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$\dot{V}O_{2\max}$ and the kinetics of $\dot{V}O_2$, muscle oxygen delivery, and muscle deoxygenation

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Introduction: Aerobic fitness and oxygen uptake kinetics ($\tau\dot{V}O_2$) at the onset of exercise appear to be inversely correlated, however, the mechanisms underlying changes in $\tau\dot{V}O_2$ across different levels of aerobic fitness have not been elucidated. The purpose of this study was to investigate the relationship between maximal $\dot{V}O_2$ ($\dot{V}O_{2\max}$) and $\tau\dot{V}O_2$ and determine whether the capacity to deliver or to utilize O_2 limits $\tau\dot{V}O_2$ in an aerobic fitness dependent manner.

Methods: Twenty-three healthy, young males (25 ± 4 years) with a $\dot{V}O_{2\max}$ classified as superior (S; $\dot{V}O_{2\max} > 60 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $n = 7$), good (G; $\dot{V}O_{2\max} = 45\text{--}55 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $n = 8$) or poor (P; $\dot{V}O_{2\max} < 40 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $n = 8$) performed two moderate-intensity knee-extension (KE) exercise transitions (80% of gas exchange threshold) on a custom-built KE ergometer. $\dot{V}O_2$ was measured breath-by-breath. Leg blood flow (BF) was measured by doppler ultrasound at the femoral artery, and leg vascular conductance (LVC) was calculated as $\text{BF}\cdot\text{mean arterial pressure (MAP)}^{-1}$. Near-infrared spectroscopy derived-[HHb] was measured on the vastus lateralis muscle. $\tau\dot{V}O_2$, τLVC , and $\tau[\text{HHb}]$ data were averaged and fit with a mono-exponential function.

Results: $\tau\dot{V}O_2$ was faster in the S ($P < 0.01$) and G ($P < 0.05$) fitness groups compared with the P fitness group. $\tau[\text{HHb}]$ was faster in the S ($P < 0.05$) compared with the P fitness group. $\dot{V}O_{2\max}$ was inversely correlated to $\tau\dot{V}O_2$ ($r = -0.71$; $P < 0.001$) and $\tau[\text{HHb}]$ ($r = -0.55$; $P < 0.01$), but not with τLVC ($r = -0.12$; $P > 0.05$). $\tau\dot{V}O_2$ was positively correlated with $\tau[\text{HHb}]$ ($r = -0.57$; $P < 0.01$), but not with τLVC ($r = -0.25$; $P > 0.05$).

Conclusion: $\dot{V}O_{2\max}$ and $\tau\dot{V}O_2$ were inversely correlated across fitness levels. These findings indicate that O_2 delivery is not rate-limiting for $\tau\dot{V}O_2$ across fitness levels and suggest that the intracellular capacity to utilize O_2 may be the primary limiting factor for $\tau\dot{V}O_2$ in healthy young adults, regardless of aerobic fitness.

KEYWORDS

maximal oxygen uptake, aerobic fitness, oxygen uptake kinetics, blood flow kinetics, deoxyhemoglobin kinetics, oxidative phosphorylation, oxygen delivery

Introduction

In response to moderate-intensity step-transition exercise, oxygen uptake ($\dot{V}O_2$) increases in a mono-exponential manner (Margarita et al., 1965; Margarita et al., 1963; Poole and Jones, 2012). The increase in $\dot{V}O_2$ is closely related to the metabolic demand of exercise and is achieved through an integrated response of the pulmonary, cardiovascular, and muscle metabolic systems (Grassi, 2003; Poole et al., 2007; Grassi et al., 2003; Grassi, 2005; Grassi et al., 2021; Rossiter, 2011). The rate at which $\dot{V}O_2$ adjusts at the onset of

exercise, commonly referred to as $\dot{V}O_2$ kinetics ($\tau\dot{V}O_2$), varies across individuals/populations and serves as an important index of aerobic metabolic function, with implications for metabolic stability (Grassi et al., 2015; Grassi et al., 2011; Grassi et al., 1996) and exercise tolerance (Poole and Jones, 2012; Grassi et al., 2011; Goulding et al., 2021).

Convective and diffusive O_2 delivery to active muscles involves a complex interaction between motor unit recruitment, cardiac output, sympathetic vasoconstriction, and local vasodilation that matches muscle blood flow (BF) to metabolism (Pittman, 2016; Pittman, 2011; Poole et al., 2011; Poole and Musch, 2023; Poole et al., 2022; Marinari et al., 2025; DeLorey and Clifford, 2022; Joyner and Casey, 2015; Zoladz et al., 2016). Previous studies in healthy active individuals have reported that bulk leg BF increases at a rate similar to or faster than $\tau\dot{V}O_2$ (Macdonald et al., 1998; Fukuba et al., 2004; Nyberg et al., 2017; duManoir et al., 2010; DeLorey et al., 2007; MacPhee et al., 2005; Koga et al., 2005; Endo et al., 2005; Harper et al., 2006; Jones et al., 2012; Schlup et al., 2015; Paterson et al., 2005; Love et al., 2023), suggesting that bulk O_2 delivery may not be a limiting factor for $\tau\dot{V}O_2$. In contrast, in disease states where pulmonary and cardiovascular function may be impaired and muscle O_2 delivery is significantly slowed, $\tau\dot{V}O_2$ is also slowed (Poole and Jones, 2012; Poole et al., 2007), suggesting that there may be a critical rate of O_2 delivery required to support an increase in $\dot{V}O_2$ at the onset of exercise. However, measures of bulk leg BF do not provide any information related to the distribution of leg BF and may not reflect BF/ O_2 delivery to active muscle(s). Near-infrared spectroscopy (NIRS)-derived [deoxyhemoglobin] ([HHb]) provides an index of changes in muscle O_2 extraction in response to exercise in a discrete region of the active muscle microcirculation (Grassi et al., 2003; DeLorey et al., 2003; Grassi and Quaresima, 2016). Consistent with the Fick equation, changes in [HHb] reflect the balance between changes in microvascular O_2 delivery and those in muscle $\dot{V}O_2$. A faster τ [HHb] (i.e., O_2 extraction) relative to $\tau\dot{V}O_2$ may result from either slowed muscle O_2 delivery relative to muscle $\dot{V}O_2$ or faster muscle $\dot{V}O_2$ relative to the rate of muscle O_2 delivery. Previous studies have reported that [HHb] adapts at a faster rate than $\dot{V}O_2$ in healthy individuals (Grassi et al., 2003; DeLorey et al., 2003; Adami et al., 2011), demonstrating a mismatch between microvascular O_2 delivery and muscle $\dot{V}O_2$ at the onset of exercise. The faster τ [HHb] relative to $\tau\dot{V}O_2$ observed in these studies could reflect the following: (i) a slowed O_2 delivery relative to the metabolic demand, with O_2 delivery potentially limiting $\tau\dot{V}O_2$; (ii) a faster O_2 intracellular utilization relative to O_2 delivery, with the slower O_2 delivery not being rate-limiting for $\tau\dot{V}O_2$. Unfortunately, these studies did not include measures of leg BF/ O_2 delivery to facilitate resolution of the underlying cause of the faster τ [HHb].

Individuals with high aerobic fitness appear to have faster $\tau\dot{V}O_2$ than those with low aerobic fitness (Caputo et al., 2003; Caputo and Denadai, 2004; Cerretelli et al., 1979; George et al., 2018; Grey et al., 2015; Inglis et al., 2021; Koppo et al., 2004a), and an inverse relationship between maximal oxygen uptake ($\dot{V}O_{2max}$) and $\tau\dot{V}O_2$ has been reported (Inglis et al., 2021; Murias et al., 2011a; Fawcner et al., 2002; Chilibeck et al., 1996; Murgatroyd et al., 2011; Norris and Petersen, 1998; Powers et al., 1985). Although it seems unlikely that $\dot{V}O_{2max}$ and $\tau\dot{V}O_2$ have a direct mechanistic basis, the

relationship between $\dot{V}O_{2max}$ and $\tau\dot{V}O_2$ suggests that aerobic fitness may influence the physiological determinants of $\tau\dot{V}O_2$.

Therefore, the purpose of this study was to investigate the following hypotheses: 1) $\dot{V}O_{2max}$ and $\tau\dot{V}O_2$ would be inversely correlated; and 2) the limiting factor to $\tau\dot{V}O_2$ would be a function of $\dot{V}O_{2max}$, with O_2 delivery limiting $\tau\dot{V}O_2$ in participants with “poor” aerobic fitness, but not in participants with “good” and “superior” aerobic fitness.

Methods

Participants

This study was approved by the University of Alberta Health Sciences Research Ethics Board (Pro00015860). Twenty-three healthy young male individuals volunteered and provided written informed consent to participate in the study (Table 1). Participants were not undertaking any training program during the study period and were stratified into three aerobic fitness groups based on their relative $\dot{V}O_{2max}$, according to the American College of Sports Medicine for young male individuals (ages 20–29 years) (Kaminsky et al., 2015), as follows: “poor” (P; $\dot{V}O_{2max} < 40 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $n = 8$), “good” (G; $\dot{V}O_{2max} = 45\text{--}55 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $n = 8$), and “superior” (S; $\dot{V}O_{2max} > 60 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $n = 7$). All subjects were non-obese (BMI $< 30 \text{ kg}\cdot\text{m}^{-2}$), non-smokers, and free from any previously diagnosed respiratory, cardiovascular, metabolic, or musculoskeletal disease. No subjects were using medications known to alter the cardiorespiratory response to exercise during this study.

Experimental protocol

All testing was completed in the Integrative Human Exercise Physiology Laboratory at the University of Alberta. Participants reported to the laboratory on three separate occasions. Participants were instructed to abstain from exercise, caffeine, alcohol, and ibuprofen for 24 h prior to testing and to eat a light meal ~ 2 h before exercise testing. Laboratory temperature was maintained between 20 °C and 22 °C.

Day 1. Participants completed an incremental exercise test to volitional exhaustion on a cycle ergometer (Ergoselect 200 K, Ergoline, Bitz, Germany) to determine $\dot{V}O_{2max}$. Following 2 min of baseline data collection, participants began pedaling, and the work rate was progressively increased in a ramp-like fashion at 30 watts ($\text{W}\cdot\text{min}^{-1}$) to volitional exhaustion. Criteria used to establish a maximal test included the observation of a plateau in peak $\dot{V}O_2$, despite an increased work rate, a respiratory exchange ratio (RER) > 1.1 , achievement of $>90\%$ age-predicted maximal heart rate (HR), and volitional exhaustion. Participants were then assigned to pre-determined aerobic fitness groups described above.

Day 2. Participants completed an incremental alternate-leg knee-extension (KE) exercise test to volitional exhaustion on a custom-built KE ergometer, as previously described (DeLorey et al., 2007). This test was conducted to determine individual work rates for moderate-intensity KE exercise. After 2 min of resting baseline data collection, participants completed 1-min of passive (unloaded)

TABLE 1 Participant characteristics.

	Superior (<i>n</i> = 7)	Good (<i>n</i> = 8)	Poor (<i>n</i> = 8)
Age (years)	25 ± 5	24 ± 4	26 ± 2
Height (cm)	181 ± 7	181 ± 6	180 ± 6
Body mass (kg)	76.1 ± 11.7	74.1 ± 7.5	79.7 ± 8.6
$\dot{V}O_{2max}$ (mL·kg ⁻¹ ·min ⁻¹)	68.5 ± 3.6*	50.5 ± 3.0*	32.8 ± 4.8*
$\dot{V}O_{2max}$ (L·min ⁻¹)	5.17 ± 0.54*	3.75 ± 0.49*	2.60 ± 0.43*
KE WR _{peak} (W)	84 ± 41	78 ± 19	56 ± 15
KE WR moderate (W)	47 ± 11*	33 ± 9*	23 ± 7*
KE $\dot{V}O_{2peak}$ (mL·kg ⁻¹ ·min ⁻¹)	32.3 ± 4.4*	27.6 ± 4.9*	20.8 ± 4.9*
KE $\dot{V}O_{2peak}$ (L·min ⁻¹)	2.41 ± 0.47*	2.05 ± 0.46*	1.63 ± 0.34*

Values are mean ± standard deviation. $\dot{V}O_{2max}$, maximal oxygen uptake; $\dot{V}O_{2peak}$, peak oxygen uptake; WR, work rate; W, watts; KE, knee extension.

*Indicates significant difference (*P* < 0.05) between all aerobic fitness groups.

KE exercise, followed by alternate-leg KE exercise at a cadence of 30 contractions per leg per minute (cpm) from an initial work rate of 18 W. The work rate was then increased 3 W·min⁻¹ until volitional exhaustion or until participants were unable to maintain a cadence of 30 cpm. Criteria used to establish a maximal test were a plateau in $\dot{V}O_2$ despite an increase in the work rate, an RER >1.10, and volitional exhaustion. The gas exchange threshold (GET) was defined as the $\dot{V}O_2$ at which CO₂ production ($\dot{V}CO_2$) began to increase disproportionately with respect to $\dot{V}O_2$, concurrent with an increase in the ratio of minute ventilation ($\dot{V}E$) to $\dot{V}O_2$ and end-tidal PO₂, while $\dot{V}E/\dot{V}CO_2$ and end-tidal PCO₂ remained stable. Moderate-intensity KE exercise was defined as a work rate corresponding to 80% of the work rate at the GET.

Day 3. Participants completed two step transitions from passive KE exercise to moderate-intensity KE exercise to determine the on-transient $\tau\dot{V}O_2$, $\tau[HHb]$, and τLVC . Testing began with 2 min of resting baseline data collection, followed by 1-min of passive KE exercise. Thereafter, the work rate was increased in a stepwise manner, and participants performed 5 min of constant-load moderate-intensity KE exercise. Following a 15-min recovery period, the protocol was repeated, and the data from the two exercise transitions were ensemble-averaged (see *data analysis*). All KE exercise was performed at a cadence of 30 cpm and was preceded by 1-min of passive, unloaded exercise to minimize the effects of mechanical inertia and muscle mechanical factors and to increase the amplitude of the on-transient responses, thereby improving the signal-to-noise ratio and the accuracy of kinetics analysis. Participants' legs were secured to the lever arms of the KE ergometer to facilitate passive exercise.

Measurements

For all exercise testing, participants breathed through a mouthpiece, with their nose occluded. A low-resistance mass-flow meter was used to measure pulmonary gas exchange ($\dot{V}O_2$,

$\dot{V}CO_2$, and RER) and $\dot{V}E$ breath-by-breath via open-circuit indirect calorimetry (Vmax[®] 229d; Viasys[™] Healthcare, Palm Springs, CA). Prior to each test, the flow meter was calibrated with a 3-L calibration syringe, and the O₂ and CO₂ analyzers were calibrated with gases of known concentrations.

A three-lead electrocardiogram (ECG) was measured continuously (Power Laboratory 16/30, AD Instruments, Colorado Springs, CO), and HR was derived from the ECG. Beat-by-beat arterial blood pressure (BP) was measured using photoplethysmography on the middle finger of the right hand (Finometer[™], Finapres Medical Systems, Amsterdam, Netherlands). BP was also measured using a sphygmomanometer, and Finometer BP was corrected to manually measured pressures when pressure differences were observed. Mean arterial pressure (MAP) was calculated on a beat-by-beat basis.

Mean blood velocity (MBV) of the right femoral artery was measured using pulsed-Doppler ultrasonography (Vivid I, General Electric, Waukesha, WI). Data were acquired continuously using a 7.5 MHz probe positioned 2–3 cm distal to the inguinal ligament and proximal to the femoral artery bifurcation, while the probe was maintained at a 45-degree angle of insonation. Prior to exercise testing on days 2 and 3, the resting diameter of the femoral artery was measured in triplicate during diastole. The three measures were then averaged to determine the baseline femoral artery diameter. Previous studies have demonstrated that the common femoral artery diameter does not change from resting values during exercise. Thus the resting diameter was used for blood flow calculations during exercise (Macdonald et al., 1998; MacPhee et al., 2005; Paterson et al., 2005; Rådegran and Saltin, 2000). Mean blood velocity in cm·s⁻¹ was measured on a beat-by-beat basis. Limb BF was calculated as BF (mL·min⁻¹) = MBV· π ·*r*²·60, where *r* is the measured radius of the femoral artery. LVC was then calculated as follows: LVC (L·min⁻¹·mmHg⁻¹) = BF·MAP⁻¹. Data were recorded using a PowerLab 16/30 system and Chart 7 data acquisition software (AD Instruments) at a sampling frequency of 100 Hz.

Relative [HHb] was measured in the vastus lateralis (VL) muscle using NIRS (NIRO 300, Hamamatsu Photonics, Hamamatsu, Japan), as described previously (DeLorey et al., 2007). In short, optodes were placed on the belly of the VL at the midpoint between the lateral epicondyle and the greater trochanter of the femur. These optodes were contained within an optically dense plastic holder to minimize extraneous light and the loss of NIR light from the field of interrogation and ensure the position of optodes relative to each other. This optode assembly was affixed to the skin using tape and was wrapped in an elastic bandage to further prevent movement of the optodes and interference of extraneous light.

The intensities of incident and transmitted light were continuously recorded, along with relevant extinction coefficients and estimated optical path length, assuming a differential path length factor of 3.83 (DeLorey et al., 2007). These values were used for online estimation and display of changes in concentrations of oxyhemoglobin (O_2Hb), HHb, and total hemoglobin (Hb_{tot}). The raw attenuation signal in optical density units was sampled at 1Hz and transferred to a computer and stored for future analysis. Prior to testing, the NIRS unit was “zeroed” to a stable, resting baseline.

Data analysis

$\tau\dot{V}O_2$

Breath-by-breath $\dot{V}O_2$ data were filtered for aberrant data points, interpolated to 1-s intervals and then ensemble-averaged into 5-s time bins to yield a single response for each subject. The on-transient responses were modeled using nonlinear, least squares regression procedures (OriginLab, Northampton, MA, United States), with a mono-exponential function:

$$Y(t) = Y_{(b)} + A \left\{ 1 - e^{[-(t-TD)/\tau]} \right\}, \quad (1)$$

where Y represents $\dot{V}O_2$ at any time (t), b is the baseline value of Y at the point in time from which the data were fit, A is the amplitude of the increase in Y above the baseline value, τ is the time constant defined as the duration of time at which Y increases to a value equivalent to 63% of A , and TD is the time delay. Only the primary component (*phase II*) of the on-transient $\dot{V}O_2$ response was included in the fitting window, excluding the so-called cardio dynamic component (*phase I*). *Phase I* was identified by extending the fitting window backward from ~ 40 s until τ , χ^2 , and confidence interval (CI) began to increase, as described elsewhere (Love et al., 2023; Rossiter et al., 2001).

τLVC

Similar to $\dot{V}O_2$, LVC data were filtered for aberrant data points, interpolated to 1-s intervals and then ensemble-averaged into 5-s time bins to yield a single response for each subject. Subsequently, LVC data were fit with a mono-exponential model as described in Equation 1 from the onset of exercise to either the end of the exercise or a potential peak (overshoot) manifested within the first minutes of exercise (Love et al., 2023).

$\tau[HHb]$

Similarly, [HHb] data were ensemble-averaged into 5-s time bins to yield a single response for each subject. Subsequently, [HHb] data

were fit with a mono-exponential model as described in Equation 1 from the end of the calculated TD (CTD), representing the first value following the exercise onset at which [HHb] began to systematically increase. Thereafter, [HHb] was fit (i) to the end of exercise in the case of stable responses, (ii) to a potential overshoot within the first seconds/minutes of exercise, or (iii) to the point preceding a potential gradual increase in the response following an initial steady-state behavior (Love et al., 2023).

Following the observation of a consistent “overshoot” in [HHb] at the onset of exercise in the S fitness group, further analyses were performed to quantify its magnitude and make inferences about microvascular and intracellular oxidative responses across groups. A 30-s moving average was performed within the first 3 minutes of exercise of the normalized [HHb] for all groups. Thereafter, the time points at which the highest 30-s moving average occurred served to identify the time window with higher [HHb] overshoot incidence, which ranged from 40 s to 120 s of the exercise on-transient. The difference between the average [HHb] between 40 s and 120 s and the last minute of [HHb] during exercise was computed for each subject and compared across groups.

Relationships between kinetics and $\dot{V}O_{2max}$

Correlation analyses were performed to examine the relationship between $\tau\dot{V}O_2$, τLVC , and $\tau[HHb]$ with varying $\dot{V}O_{2max}$ and elucidate the relationship between O_2 delivery (i.e., τLVC) and extraction (i.e., $\tau[HHb]$) with varying $\tau\dot{V}O_2$.

Gain

The gain for $\dot{V}O_2$, LVC, and [HHb] was computed as the amplitude of the response of each variable divided by the work rate amplitude of each subject ($\dot{V}O_{2GAIN}$, $mL \cdot min^{-1} \cdot W^{-1}$; LVC_{GAIN} , $mL \cdot min^{-1} \cdot mmHg^{-1} \cdot W^{-1}$; $[HHb]_{GAIN}$, $\mu M \cdot min^{-1} \cdot W^{-1}$).

Statistical analysis

All data are reported as the mean \pm standard deviation. A one-way ANOVA was performed for between-group comparisons of $\dot{V}O_{2max}$, gain, $\tau\dot{V}O_2$, τLVC , and $\tau[HHb]$. Within group differences between $\tau\dot{V}O_2$, τLVC and $\tau[HHb]$ were determined by one-way ANOVA. When significant F-ratios were found, Tukey’s HSD *post hoc* analysis was performed. A paired Student’s t-test was performed to compare a potential initial [HHb] overshoot within groups. Relationships between variables were determined using Pearson’s r correlation. A p -value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (v. 29.0, IBM, Chicago, United States).

Results

Participant characteristics

Participant characteristics are reported in Table 1. Consistent with the design of the study, both absolute and relative $\dot{V}O_{2max}$ values were different between S, G and P fitness groups ($p < 0.001$). Similarly, absolute and relative KE $\dot{V}O_{2peak}$ were also different between the S, G and P fitness groups ($p < 0.01$). Additionally,

TABLE 2 Baseline values.

Group	$\dot{V}O_2$ (L·min ⁻¹)	LVC (mL·min ⁻¹ ·mmHg ⁻¹)	[HHb] (μ M)
S (n = 7)	0.49 ± 0.09	14.0 ± 0.5	-2.4 ± 0.8
G (n = 8)	0.44 ± 0.07	14.0 ± 0.4	-1.4 ± 1.4
P (n = 8)	0.46 ± 0.09	10.0 ± 0.3	-0.8 ± 1.2

Values are mean ± standard deviation. $\dot{V}O_2$, oxygen uptake; LVC, leg vascular conductance; [HHb], deoxyhemoglobin concentration; S, superior; G, good; P, poor.

peak and moderate KE work rates were significantly different across groups (all $p < 0.01$).

Pre-transition baseline values for $\dot{V}O_2$, LVC, and [HHb] are reported in Table 2. Averaged absolute and normalized profiles for $\dot{V}O_2$, LVC, and [HHb] are depicted in Figure 1 (upper and lower panel, respectively).

$\tau\dot{V}O_2$

$\tau\dot{V}O_2$ values for S, G, and P were 22 ± 3 s (CI₉₅: 8 s range), 39 ± 23 s (CI₉₅: 11 s range), and 69 ± 30 s (CI₉₅: 23 s range), respectively, and were different across the fitness groups ($p < 0.05$; Figure 2A). In particular, post hoc analysis revealed that $\tau\dot{V}O_2$ in S and G was faster than $\tau\dot{V}O_2$ in P ($p < 0.01$ and $p < 0.05$, respectively), whereas $\tau\dot{V}O_2$ was not different between S and G ($p > 0.05$).

τ LVC

τ LVCs for S, G, and P were 27 ± 22 s (CI₉₅: 9 s range), 18 ± 23 s (CI₉₅: 7 s range), and 31 ± 18 s (CI₉₅: 16 s range), respectively, and were not significantly different ($p > 0.05$; Figure 2A).

τ [HHb]

The CTDs for S, G, and P, from which the exponential fit began, were 13 ± 4 s, 12 ± 6 s, and 12 ± 5 s, respectively, and not significantly different ($P > 0.05$). τ [HHb] values for S, G, and P were 11 ± 3 s (CI₉₅: 3 s range), 18 ± 11 s (CI₉₅: 5 s range), and 26 ± 13 s (CI₉₅: 4 s range), respectively, and were different between fitness groups ($P < 0.05$; Figure 2A). In particular, post hoc analysis revealed that τ [HHb] was faster in S compared with P ($p < 0.05$), whereas no significant difference was observed in τ [HHb] between S and G ($p > 0.05$; Figure 2A).

An overshoot in [HHb] in the S fitness group was confirmed ($p < 0.05$), whereas no [HHb] overshoot was observed for the G or P fitness group.

Within-group kinetics

Comparison between $\tau\dot{V}O_2$, τ LVC, and τ [HHb] is depicted in Figure 2B. No within-group differences between $\tau\dot{V}O_2$, τ LVC, and τ [HHb] were observed for S and G fitness groups ($p > 0.05$), whereas a within-group difference in the P fitness group was detected ($p < 0.05$). In particular, post hoc analysis revealed that τ LVC and τ [HHb] were faster ($p < 0.01$) than $\tau\dot{V}O_2$ in P ($p < 0.05$).

Correlations

Correlations of $\dot{V}O_{2max}$ with $\tau\dot{V}O_2$, τ LVC, and τ [HHb] are displayed in Figure 3 (A, B, and C). When the data from all groups

were pooled, both $\tau\dot{V}O_2$ ($r = -0.71$; $p < 0.001$) and τ [HHb] ($r = -0.57$; $p < 0.01$) showed a significant negative correlation with $\dot{V}O_{2max}$, whereas τ LVC and $\dot{V}O_{2max}$ were not correlated ($r = -0.12$; $p > 0.05$). All within-group correlations were not significant (all $p > 0.05$).

Correlations of $\tau\dot{V}O_2$ with τ LVC and τ [HHb] are depicted in Figures 4A,B. When the data from all groups were pooled, a significant positive correlation was found between τ [HHb] and $\tau\dot{V}O_2$ ($r = 0.57$; $p < 0.01$), whereas τ LVC and $\tau\dot{V}O_2$ were not correlated ($r = -0.25$; $p > 0.05$). Within-group correlations were all non-significant (all $p > 0.05$), except for a negative correlation between $\tau\dot{V}O_2$ and τ LVC in the P fitness group ($r = -0.74$; $p < 0.05$).

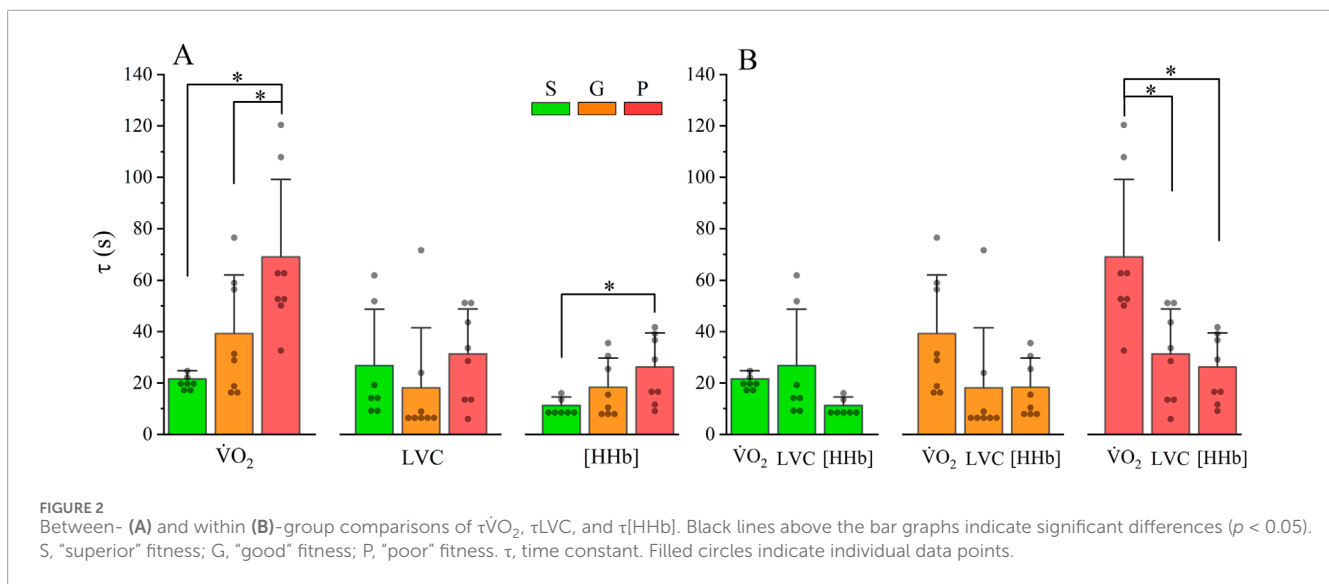
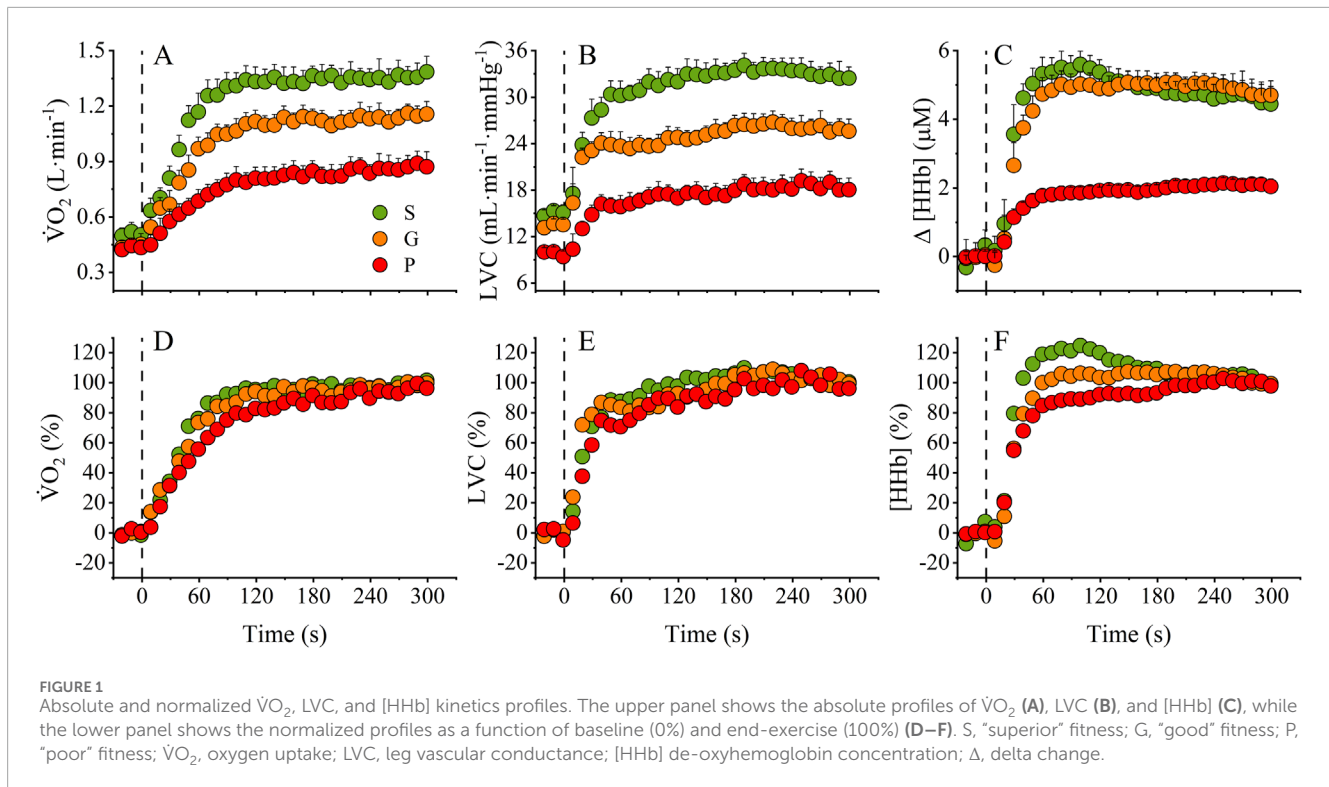
Gains

The gain for all variables are reported in Table 3. No differences in $\dot{V}O_{2GAIN}$ ($p > 0.05$), LVC_{GAIN} ($p > 0.05$), and $[HHb]_{GAIN}$ ($p > 0.05$) were observed between fitness groups.

Discussion

The purpose of the present study was to investigate the relationship between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$, and determine whether the capacity to deliver or to utilize O₂ limits $\tau\dot{V}O_2$ in an aerobic fitness-dependent manner. $\dot{V}O_{2max}$ was inversely correlated with $\tau\dot{V}O_2$, and $\tau\dot{V}O_2$ was faster in the S and G fitness groups than in the P fitness group. τ LVC was not different between groups, and it was not positively correlated with $\dot{V}O_{2max}$ or $\tau\dot{V}O_2$ across and within groups, indicating that O₂ delivery kinetics were similar between groups despite large differences in aerobic fitness. τ [HHb] was faster in the S than in the P fitness group and was inversely correlated with $\dot{V}O_{2max}$ and positively correlated with $\tau\dot{V}O_2$ across groups. Collectively, these data indicate that O₂ delivery was not limiting for $\tau\dot{V}O_2$ and that intracellular oxidative metabolism may limit $\tau\dot{V}O_2$ in healthy individuals, regardless of aerobic fitness.

In the present study, $\tau\dot{V}O_2$ was slower in the P than in the G and S fitness groups, whereas $\tau\dot{V}O_2$ was not different between the S and G fitness groups. Consistent with the present data, several cross-sectional studies have also reported faster $\tau\dot{V}O_2$ in trained or active individuals than in untrained or sedentary individuals (Caputo et al., 2003; Caputo and Denadai, 2004; Cerretelli et al., 1979; George et al., 2018; Grey et al., 2015; Inglis et al., 2021; Koppo et al., 2004a), and although the data are not conclusive, an inverse relationship between $\dot{V}O_{2max}$ and $\tau\dot{V}O_2$ has often been reported (Inglis et al., 2021; Murias et al., 2011a; Fawcner et al., 2002; Chilibeck et al., 1996; Murgatroyd et al., 2011; Norris and Petersen, 1998; Powers et al., 1985). Inglis et al. (2021) investigated the relationship between $\dot{V}O_{2max}$ and $\tau\dot{V}O_2$ in untrained ($\dot{V}O_{2max} \sim 40$ mL·kg⁻¹·min⁻¹) and trained ($\dot{V}O_{2max} \sim 58$ mL·kg⁻¹·min⁻¹) participants and reported an inverse relationship between $\dot{V}O_{2max}$ and $\tau\dot{V}O_2$ within the untrained group, but not within the trained group. The kinetics of cardiac output (Q; measured through impedance cardiography) were not different between untrained and trained groups and were similar to or even faster than $\tau\dot{V}O_2$ in both groups, suggesting that O₂ delivery was not limiting in either group. Although Q kinetics do not provide information related to the distribution of Q or muscle blood flow, Inglis et al. (2021) reported a higher [HHb]/ $\dot{V}O_2$ ratio in the vastus lateralis muscle



of the untrained group than that of the trained group, suggesting that microvascular O_2 delivery may be slower within active muscle and contribute to a slower $\dot{V}O_2$ response in untrained participants. Whether $\tau\dot{V}O_2$ is limited by O_2 delivery (DeLorey et al., 2003; Hughson et al., 1996; Murias et al., 2011b; Murias et al., 2011c), intracellular oxidative metabolism (Zoladz et al., 2016; Grassi, 2000; Christensen et al., 2011; Korzeniewski and Rossiter, 2015), or a combination of both (Murias et al., 2014) within the active limbs across fitness levels remains controversial.

This study, in line with others (Macdonald et al., 1998; Fukuba et al., 2004; Nyberg et al., 2017; duManoir et al., 2010;

DeLorey et al., 2007; MacPhee et al., 2005; Koga et al., 2005; Endo et al., 2005; Harper et al., 2006; Jones et al., 2012; Schlup et al., 2015; Paterson et al., 2005; Love et al., 2023; Inglis et al., 2021), indicated that O_2 delivery (i.e., τ LVC) was faster or as fast as $\tau\dot{V}O_2$ within each fitness group. Furthermore, τ LVC and LVC_{GAIN} were not different between groups despite large differences in aerobic fitness, and τ LVC was not correlated with either $\tau\dot{V}O_2$ or $\dot{V}O_{2max}$, suggesting that O_2 delivery is not a rate-limiting factor for $\tau\dot{V}O_2$ across fitness levels. Consistent with this notion, pump perfusion of canine muscle to eliminate temporal delays in O_2 delivery and enhancement of muscle O_2 diffusive

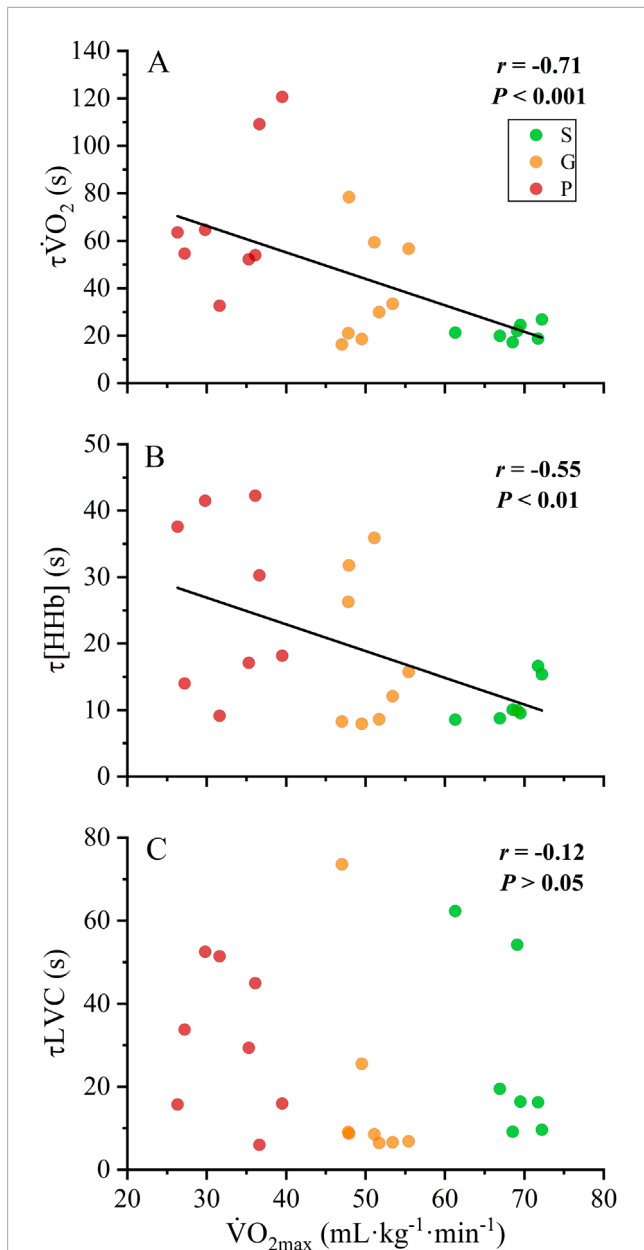


FIGURE 3 Between-group correlations of $\dot{V}O_{2\max}$ with $\tau\dot{V}O_2$ (A), $\tau[\text{HHb}]$ (B) and τLVC (C). S, "superior" fitness; G, "good" fitness; P, "poor" fitness; $\dot{V}O_{2\max}$, maximal oxygen uptake; $\tau\dot{V}O_2$, oxygen uptake kinetics; τLVC , leg vascular conductance kinetics; $\tau[\text{HHb}]$ de-oxyhemoglobin concentration kinetics. Black lines indicate significant correlations ($p < 0.05$) across groups.

capacity did not accelerate $\tau\dot{V}O_2$ during moderate-intensity exercise (Grassi et al., 1998a; Grassi et al., 1998b).

Although the present study suggests that at the onset of exercise, O_2 delivery to the active muscles is not limiting for $\tau\dot{V}O_2$ across fitness levels (evidenced by similar τLVC and LVC_{GAIN} in all groups), it is important to acknowledge that LVC reflects bulk O_2 delivery to the whole limb and does not reflect microvascular O_2 delivery to active muscle fibers. Therefore, it could be argued that either better microvascular O_2 distribution or intracellular oxidative

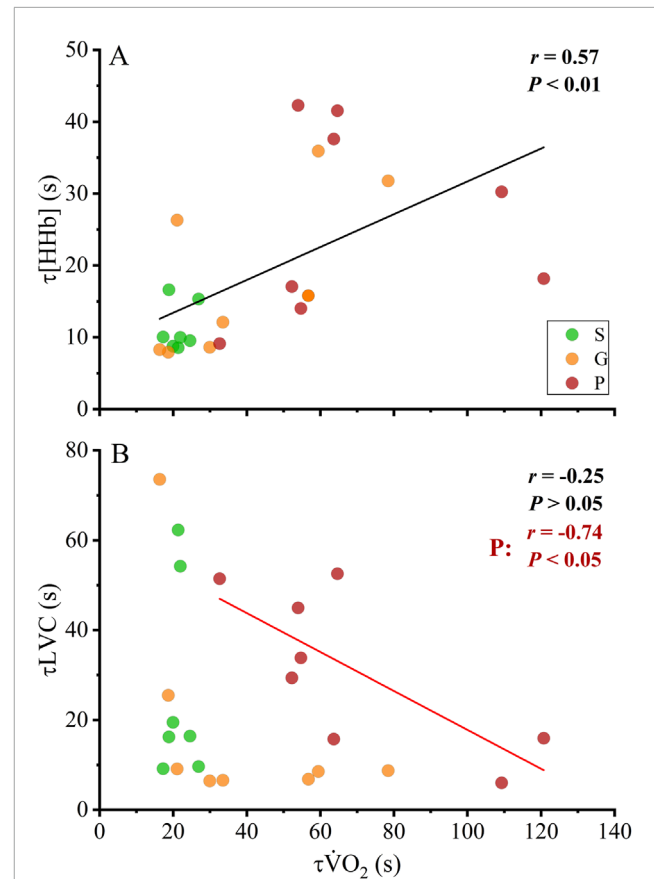


FIGURE 4 Between- and within-group correlations of $\tau\dot{V}O_2$ with $\tau[\text{HHb}]$ (A) and τLVC (B). S, "superior" fitness; G, "good" fitness; P, "poor" fitness; $\tau\dot{V}O_2$, oxygen uptake kinetics; τLVC , leg vascular conductance kinetics; $\tau[\text{HHb}]$ de-oxyhemoglobin concentration kinetics. Black lines indicate significant correlations ($p < 0.05$) across groups. The red line indicates a significant correlation within the P fitness group.

mechanisms underlie differences in $\tau\dot{V}O_2$ between fitness levels. If microvascular O_2 delivery limits $\tau\dot{V}O_2$ across fitness levels, an inverse relationship between $\tau[\text{HHb}]$ and $\tau\dot{V}O_2$ should be observed, and faster $\tau[\text{HHb}]$ would be expected in the P fitness group (i.e., the group with the slowest $\tau\dot{V}O_2$) than in the G and S fitness groups. However, $\tau[\text{HHb}]$ was significantly faster in the S fitness group than in the P fitness group and positively correlated with $\tau\dot{V}O_2$ and negatively correlated with $\dot{V}O_{2\max}$ across fitness groups. Potential contributions of microvascular O_2 delivery to $\tau\dot{V}O_2$ in our P fitness group, where $\tau[\text{HHb}]$ was faster than $\tau\dot{V}O_2$, cannot be dismissed. The direction of the relationships between $\tau[\text{HHb}]$ with $\tau\dot{V}O_2$ and $\dot{V}O_{2\max}$, as well as the faster $\tau[\text{HHb}]$ in the S than in the P fitness group, and, more importantly, the similar τLVC and LVC_{GAIN} between groups support the notion that intracellular oxidative metabolism is the rate-limiting factor for $\tau\dot{V}O_2$ across fitness levels.

Supporting enhanced intracellular oxidative metabolism in the S fitness group is the observed initial $[\text{HHb}]$ overshoot. With τLVC not being limiting for $\tau\dot{V}O_2$, the $[\text{HHb}]$ overshoot may be attributed to a transient enhanced oxidative metabolism response and/or to specific motor unit recruitment strategies in highly

TABLE 3 Gain values.

Group	$\dot{V}O_{2GAIN}$ (mL·min ⁻¹ ·W ⁻¹)	LVC _{GAIN} (mL·min ⁻¹ ·mmHg ⁻¹ ·W ⁻¹)	[HHb] _{GAIN} (μM·min ⁻¹ ·W ⁻¹)
S (n = 7)	18.8 ± 2.2	0.39 ± 0.19	0.10 ± 0.06
G (n = 8)	21.5 ± 4.3	0.39 ± 0.23	0.16 ± 0.10
P (n = 8)	20.7 ± 3.5	0.48 ± 0.56	0.09 ± 0.05

Values are mean ± standard deviation. $\dot{V}O_{2GAIN}$, oxygen uptake gain; LVC_{GAIN}, leg vascular conductance gain; [HHb]_{GAIN}, deoxyhemoglobin concentration gain. S, superior; G, good; P, poor.

trained individuals at the onset of exercise (Grassi et al., 2011; Marinari et al., 2025; Korzeniewski and Zoladz, 2003; Bowen et al., 2013; do Nascimento Salvador et al., 2023). Accordingly, it has recently been demonstrated that muscle excitation increases “disproportionally” at the onset of a step-transition exercise without prior warm-up in recreationally active individuals, which was connected to a greater [HHb] response (Marinari et al., 2025). A similar interpretation was proposed to explain the overshoot in $\dot{V}O_2$ observed in trained cyclists at intensities below the GET (Kilding and Jones, 2008; Koppo et al., 2004b).

Interestingly, end-exercise gains in $\dot{V}O_2$, LVC, and [HHb] were not different between fitness groups (Table 3), indicating similar adaptations at different levels of the O₂ cascade system per unit work rate.

Experimental considerations

In this study, $\dot{V}O_2$, LVC, and [HHb] were averaged over two trials. Increasing the number of trials would have likely improved the accuracy of our kinetics analyses. Nevertheless, the CI ranges of the parameter estimate “ τ ” in the S and G fitness groups were similar to those of a recent study where similar variables were averaged using five trials (Love et al., 2023). Our P fitness group reported greater variability for the estimation of $\tau\dot{V}O_2$ and τ LVC (but not for τ [HHb]), which may be caused by the reduced amplitude changes in $\dot{V}O_2$ and LVC due to smaller work rates. However, different $\dot{V}O_2$ and similar O₂ delivery kinetics between fitness levels are in line with previous findings (Inglis et al., 2021), suggesting that our kinetics analyses were not significantly affected by the number of trials.

Conclusion

In this study, $\dot{V}O_{2max}$ and $\tau\dot{V}O_2$ were inversely correlated across three fitness levels. Although $\tau\dot{V}O_2$ was faster in the “good” and “superior” fitness groups than in the “poor” fitness group, τ LVC was similar between fitness groups and not correlated to either $\tau\dot{V}O_2$ or $\dot{V}O_{2max}$. Conversely, τ [HHb] was inversely correlated to $\dot{V}O_{2max}$ and positively correlated to $\tau\dot{V}O_2$ across fitness groups. Furthermore, τ [HHb] was faster in the “superior” fitness group than in the “poor” fitness group. Collectively, the present study suggests that O₂ delivery is not a rate-limiting factor for $\tau\dot{V}O_2$ and that the intracellular capacity to utilize O₂ may be the primary limiting factor for $\tau\dot{V}O_2$ in healthy individuals, regardless of aerobic fitness.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the University of Alberta Human Research Ethics Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

GM: Writing – review and editing, Writing – original draft. DD: Writing – original draft, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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