; *3*) autonomic or distal neuropathy; *4*) LDL cholesterol >130 mg/dl, total cholesterol >200 mg/dl, or triglycerides >250 mg/dl; or *5*) A1C >9.0%; or 6) if they were taking exclusionary medicines (insulin, thiazolidinediones [pioglitazone or rosiglitazone], α-glucosidase inhibitors, β-blockers, or calcium channel blockers). Women who were included were premenopausal and were not taking birth control or hormone replacement therapy.

Study participants completed three visits at the laboratory to obtain initial screening measurements, establish baseline peak exercise capacity, and perform constant work rate exercise protocols. Exercise was performed using a bicycle ergometer (Lode, Groningen, Netherlands), and subjects were instructed to avoid the consumption of alcohol, caffeine, and food within 4 h before each exercise visit. To assess peak exercise performance (peak $\dot{V}_{O_2}$) and provide an estimate of lactate threshold, subjects performed an incremental exercise test (10–20 W/min) to volitional fatigue. On a separate day, subjects performed two 6-min constant work rate (CWR) exercise tests at a work rate equivalent to ~85% of the individual's estimated lactate threshold. Each CWR test was preceded by a baseline resting period and 4 min of unloaded cycling before a step increase to the prescribed CWR was initiated. A 30-min period of seated rest separated each test.

Measurements

For all exercise tests, $\dot{V}_{O_2}$, carbon dioxide production ($\dot{V}_{CO_2}$), minute ventilation ($\dot{V}E$), and other ventilatory variables were measured using a breath-by-breath metabolic system (Ultima CPX; Medical Graphics, St. Paul, MN). The O_2 and CO_2 analyzers were calibrated before each test, and pneumotach volumes were calibrated using a syringe of known volume (3.0 liters). Heart rate was monitored continuously by a 12-lead electrocardiogram (Q-stress; Quinton Instruments, Seattle, WA) and recorded synchronously with the ventilatory data for offline analysis. Arterial hemoglobin saturation was monitored and recorded during rest, exercise, and recovery for all experiments by an oximeter placed on the index finger of the dominant hand (Ohmeda, Louisville, CO).

Skeletal muscle [HHb] was assessed by a frequency domain multidistance NIRS monitor (Optiplex TS; ISS, Champaign, IL) during each CWR exercise test. The use and limitations of NIRS have been extensively reviewed (18,19). The NIRS monitor uses two wavelengths of near-infrared light (690 and 830 nm) and four light source detector distances at 2.0, 2.5, 3.0, and 3.5 cm. Local muscle oxygen extraction was determined as the change in [HHb] as described previously (13,20). The near-infrared data were sampled continuously and recorded at 50 Hz. The device probe was positioned on the distal third of the vastus lateralis of the dominant limb, secured using a Velcro strap, and covered with a cloth bandage to exclude ambient light. The NIRS monitor was calibrated before each visit using a calibration phantom of known scattering and optical properties.

Data analysis

Breath-by-breath gas exchange data for each CWR exercise transition were processed using a software program as described previously (21). Data from the two CWR tests were time aligned and averaged to provide a single, average kinetic response for each subject ($\dot{V}_{O_2}$, heart rate, and [HHb]). The kinetic responses were

then evaluated by computerized nonlinear regression (Sigmaplot 9.0; SPSS, Chicago, IL) using standard techniques (20,21) to define the primary end point (i.e., the kinetic time constant reflecting the time to reach ~63% of the exponential response). A one-component exponential model was used to describe the simple exponential increase in [HHb] and heart rate:

$$[HHb](t) = [HHb])(baseline) + A_1(1-e^{-(t-TD1)/\tau}) \quad (1)$$

and a two-component model was used to describe the two phases of pulmonary $\dot{V}O_2$ (for determination of $\dot{V}O_{2muscle}$) and Qm kinetics, where for Qm or $\dot{V}O_2 = X$,

$$X(t)=X(baseline)+A_1(1-e^{-(1\text{-}TD1)/\tau 1}) \quad (phase\ 1)$$

$$+ A_2[1-e^{-(\tau\text{-}TD2)/\tau 2}] \quad (phase\ 2) \quad (2)$$

In the exponential models, the curve fit provided estimates of the baseline and amplitude for each exponential phase (A_1 and A_2) as well as the time delays (TD_1 and TD_2) and time constants (τ_1 and τ_2) for each of the measured exponential phases (see Fig. 1*E* for a graphic definition of the two-component model fit). Thus, the resulting curve fit described the time course and magnitude of increase of the respective phases from baseline to steady-state exercise.

Qm responses were calculated using the measured [HHb] as a surrogate of muscle oxygen extraction and the phase 2 response of pulmonary $\dot{V}O_2$ kinetics (e.g., representing muscle $\dot{V}O_2$ kinetics, $\dot{V}O_{2muscle}$ [22,23]) as described previously (16,17):

$$Qm(t) = \dot{V}O_2(phase\ 2)(t)/[HHb](t) \quad (3)$$

Because the absolute volume of muscle tissue represented in the NIRS signal is not known, the Qm responses were calculated in arbitrary units. However, this method has been previously compared and contrasted with that of conduit artery blood flow with qualitative agreement (17). The kinetics of Qm were then evaluated using the two-component exponential model. The mean response time (MRT) for [HHb] was calculated as the sum of TD and τ from the single exponential model. The MRT for Qm was calculated using a weighted model, adjusting for the amplitude, time delay, and time constant of each phase as described (17).

Table 2—*Kinetic parameters for $\dot{V}O_2$, HHb, heart rate, and Qm*

	Control	Type 2 diabetic
$\tau\dot{V}O_2$ (s)	34.2 ± 8.2	43.8 ± 9.6*
τHR (s)	45.1 ± 15.9	51.2 ± 14.1
τ[HHb] (s)	10.2 ± 4.4	8.8 ± 4.8
MRT [HHb] (s)	17.8 ± 5.5	18.5 ± 4.6
τ_1 Qm phase 1 (s)	6.6 ± 2.8	5.1 ± 3.2
τ_2 Qm phase 2 (s)	32.0 ± 9.7	43.6 ± 12.9*
MRT Qm (s)	35.8 ± 10.7	47.7 ± 14.3*
$\tau\dot{V}O_2$ (s)	34.2 ± 8.2	43.8 ± 9.6*

Data are means ± SD. Refer to text for calculation of τ, τ1, τ2, and MRT. $\tau\dot{V}O_2$, time constant for $\dot{V}O_2$ kinetics; τHR, time constant for heart rate; τ[HHb], time constant for increase in [HHb]; τ_1 Qm, time constant for phase 1 of Qm; τ_2 Qm, time constant for phase 2 of Qm. *$P < 0.05$, type 2 diabetic versus control subjects.

Statistical analysis

Two-tailed independent Student's *t* tests were used for comparison of the kinetic responses between type 2 diabetic and healthy subjects (NCSS Statistical Software, Kaysville, UT). Pearson's *r* was used to evaluate the correlations between Qm kinetics and peak exercise capacity ($\dot{V}O_{2peak}$). Statistical significance was declared at $P < 0.05$.

RESULTS — Subject characteristics did not differ between groups (Table 1) except for habitual physical activity scores (using the Low Level Physical Activity Recall), which were higher in the type 2 diabetic group compared with those in control subjects ($P < 0.05$). As expected, fasting glucose levels and A1C were higher in the diabetic subjects (Table 1). However, although numerically lower in type 2 diabetes, the peak $\dot{V}O_2$ from incremental exercise testing was not different between type 2 diabetic and control subjects (24.6 ± 4.8 vs. 20.9 ± 5.1 ml · kg^{-1} · min^{-1}, NS). In all subjects, resting arterial hemoglobin saturation was ≥95% and revealed no changes in any subject during exercise testing.

The time constants indicating $\dot{V}O_{2muscle}$ in type 2 diabetic subjects were significantly slowed compared with those for control subjects ($P < 0.05$) (Table 2). Heart rate kinetics were not different between type 2 diabetic and healthy control subjects, and no differences were observed between groups for the initial kinetic parameters of [HHb] (Table 2). Representative plots of the $\dot{V}O_{2muscle}$, [HHb], and calculated Qm responses and curve fit for a control subject and a subject with type 2 diabetes are presented in Fig. 1. After the onset of exercise, the [HHb] response profile demonstrated a noticeable excursion of [HHb] above the level observed for steady-state exercise (e.g., during the first ~90–100 s) in the majority of subjects with type 2 diabetes.

There was no difference between groups for the time constant of phase 1 of the Qm response (Table 2). However, the type 2 diabetic subjects demonstrated a significantly slower time constant for phase 2 of the Qm response ($P < 0.05$), and the calculated MRT of Qm was significantly slower in the type 2 diabetic subjects compared with healthy control subjects ($P < 0.05$). Correlations between Qm kinetic parameters and $\dot{V}O_{2peak}$ were not significant ($P > 0.05$).

CONCLUSIONS — This study demonstrated differences in the pattern of skeletal muscle deoxygenation after the onset of exercise in humans with type 2 diabetes compared with healthy subjects. Given the prolonged increase of oxygen uptake during exercise in type 2 diabetic subjects, these data indicate that the increase in microvascular blood flow with exercise is abnormally slow in type 2 diabetes and suggest that the limitation of oxygen uptake during submaximal exercise in type 2 diabetes may be related to impaired control or maldistribution of muscle blood flow. Impaired skeletal muscle oxygen delivery in response to exercise may thus contribute to the observed exercise deficit of type 2 diabetes.

In the present study, we observed a transient excursion of [HHb] (e.g., "overshoot") above the level achieved for steady-state exercise in the majority of type 2 diabetic subjects. Because the increase in [HHb] is a measure of the increase in the local muscle deoxygenated hemoglobin/myoglobin concentration (hence reflecting tissue oxygen extraction), the overshoot [HHb] response observed in type 2 diabetic subjects provides evidence of an impaired increase of muscle blood flow relative to muscle oxygen

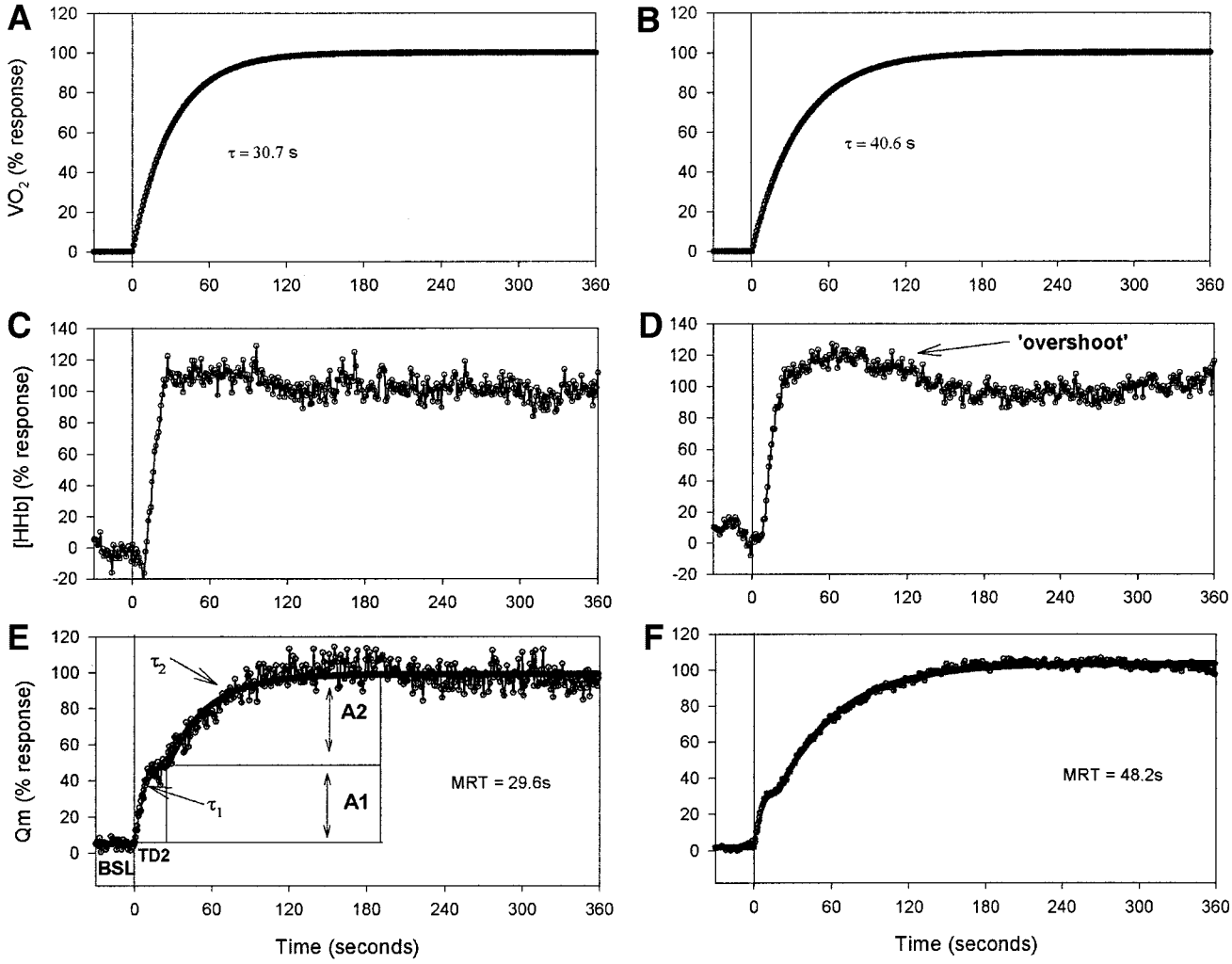

Figure 1—*Representative example of $\dot{V}O_{2muscle}$ derived from pulmonary $\dot{V}O_2$ kinetics (A and B), [HHb] responses (C and D), and estimated Qm responses (E and F) during the transition from unloaded to moderate cycling in a healthy control subject (A, C, and E) and type 2 diabetic subject (B, D, and F). Data are presented as a function of end exercise response. Note the transient overshoot of the [HHb] response in the type 2 diabetic subject. The estimated Qm profile was calculated from $\dot{V}O_{2muscle}$ divided by [HHb] in arbitrary units. Loaded cycling exercise begins at time = 0. Qm kinetic model parameters: BSL, baseline; TD, time delay; τ_1 and τ_2, time constants; A1 and A2, response amplitudes; τ, time constant of $\dot{V}O_{2muscle}$; MRT, Qm MRT. Solid lines represent curve fitting of the Qm kinetic response (E and F).*

uptake after onset of exercise (7,24,25). This reflects an increased dependence on oxygen extraction in type 2 diabetic muscle compared with muscle of control subjects that occurs early in exercise. This response is qualitatively equivalent to the capillary PO_2 responses previously observed only in the exercising muscle of diabetic animals (7,8). The significance of this response is related to a transient lowering of capillary PO_2 that, in turn, may impair capillary to myocyte O_2 transport (via a lowered diffusion gradient) and constrain early increases in muscle oxygen uptake (7,8). Our [HHb] findings appear to support the concept that the early increase in muscle blood flow may be attenuated in type 2 diabetes, and this abnormality may contribute to the slowed $\dot{V}O_2$ kinetics and exercise deficit observed in type 2 diabetes.

Consistent with previous reports (16,17) and other measures of exercise blood flow in animals (26) and humans (27), our estimated Qm demonstrated a biphasic response in all type 2 diabetic and control subjects after the onset of moderate exercise. The phases of blood flow responses after exercise onset have previously been characterized (27,28) with the first phase of blood flow increase generally considered to result from muscle contractions (e.g., muscle pump) and rapid vasodilatation, although the precise factors responsible for the latter mechanism remain unclear (28,29). The second phase of blood flow increase is closely matched with metabolic demand, resulting from metabolic feedback control (e.g., H+, K+, prostaglandins, nitric oxide, and others). Although we found similar phase 1 kinetics of estimated Qm in type 2 diabetic and control subjects, the time constants for phase 2 of Qm were significantly longer in type 2 diabetic compared with healthy subjects. We acknowledge that our estimate of Qm is qualitative in nature and dependent on assumptions of homogeneous muscle [HHb] characteristics; however, there is evidence to support the assumption that the sampled muscle (vastus lateralis) reflects the predominant active muscles during cycling as a whole (30), and, therefore, the relative kinetics of estimated Qm responses should be preserved. Thus, the slower phase 2 time constant and MRT of Qm demonstrates

the plausible notion that metabolic feedback control during exercise may be altered in type 2 diabetes. Indeed, there is evidence for macro- and microvascular dysfunction in type 2 diabetes (31,32) that could explain impaired microvascular blood flow responses during exercise.

It is well established that nitric oxide–dependent endothelial function is impaired in the conduit arteries in type 2 diabetes (33,34), and this mechanism has been associated with reduced steady-state leg blood flow in type 2 diabetic subjects during submaximal exercise (9). However, it is unclear whether conduit artery blood flow dynamics after onset of exercise are altered in type 2 diabetes or to what extent vascular dysfunction or changes in microvascular architecture in type 2 diabetes may impair macro- or microvascular blood flow dynamics and the distribution of muscle blood flow after the onset of exercise. We have previously observed prolonged heart rate responses in subjects with type 2 diabetes (2). Thus, it is plausible that a central impairment of cardiac output could undermine blood flow and oxygen delivery to the skeletal muscle vascular beds during exercise. However, cardiac output during submaximal exercise appears normal in type 2 diabetes (35), and we observed no differences in heart rate kinetics between groups. Therefore, the putative Qm abnormality observed during submaximal exercise in type 2 diabetic subjects is probably specific to the control of blood flow of the exercising legs.

The role of skeletal muscle in the impaired submaximal exercise response of type 2 diabetes has not been elucidated. However, the likelihood of an integral role is suggested by the available data. For example, capillary density appears reduced in type 2 diabetic skeletal muscle (36), and basement membrane structures are altered (37). These structural changes could directly contribute to alterations in microvascular hemodynamics, exacerbate potential mismatching of muscle blood flow-to-oxygen uptake, and impair O_2 exchange from capillary to myocyte as suggested by the work in rodent models (6,8,38). However, the skeletal muscle of type 2 diabetic patients also demonstrates reduced mitochondrial content (10) and increased potential for mitochondrial dysfunction compared with healthy counterparts (5,10,11,39), although the functional evidence for this notion is controversial (40). Whether the changes observed in the skeletal muscle of individuals with type 2 diabetes are related to altered muscle fiber type composition (greater numbers of type IIb fibers relative to type I fibers) (41), detraining, or other factors is unclear. However, it appears that both the ability to deliver oxygen to the skeletal muscle and use of oxygen during exercise by the muscle may be compromised in type 2 diabetes. The findings of the present study appear to support the importance of impaired skeletal muscle oxygen delivery as a significant determinant of the submaximal exercise impairment in type 2 diabetes. However, given the similar (and not faster) [HHb] kinetics in type 2 diabetic subjects compared with control subjects, these findings could also indicate, to a lesser extent, the potential contribution of muscle oxidative dysfunction or other factors in limiting the submaximal exercise response.

In contrast to the long-recognized defects in $\dot{V}O_{2peak}$ observed in type 2 diabetes, defects in the response at the onset of submaximal exercise represent a challenge that will be encountered during routine activities. Thus, the finding of impaired submaximal exercise responses in otherwise uncomplicated type 2 diabetes is clinically relevant. In the present study, we showed slowed $\dot{V}O_2$ kinetics in type 2 diabetic compared with healthy subjects, consistent with previous reports (2,42), which may be a mechanism for the type 2 diabetes exercise intolerance. The significance of slowed $\dot{V}O_2$ kinetics is that it indicates a prolonged period of adaptation to any acute submaximal exercise demand, such as that regularly encountered during daily life. Importantly, the prolonged $\dot{V}O_2$ kinetics results in a greater oxygen deficit and, hence, greater dependence upon substrate level phosphorylation (phosphocreatinine degradation and glycolysis) to support even low and moderate levels of exercise. This finding is significant because activities of daily life are carried out at these low levels of physical activity. Thus, the accumulated oxygen deficit that occurs with the initiation of exercise may ultimately affect the ability or willingness of individuals to sustain the activity, resulting in the limited exercise tolerance and reduced peak exercise capacity observed in type 2 diabetes.

In summary, skeletal muscle [HHb] responses are altered in type 2 diabetes during the transition from light to moderate exercise, indicating a slowed increase of microvascular blood flow in response to exercise in type 2 diabetic patients. The prolonged kinetics of estimated Qm suggests that muscle $\dot{V}O_2$ during exercise may be constrained by an impairment of muscle oxygen delivery in type 2 diabetic skeletal muscle, potentially leading to diminished submaximal exercise function in type 2 diabetes. Impairments in skeletal muscle oxygen delivery due to abnormal vascular control or other abnormalities of type 2 diabetic skeletal muscle may explain, in part, the observed exercise deficit observed in individuals with type 2 diabetes.

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