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ORIGINAL ARTICLE

Association between $\dot{V}O_2$ kinetics and $\dot{V}O_{2max}$ in groups differing in fitness status

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Abstract

Purpose This study evaluated (i) the relationship between oxygen uptake ($\dot{V}O_2$) kinetics and maximal $\dot{V}O_2$ ($\dot{V}O_{2max}$) within groups differing in fitness status, and (ii) the adjustment of $\dot{V}O_2$ kinetics compared to that of central [cardiac output (Q), heart rate (HR)] and peripheral (deoxyhemoglobin over $\dot{V}O_2$ ratio ([HHb]/$\dot{V}O_2$)] O_2 delivery, during step-transitions to moderate-intensity exercise.

Methods Thirty-six young healthy male participants (18 untrained; 18 trained) performed a ramp-incremental test to exhaustion and 3 step-transitions to moderate-intensity exercise. $\dot{Q}$ and HR kinetics were measured in 18 participants (9 untrained; 9 trained).

Results No significant correlation between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ was found in trained participants ($r = 0.29$; $p > 0.05$) whereas a significant negative correlation was found in untrained ($r = -0.58$; $p < 0.05$) and all participants ($r = -0.82$; $p < 0.05$). $\tau\dot{Q}$ (18.8 ± 5.5 s) and τHR (20.1 ± 6.2 s) were significantly greater than $\tau\dot{V}O_2$ (13.9 ± 2.7 s) for trained ($p < 0.05$). No differences were found between $\tau\dot{Q}$ (22.8 ± 8.45 s), τHR (21.2 ± 8.3 s) and $\tau\dot{V}O_2$ (28.9 ± 5.7 s) for untrained ($p > 0.05$). $\tau\dot{Q}$ demonstrated a significant strong positive correlation with τHR in trained ($r = 0.76$; $p < 0.05$) but not untrained ($r = 0.61$; $p > 0.05$). A significant overshoot in the [HHb]/$\dot{V}O_2$ ratio was found in the untrained groups ($p < 0.05$) but not in the trained groups ($p > 0.05$)

Conclusion The results indicated that when comparing participants of different fitness status (i) there is a point at which greater VO_{2max} values are not accompanied by faster $\dot{V}O_2$ kinetics; (ii) central delivery of O_2 does not seem to limit the kinetics of $\dot{V}O_2$; and (iii) O_2 delivery within the active tissues might contribute to the slower $\dot{V}O_2$ kinetics response in untrained participants.

Keywords Maximal oxygen uptake · HR · $\dot{Q}$ · Moderate-intensity exercise

Abbreviations

ATP	Adenosine triphosphate
GET	Gas-exchange threshold
[HHb]	Deoxygenated hemoglobin
[HHb]/$\dot{V}O_2$	Deoxygenated hemoglobin over oxygen uptake ratio
HR	Heart rate
NIRS	Near-infrared spectroscopy
O_2	Oxygen
Q	Cardiac output
PCr	Phosphocreatine
τ	Time-constant
T	Trained
UT	Untrained
$\dot{V}E$	Ventilation
$\dot{V}CO_2$	Carbon dioxide production
$\dot{V}O_2$	Oxygen uptake
$\dot{V}O_{2max}$	Maximal oxygen uptake

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Introduction

The kinetics of oxygen uptake ($\dot{V}O_2$) represents the dynamic adjustment of oxidative phosphorylation supporting the resynthesis of adenosine triphosphate (ATP) in the exercising muscles in response to an increase in metabolic demand (Tschakovsky and Hughson 1999; Grassi et al. 2003). Fitness level seems to be a factor modulating the $\dot{V}O_2$ kinetics response, with young trained participants having faster

$\dot{V}O_2$ kinetics compared to their untrained counterparts (Koppo et al. 2004; George et al. 2018). Additionally, when untrained participants undergo a period of intensified training their $\dot{V}O_2$ kinetics becomes progressively faster (Berger et al. 2006; Murias et al. 2011a, 2016). In fact, during exercise transitions within the moderate intensity domain, there is a negative correlation between the speed of $\dot{V}O_2$ kinetics and fitness level, as represented by the maximal O_2 uptake ($\dot{V}O_{2max}$) (Powers et al. 1985; Zhang et al. 1991; Chilibeck et al. 1996; Murgatroyd et al. 2011). However, despite this evidence, the strength of this relationship might vary across the fitness spectrum. For example, the existence of a hyperbolic relationship between $\dot{V}O_2$ kinetics and $\dot{V}O_{2max}$ across different species has been demonstrated (Poole et al. 2005). Additionally, it has been shown that chronically trained older individuals had $\dot{V}O_2$ kinetics that were as fast as those of chronically trained young individuals, despite both groups having markedly different $\dot{V}O_{2max}$ (Grey et al. 2015; George et al. 2018). Furthermore, several studies have shown speeding of $\dot{V}O_2$ kinetics after only a few sessions of exercise training that should not have resulted in any change in $\dot{V}O_{2max}$ (McKay et al. 2009; Murias et al. 2016; McLay et al. 2017). Taken together, these data suggest that the notion of a strong relationship between $\dot{V}O_2$ kinetics and $\dot{V}O_{2max}$ may not be true across the entire fitness spectrum, as these two measures might be influenced by different mechanistic underpinnings. Thus, although a correlation between $\dot{V}O_{2max}$ and the $\dot{V}O_2$ kinetics response to exercise in the moderate intensity domain has previously been discussed in humans (Whipp et al. 2002), no study has investigated potential differences in this correlation between groups with markedly different $\dot{V}O_{2max}$.

The speed at which $\dot{V}O_2$ adjusts to a change in metabolic demand is the result of the integration of O_2 delivery and intracellular components (Poole and Jones 2012; Murias et al. 2014). It is often proposed that intracellular components are the main rate limiting factor controlling the speed of the $\dot{V}O_2$ kinetics response (Grassi et al. 1996, 1998; Poole and Jones 2012) up to a "tipping point" beyond which the $\dot{V}O_2$ kinetics response becomes O_2 delivery-dependent (from both convective and diffusive standpoints) (Poole and Jones 2012; Murias et al. 2014). While this O_2 delivery "dependent zone" is suggested to be relevant mostly in clinical and older populations (Poole and Jones 2012; Poole et al. 2020), some have proposed that O_2 provision to the active tissues is critically important even in healthy untrained populations once the time-constant (τ) of the $\dot{V}O_2$ kinetics response exceeds ~ 20 s (Murias et al. 2014). This is important as it may be that, once a certain level of $\dot{V}O_{2max}$ is reached, the overall O_2 transport system is adequately adapted to support adjustments to moderate intensity exercise at the fastest rate possible. That is, although there may be room for further improvements in the maximal response of the system (i.e., $\dot{V}O_{2max}$), an upper limit may exist such that greater $\dot{V}O_{2max}$ alues are no longer associated with subsequent speeding of $\dot{V}O_2$ kinetics at the submaximal level (i.e., moderate intensity exercise). This is evidenced by the fact that there are certain intrinsic metabolic controls [i.e., phosphocreatine (PCr)] preventing further speeding of oxidative phosphorylation (Grassi et al. 2011). However, although previously suggested (Figueira et al. 2008), this hypothesis needs further corroboration.

From an O_2 delivery/provision perspective, it is important to differentiate between central and peripheral contributions. Given the technical challenges associated with measuring the dynamic adjustment of cardiac output (Q) (i.e., $\dot{Q}$ kinetics) during exercise in humans, studies have often relied on measurements of heart rate (HR) kinetics as a proxy for $\dot{Q}$ kinetics, with the time constant of HR kinetics (τHR) often being as fast as, or faster than, the $\tau\dot{V}O_2$ (Chilibeck et al. 1997; Lador et al. 2005; Murias et al. 2010; Zuccarelli et al. 2018). Some studies estimating $\dot{Q}$ kinetics from arterial pulse pressure profiles and/or ultrasound measurements have indicated that $\dot{Q}$ kinetics is faster than the kinetics of $\dot{V}O_2$ (De Cort et al. 1991; Lador et al. 2005; Faisal et al. 2009). Additionally, the kinetics of blood flow at the conduit artery level have shown similar dynamics of $\dot{Q}$ and $\dot{V}O_2$ (Dumanoir et al. 2010). Together, it seems that central delivery of O_2 is not an impairment for the kinetics of $\dot{V}O_2$. However, indirect estimations of microvascular blood flow distribution using near-infrared spectroscopy (NIRS) measurements of deoxygenated hemoglobin ([HHb]; a proxy for local O_2 extraction) in combination with pulmonary $\dot{V}O_2$ measurements (i.e., the [HHb]/$\dot{V}O_2$ ratio as described in detail elsewhere) (Murias et al. 2012) have suggested that O_2 provision to the active tissues might play a role in determining the speed of the $\dot{V}O_2$ kinetics response (Murias et al. 2010). To date, although studies have compared central versus peripheral responses to moderate intensity exercise transitions (Dumanoir et al. 2010; Murias et al. 2011c), no study has directly compared how central and peripheral components of O_2 delivery might affect the kinetics of $\dot{V}O_2$ during moderate-intensity exercise transitions in adult participants of different fitness levels.

This study aimed to (i) evaluate the relationship between $\dot{V}O_2$ kinetics and $\dot{V}O_{2max}$ within two groups with markedly different $\dot{V}O_{2max}$, and (ii) compare the adjustment of $\dot{V}O_2$ kinetics to that of central and peripheral O_2 delivery, as examined by the adjustment of $\dot{Q}$ and HR kinetics (i.e., central) and the [HHb]/$\dot{V}O_2$ ratio (i.e., peripheral), during step transitions to moderate intensity exercise. We hypothesized that (i) the negative correlation between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ would exist only in untrained individuals, (ii) $\dot{Q}$ kinetics would be as fast as, or faster than, $\dot{V}O_2$ kinetics in both trained and untrained participants, and (iii) trained

participants would display a faster $\dot{V}O_2$ kinetics and a better matching of O_2 distribution to local $\dot{V}O_2$ compared to their untrained counterparts.

Methods

Participants

Thirty-six young healthy male participants volunteered and provided written informed consent to participate in this study after completing the physical activity readiness questionnaire (PAR-Q+), answering "no" to each question, and being cleared for exercise by a certified exercise physiologist. Based on self-reported physical activity levels (i.e., cycling frequency), participants were grouped within untrained (i.e., reporting < 2–3 days per week of physical activity and not following a structured training program) ($n = 18$) or trained (i.e., reporting ≥ 5 days per week of physical activity and following a structured training program) ($n = 18$) groups (De Pauw et al. 2013). On average, untrained and trained participants performed 1.7 ± 1.0 and 5.3 ± 0.5 days of physical activity per week, respectively. Data from 18 participants were previously reported (George et al. 2018). The Conjoint Health Research Ethics Board at the University of Calgary approved all procedures included in this study.

Protocol

All testing sessions were performed on an electromagnetically braked cycle ergometer (Velotron Dynafit Pro, Racer Mate, Seattle, WA, USA). Each participant reported to the laboratory for twoeparate visits separated by at least 48 h but no longer than 96 h. The first visit consisted of a ramp-incremental test to exhaustion and the second visit consisted of three consecutive step-transitions within the moderate intensity exercise domain (Spencer et al. 2011). Participants were asked to refrain from performing vigorous intensity exercise the day before each session. All testing sessions were performed at the same time of day (±30 min).

Ramp-incremental test

To determine $\dot{V}O_{2max}$ and to derive the power output for the subsequent moderate intensities step-transitions, participants performed a ramp-incremental test to exhaustion (Iannetta et al. 2019). The ramp-incremental test began with a 4-min warm-up at 50 W followed by a 25 W·min^{-1} (1 W every 2.4 s) ramp for untrained participants and a 30 W·min^{-1} (1 W every 2 s) ramp for trained participants.

Step-transitions

The second visit to the laboratory consisted of 3 cycling moderate step-transitions, from 20 W (6 min) to 80–90% of the gas exchange threshold (GET) (6 min)), as proposed elsewhere (Spencer et al. 2011). Throughout this session, participants were asked to maintain a steady cadence between 65 and 75 rpm.

Measurements

During each session breath-by-breath gas exchange and ventilatory variables were measured using a metabolic cart (Quark CPET, Cosmed, Rome, Italy). Expired gasses were sampled at the mouth and analyzed for fractional concentrations of oxygen (O_2) and carbon dioxide (CO_2), and a low-dead space turbine was used to measure inspired and expired flow rates. Prior to each testing session, both gas analyzers and the flowmeter were calibrated as per manufacturer's recommendations. Heart rate (HR) was continuously monitored using radio telemetry (Garmin, USA). During the moderate step-transitions, NIRS-derived [HHb] was measured in the vastus lateralis muscle of the right leg (Oxiplex TS; ISS, Champaign, USA) at a sampling rate of 2 Hz and automatically interpolated to 1 s by the Oxiplex software. The specifics of this system can be found elsewhere (Inglis et al. 2017). The probe was placed on the belly of the vastus lateralis muscle midway between the inguinal crease and the proximal border of the patella. The probe was then secured and covered to prevent any movement and/or the intrusion of external light as previously described (Inglis et al. 2017). In 18 participants (9 untrained ($\dot{Q}$-UT), 9 trained ($\dot{Q}$-T)) we also continuously recorded beat-by-beat $\dot{Q}$ responses using an impedance cardiography system (Physioflow, Manatec Biomedical, Macheren, France) during the moderate step-transitions. Briefly, $\dot{Q}$ is calculated by multiplying stroke volume by body surface and heart rate. To calculate stroke volume, the system relies on variation in trans-thoracic impedance occurring due to alterations in aorta blood volume. Electrode positioning and system calibration were performed according to manufacturer's instructions. This system has been proven to be valid and has been utilized in previous studies examining HR and $\dot{Q}$ kinetics (Charloux et al. 2000; Zuccarelli et al. 2018).

Data analysis

Breath-by-breath $\dot{V}O_2$ data from each test (i.e., ramp-incremental test and moderate step-transitions) were processed as follows: (i) aberrant data points that were ± 3 SD from the local mean were removed, (ii) each profile was then time-aligned (such that time "zero" represented the onset of the ramp test or the moderate step-transition) and linearly interpolated to 1 s intervals (Keir et al. 2014).

Ramp-incremental test

Two exercise physiologists independently inspected the gas exchange and ventilatory profiles for the determination of GET. In the event of a disagreement between the physiologists (> 100 mL•min^{-1} difference), a second conjoint evaluation was performed until a consensus was reached. Briefly, GET corresponded to the $\dot{V}O_2$ at which a first breakpoint in the minute-ventilation ($\dot{V}_E$) versus $\dot{V}O_2$ relationship was evident in concomitance with CO_2 output ($\dot{V}CO_2$) beginning to increase out of proportion in relation to $\dot{V}O_2O_2$ while end-tidal partial pressure of CO_2 remained stable (Beaver et al. 1986; Whipp et al. 1989). To account for the muscle-lung transit delay and the $\dot{V}O_2$ kinetics at ramp-onset (Boone et al. 2008), the mean response time of the $\dot{V}O_2$ was calculated on an individual basis and used to align (left-shift) the $\dot{V}O_2$ data to its corresponding power output, as previously described (Boone and Bourgois 2012). $\dot{V}O_{2max}$ was defined as the highest $\dot{V}O_2$ computed from a 30-s rolling average.

Constant-load transitions

$\dot{V}O_2$ kinetics

Once the $\dot{V}O_2$ data for each step transition were cleaned, time aligned, and interpolated (as previously described (Keir et al. 2014)) they were ensemble-averaged into a single time-averaged response. Each individual rofile was then further time-averaged into 5 s bins (Keir et al. 2014) and fit using the following equation:

$$\dot{V}O_2(t) = \dot{V}O_{2bsln} + \dot{V}O_{2AMP}\left(1 - e^{-(t-TD)/\tau}\right),$$

where $\dot{V}O_2(t)$ represents the $\dot{V}O_2$ at any given time (t) during the transition, $\dot{V}O_{2bsln}$ is the steady-state baseline value of $\dot{V}O_2$ before the moderate step-transition, $\dot{V}O_{2AMP}$ is the amplitude of the increase in $\dot{V}O_2$ above $\dot{V}O_{2bsln}$, TD is the time delay of the response, and τ is the time constant of the response (defined as the time required for the $\dot{V}O_2$ response to attain 63% of the steady-state amplitude). The first 22 s of the ensemble-averaged $\dot{V}O_2$ profile were not included in the fitting window of the phase II $\dot{V}O_2$ (i.e., the primary component reflecting the adjustment of muscle $\dot{V}O_2$) to account for the phase I (i.e., the cardiodynamic phase) of the $\dot{V}O_2$ response, as previously recommended (Murias et al. 2011b). The exclusion of 22 s represents the data point comprising 20–25 s of the 5-s average used for fitting. Data were modeled from the beginning of phase II up to 240 s of the step-transition, after ensuring that steady-state $\dot{V}O_2$ had been attained in each participant within this time window. This approach aims to maximize the quality of the model fit, as indicated by Bell et al. (2001). The model parameters were estimated by least-squares nonlinear regression (Origin, OriginLab Corp., Northhampton, MA, USA) in which the best fit was defined by minimization of the residual sum of squares and minimal variation around the Y-axis ($\dot{V}O_2 = 0$). The 95% confidence interval for the estimated τ was determined after preliminary fit of the data with $\dot{V}O_{2bsln}$, $\dot{V}O_{2AMP}$, and TD constrained to the best fit values and the τ allowed to vary.

$\dot{Q}$ and HR kinetics

$\dot{Q}$ and HR data were cleaned and fit using the same procedure for the breath-by-breath $\dot{V}O_2$ data (as described above) with the exception that $\tau\dot{Q}$ and τHR were computed by fitting the profiles from exercise onset (i.e., time zero).

[HHb]/$\dot{V}O_2$ ratio

The calculation of the [HHb]/$\dot{V}O_2$ ratio was similar to that previously described (Murias et al. 2011c). Briefly, the second-by-second [HHb] and $\dot{V}O_2$ data were normalized for each participant (0–100% of the transition response). The $\dot{V}O_2$ data were left-shifted by 20 s to account for the duration of the phase I response. A mean [HHb]/$\dot{V}O_2$ ratio was derived for each participant by taking the average response from 20 to 120 s (Keir et al. 2014).

Statistics

All data processing and modeling were performed with a commercially available computer software (Origin 2016; OriginLab, Northhampton, MA) and statistical analysis was performed using SPSS version 23 (SPSS, Chicago, USA) with statistical significance set at a $p < 0.05$. Descriptive data are presented as mean ± SD. Paired t tests and Pearson product moment correlations were used to compare all variables between groups. Pearson product moment correlations were used to analyze the relationship between variables on the mean data of all participants. Normality and independence of observations were checked a priori.

Results

All participants

Trained participants had a greater $\dot{V}O_{2max}$ (4.47 ± 0.37 L • min^{-1}, 58.3 ± 4.9 mL • kg^{-1} • min^{-1}) compared to untrained (3.17 ± 0.51 L • min^{-1}, 39.4 ± 5.8 mL • kg^{-1} • min^{-1}) ($p < 0.05$). No difference was found in height and weight between the trained (178.9 ± 5.6 cm; 77.4 ± 7.6 kg, respectively) and untrained (176.2 ± 5.8 cm; 81.4 ± 14.8 kg, respectively) groups ($p > 0.05$). However, the trained group (34 ± 7 years) was significantly older than the untrained group (28 ± 5 years) ($p < 0.05$).

Summary data for $\dot{V}O_2$ kinetics and the [HHb]/$\dot{V}O_2$ ratio can be found in Table 1. The trained group demonstrated faster $\dot{V}O_2$ kinetics compared to their untrained counterparts ($p < 0.05$). The untrained group demonstrated a greater [HHb]/$\dot{V}O_2$ ratio compared to the trained group ($p < 0.05$). The overshoot of the [HHb]/$\dot{V}O_2$ ratio was significant in the untrained ($p < 0.05$) but not in the trained group ($p > 0.05$). Figure 1 shows the correlations between $\tau\dot{V}O_2$ and relative $\dot{V}O_{2max}$ for trained, untrained and all participants. While there was a strong correlation when all participants were aggregated ($r = -0.82$; $p < 0.05$), at the group level this significant correlation persisted only in the untrained group ($r = -0.58$; $p < 0.05$) as no significant correlation was found for trained participants ($r = 0.29$; $p > 0.05$).

Table 1 Mean and standard deviation values for oxygen uptake ($\dot{V}O_2$) kinetics, gas exchange threshold, and the NIRS-derived deoxyhemoglobin over $\dot{V}O_2$ ratio for all participants

$\dot{V}O_2$ kinetics	Untrained		Trained	
	(*n* = 18)		(*n* = 18)	
τ (s)	33.0	± 8.6	15.0*	± 3.0
CI_{95} (s)	5.0	± 3.3	1.7*	± 1.3
Time delay (s)	13.4	± 5.9	17.2*	± 2.0
Baseline (L • min^{-1})	1.00	± 0.19	0.99	± 0.09
Steady state (L • min^{-1})	1.53	± 0.20	2.18*	± 0.22
Amplitude (L • min^{-1})	0.52	± 0.12	1.20*	± 0.25
Gas-exchange threshold				
L • min^{-1}	1.77	± 0.21	2.67*	± 0.35
mL • kg^{-1} • min^{-1}	22.3	± 4.3	34.7*	± 4.5
[HHb]/$\dot{V}O_2$ ratio	1.16	± 0.09	1.02*	± 0.06

*Significantly different from untrained ($p < 0.05$)

Q̇-measurement participants

Q̇-T participants had a greater $\dot{V}O_{2max}$ (4.54 ± 0.43 L • min^{-1}, 59.0 ± 6.2 mL • kg^{-1} • min^{-1}) compared to *Q̇*-UT (3.34 ± 0.41 L • min^{-1}, 41.3 ± 6.4 mL • kg^{-1} • min^{-1}) ($p < 0.05$). No difference was found in height and weight between the *Q̇-T* (179.9 ± 6.5 cm; 78.2 ± 8.1 kg, respectively) and the Q̇-UT group (175.8 ± 6.9 cm; 82.3 ± 13.6 kg,

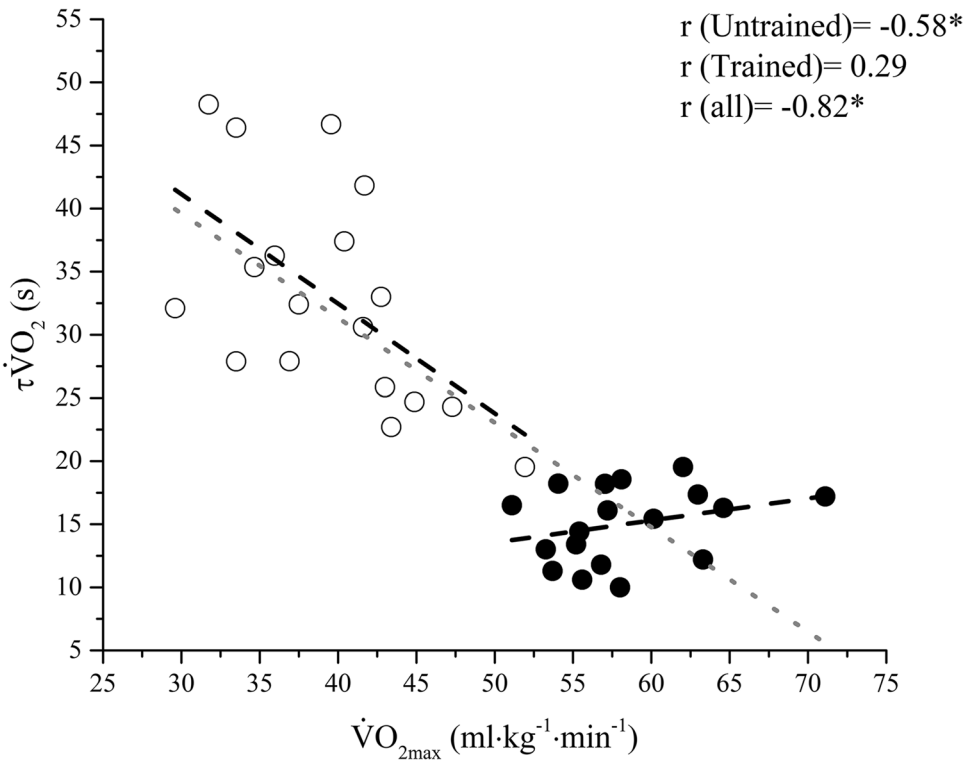

Fig. 1 Correlation between oxygen uptake kinetics ($\tau\dot{V}O_2$) and relative maximal oxygen uptake ($\dot{V}O_{2max}$) for all participants (*n* = 36). Grey dashed line represents the correlation for all participants, black dashed lines represents correlation for untrained (white circles) and trained (black circles) groups. *Denotes significant correlation ($p < 0.05$)

Table 2 Mean and standard deviation values for cardiac output ($\dot{Q}$), oxygen uptake ($\dot{V}O_2$) and heart rate (HR) kinetics, and the NIRS-derived deoxyhemoglobin over $\dot{V}O_2$ ratio for 18 participants

	Untrained		Trained	
	($n=9$)		($n=9$)	
$\dot{V}O_2$ kinetics				
τ (s)	28.9	±5.7	13.9*	±2.7
CI_{95} (s)	2.4	±0.1	1.1*	±0.2
Time delay (s)	12.6	±4.3	18.2*	±2.0
Baseline (L• min^{-1})	0.86	±0.07	0.97*	±0.10
Steady state (L• min^{-1})	1.41	±0.13	2.18*	±0.09
Amplitude (L • min^{-1})	0.56	±0.12	1.21*	±0.09
$\dot{Q}$ kinetics				
τ (s)	22.8	±8.4	18.8†	±5.5
CI_{95} (s)	2.9	±1.1	1.2*	±0.4
Time delay (s)	−1.3	±5.3	1.5	±1.5
Baseline (L • min^{-1})	7.89	±1.81	8.72	±1.16
Steady state (L • min^{-1})	10.43	±2.15	13.95*	±1.25
Amplitude (L • min^{-1})	2.54	±0.78	5.23*	±0.77
HR kinetics				
τ (s)	21.2	±8.3	20.1†	±6.2
CI_{95} (s)	2.1	±0.8	0.9*	±0.3
Time delay (s)	−3.8	±6.2	−0.5	±2.7
Baseline (bpm)	86	±9	82	±6
Steady state (bpm)	104	±10	110	±7
Amplitude (bpm)	18	±4	28*	±8
[HHb]/$\dot{V}O_2$ ratio	1.14	±0.11	1.01*	±0.07

*Significantly different from untrained ($p < 0.05$)

†Significantly different from $\tau\dot{V}O_2$

respectively) ($p > 0.05$). The $\dot{Q}$-*T* group (39 ± 5 years) was significantly older than the $\dot{Q}$-UT group (29 ± 4 years) ($p < 0.05$).

Summary data for $\dot{V}O_2$, $\dot{Q}$, HR kinetics and [HHb]/$\dot{V}O_2$ ratio can be found in Table 2. Kinetics data for a representative participant from each group as well as mean profiles are displayed in Fig. 2. The $\dot{Q}$-T group demonstrated a faster $\tau\dot{V}O_2$ compared to the $\dot{Q}$-UT group ($p < 0.05$). Baseline and amplitude of the $\dot{V}O_2$ response were greater in $\dot{Q}$-T than in $\dot{Q}$-UT ($p < 0.05$). No differences were found between groups for $\tau\dot{Q}$ and for τHR ($p > 0.05$). $\dot{Q}$ steady state and amplitude values were greater in the $\dot{Q}$-T than in the $\dot{Q}$-UT group ($p < 0.05$). HR amplitude was greater in the $\dot{Q}$-T compared to the $\dot{Q}$-UT group ($p < 0.05$). No other differences were observed in any other HR kinetics parameter estimates ($p > 0.05$). $\tau\dot{Q}$ and τHR were significantly greater than $\tau\dot{V}O_2$ in the $\dot{Q}$-T group ($p < 0.05$). There were no differences in $\tau\dot{V}O_2$, $\tau\dot{Q}$, and τHR in the $\dot{Q}$-UT group ($p > 0.05$). $\tau\dot{Q}$ demonstrated a significant strong positive correlation with τHR in the $\dot{Q}$-T group ($r = 0.76$) ($p < 0.05$) but not in the $\dot{Q}$-UT group ($r = 0.61$) ($p > 0.05$). No other significant correlations existed between $\tau\dot{V}O_2$, $\tau\dot{Q}$, and τHR within the $\dot{Q}$-UT or $\dot{Q}$-T groups.

$\tau\dot{V}O_2$ demonstrated a strong negative correlation with relative $\dot{V}O_{2max}$ when $\dot{Q}$-T and $\dot{Q}$-UT groups were combined for the regression ($r = -0.81$; $p < 0.05$); When groups were separated, $\dot{Q}$-UT showed a moderate negative correlation that did not reach statistical significance ($r = -0.64$; $p = 0.06$) while $\tau\dot{V}O_2$ was not significantly correlated with relative $\dot{V}O_{2max}$ in $\dot{Q}$-T ($r = 0.34$; $p > 0.05$) (Fig. 3). Combined data for the $\dot{Q}$-T and $\dot{Q}$-UT groups showed no difference, nor significant correlation between $\tau\dot{V}O_2$ and $\tau\dot{Q}$ ($p > 0.05$). The $\dot{Q}$-UT group demonstrated a greater [HHb]/$\dot{V}O_2$ ratio compared to the $\dot{Q}$-T group ($p < 0.05$). The overshoot of the [HHb]/$\dot{V}O_2$ ratio was significant in the $\dot{Q}$-UT ($p < 0.05$) but not in the $\dot{Q}$-*T* group ($p > 0.05$).

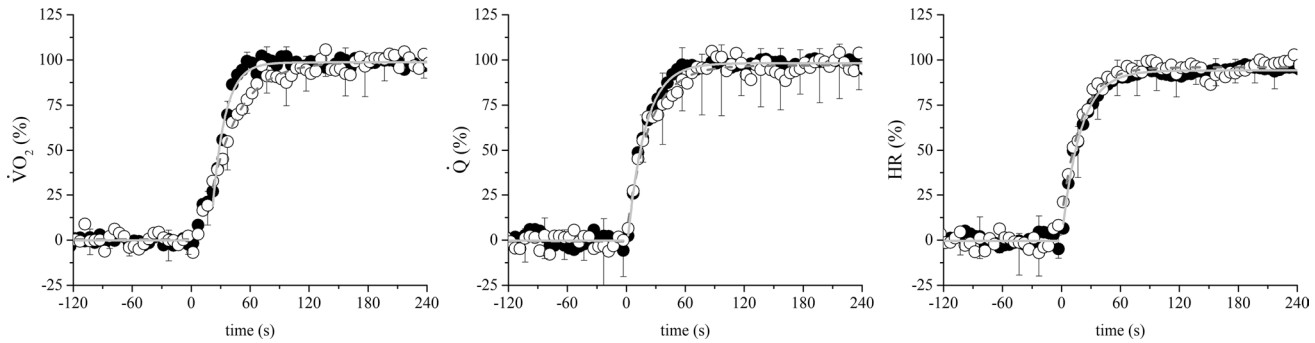

Fig. 2 Profiles of the normalized mean values for oxygen uptake kinetics ($\tau\dot{V}O_2$), cardiac output kinetics ($\tau\dot{Q}$) and heart rate kinetics (τHR) in untrained (white circles) and trained (black circles) groups. Dark gray dashed line represents the average fit for untrained, solid light gray line represents the average fit for trained participants

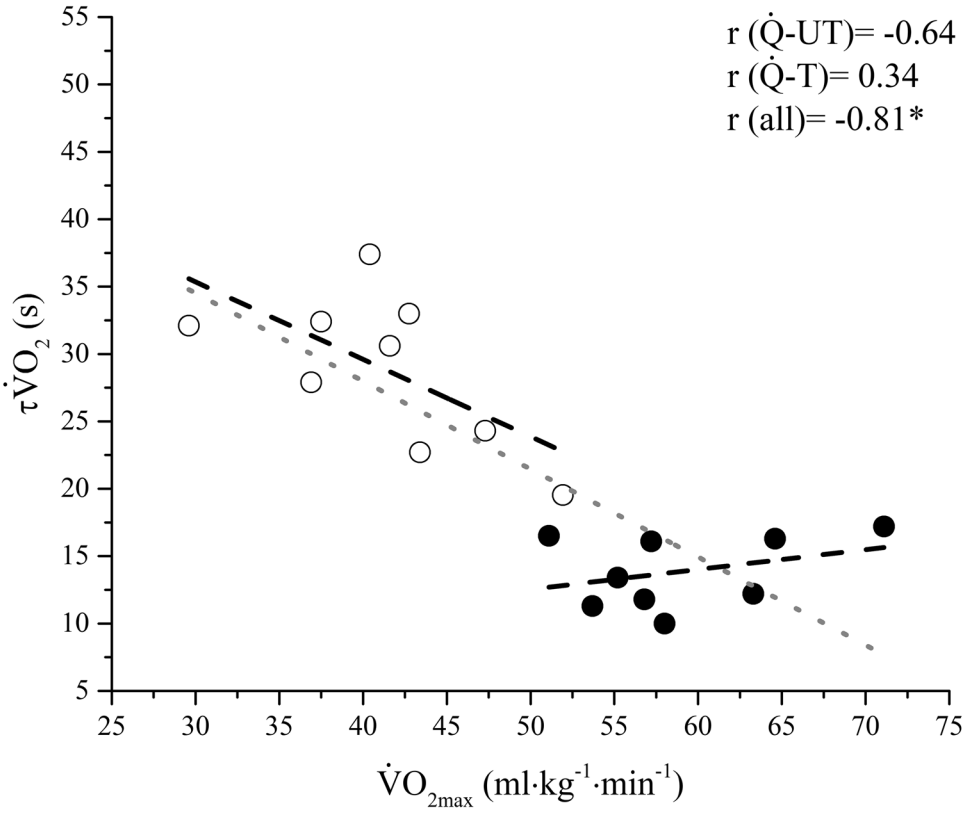

Fig. 3 Correlation between oxygen uptake kinetics ($\tau\dot{V}O_2$) and relative maximal oxygen uptake ($\dot{V}O_{2max}$) for participants with cardiac output measurements ($n = 18$). Grey dashed line represents mean correlation for all participants, black dashed line represents the correlation for untrained ($\dot{Q}$-UT) (white circles) and trained ($\dot{Q}$-T) (black circles) groups. *Denotes significant correlation ($p < 0.05$)

Discussion

This study evaluated the relationship between $\dot{V}O_2$ kinetics and $\dot{V}O_{2max}$, as well as central and peripheral dynamics of O_2 transport and $\dot{V}O_2$ kinetics within and between groups characterized by different $\dot{V}O_{2max}$ levels. Findings demonstrated (i) a negative correlation between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ in the untrained but not in the trained group suggesting that there is a point at which further increases in $\dot{V}O_{2max}$ are not accompanied by further speeding of $\dot{V}O_2$ kinetics, (ii) no differences between untrained and trained participants with respect to $\dot{Q}$ and HR kinetics, whereby $\tau\dot{Q}$ and τHR were faster than $\tau\dot{V}O_2$ in the untrained group, which suggests that the dynamics of central delivery of O_2 are not affected by training and do not limit the kinetics of $\dot{V}O_2$, and (iii) a greater [HHb]/$\dot{V}O_2$ in untrained compared to trained participants, which could imply that O_2 delivery within the active tissues (i.e., microvascular redistribution of O_2) might pose a constraint to the $\dot{V}O_2$ kinetics response in the former.

$\tau\dot{V}O_2$ and $\dot{V}O_{2max}$

Similarly to previous studies (Powers et al. 1985; Zhang et al. 1991; Chilibeck et al. 1996), when data from the trained and untrained participants are grouped together, we showed that there is a negative overall correlation between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$. However, our results show that, when these groups are analyzed separately, this negative correlation exists in untrained but not in trained participants. Our study is the first carrying out this analysis and showing these findings. A previous study by Figueira et al. (2008) compared participants of low, intermediate, and high fitness levels. In the study, it was found that there was a moderate negative correlation between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ across all groups as well as no significant difference in $\tau\dot{V}O_2$ between groups of intermediate to high fitness levels. It should be noted that this observation was based on the evaluation of mean data, and no correlation analysis was performed within groups (Figueira et al. 2008). Furthermore, the average $\tau\dot{V}O_2$ (~27 s) in the high fitness level group was substantially greater than previously reported values of $\dot{V}O_2$ kinetics in trained participants (Koppo et al. 2004; Grey et al. 2015; George et al. 2018). Conversely, the current findings are in contrast with those of Powers et al. (1985) who found a significant negative relationship between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ in trained athletes. However, although the study of Powers et al. (1985) was technically challenging and appropriate at the time it was performed, the lack of breath-by-breath analysis and use of a single exercise transition make the validity of the results questionable using current standards for $\dot{V}O_2$ kinetics analysis (Keir et al. 2014). Furthermore, they did not evaluate participants with lower fitness status. It is important to note that, in the subset group of untrained participants (i.e., $\dot{Q}$-UT), the correlation between $\tau\dot{V}O_2$ and

$\dot{V}O_{2max}$ did not reach statistical significance ($p = 0.06$). However, this specific relationship (likewise to the other relationships evaluated) was consistent with the overall group behavior and therefore it is likely that, had the subset been slightly larger, significance would have been reached.

The lack of correlation between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ in trained participants suggests the existence of an upper limit in $\dot{V}O_{2max}$ beyond which $\tau\dot{V}O_2$ does not become any faster. Specifically, within the data set explored herein, this upper limit seems to occur at a $\dot{V}O_{2max}$ level of ~ 55–60 mL kg^{-1} min^{-1}. This implies that, above these levels of $\dot{V}O_{2max}$, a further improvement in maximal oxidative capacity (i.e., $\dot{V}O_{2max}$) is dissociated from a further speeding in the dynamic responsiveness of the oxidative system (i.e., $\tau\dot{V}O_2$), at least during moderate intensity exercise. Therefore, local adaptations that support improvements in $\dot{V}O_{2max}$ (e.g., greater capillarization, increased mitochondria volume density and function) do not facilitate additional speeding of $\dot{V}O_2$ kinetics. In other words, once a given $\dot{V}O_{2max}$ is achieved, the oxidative phosphorylation "machinery" may have reached its potential for what is needed to support the very fast rate of adjustment in response to a greater metabolic demand within the moderate intensity domain, and further improvements in the O_2 transport system and/or intracellular components provide no additional effects. Therefore, these results also imply that in trained participants, some intrinsic processes prevent $\tau\dot{V}O_2$ from becoming even faster. One of these processes, for example, may be the temporal buffering of the PCr system. Indeed, it has been shown that the blockade of creatine kinase, and thus of PCr breakdown, causes $\dot{V}O_2$ kinetics to become extremely fast (Grassi et al. 2011). Additionally, two factors suggested to limit the speed of $\dot{V}O_2$ kinetics are the (i) complete activation (i.e., of all complexes and steps of the oxidative system) and (ii) overall activity level of the oxidative phosphorylation system (i.e., high mitochondrial volume density) (Korzeniewski and Zoladz 2004). In this context, a theoretical model suggested that, in trained individuals, the relationship between $\tau\dot{V}O_2$ and these factors is hyperbolic such that in order for small changes in $\tau\dot{V}O_2$ to be observed, large changes in both activation and overall activity must occur (Korzeniewski et al. 2018). Therefore, while individuals with high $\dot{V}O_{2max}$ values may indeed have a more strongly developed oxidative system (i.e., more rapid response in addition to a greater maximal capacity), the $\tau\dot{V}O_2$ in these individuals may still be restricted to a finite time which is ultimately determined by the buffering action of PCr system and/or other intracellular aspects that prevent further speeding of $\dot{V}O_2$ kinetics once the response is sufficiently rapid (e.g., < 20 s) (Grassi et al. 2011; Murias et al. 2014; Korzeniewski et al. 2018). Furthermore, the notion that oxidative capacity may dictate the linear relationship between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ in untrained and not trained individuals is corroborated by the fact that a similar relationship can be observed when evaluating mitochondrial capacity and $\dot{V}O_{2max}$. Indeed, Gifford et al. (2016) demonstrated that mitochondrial capacity is highly correlated to $\dot{V}O_{2max}$ in untrained but not trained individuals.

$\tau\dot{V}O_2$, $\tau\dot{Q}$ and τHR

This study found that in untrained participants there were no statistical differences in $\tau\dot{V}O_2$, $\tau\dot{Q}$ and τHR. Alternatively, trained participants demonstrated a faster $\tau\dot{V}O_2$, which was also faster than both $\tau\dot{Q}$ and τHR in this group. Furthermore, there were no differences between untrained and trained participants for $\tau\dot{Q}$ and τHR. Together, these results suggest that the central components of O_2 delivery (i.e., $\dot{Q}$) do not play a major role in the determination of $\tau\dot{V}O_2$ during transitions to moderate intensity exercise. However, although bulk delivery of O_2 appears to not be a rate limiting factor for the dynamic adjustment of $\dot{V}O_2$, the significant overshoot in the [HHb]/$\dot{V}O_2$ ratio in the untrained but not the trained group suggests that microvascular redistribution of O_2 might play a role. That is, trained participants displayed a better matching of O_2 delivery to O_2 utilization compared to untrained, as previously been indicated (Murias et al. 2010, 2011c; George et al. 2018). These data support the notion that, from an O_2 delivery perspective, improved blood flow redistribution within the active tissues rather than central delivery of O_2might be at least partly responsible for controlling the rate of adjustment of $\dot{V}O_2$. Given that constraints in O_2 delivery are accepted as a rate limiting factor for the $\dot{V}O_2$ kinetics response in older and diseased populations (Poole et al. 2007, 2008; Poole and Musch 2010; Poole and Jones 2012), the idea that such constraint might also contribute to a slower rate of oxidative phosphorylation in untrained participants should not be disregarded. More specifically, this finding could suggest that untrained participants may have some degree of microvascular O_2 distribution limitation when compared to their trained counterparts. In other words, even though intracellular mechanisms of control are always important and are most likely responsible for the first ~ 20 s of the $\dot{V}O_2$ adjustment, (with the breakdown of phosphocreatine being a critical spatial and temporal buffer for the accumulation of ADP (Grassi 2003; Grassi et al. 2011)), a "sluggish" provision of O_2 within the microcirculation may also affect $\tau\dot{V}O_2$ in people with slower dynamic adjustments of oxidative phosphorylation. Nevertheless, an accurate and reliable measure of capillary blood flow in humans is needed to properly address this aspect.

In relation to $\tau\dot{Q}$ and τHR, it should be noted that due to the technical challenges associated with obtaining dynamic measures of $\dot{Q}$ during exercise, the kinetics of HR are commonly used as a proxy for the $\dot{Q}$ kinetics (Chilibeck et al.

1997; Lador et al. 2005; Zuccarelli et al. 2018). This study found that there were no statistical differences between $\tau\dot{Q}$ and τHR in both trained and untrained participants. While this may suggest that these measures can be used interchangeably, it is important to point out that these two variables were not highly correlated and were subject to a large amount of variability between participants. Therefore, τHR may not be a valid proxy of $\tau\dot{Q}$ and should be used with caution. It must be acknowledged, however, that the strength of the correlation and the magnitude of the variability may vary depending on the systems used to assess $\dot{Q}$. Thus, we cannot dismiss the possibility that using a different system to measure for $\dot{Q}$ might in fact strengthen the association between $\tau\dot{Q}$ and τHR.

Limitations

While the trained group in the current study was significantly older than the untrained group (trained 39, untrained 29 years), age *per se* is not the main factor that regulates the speeding of $\dot{V}O_2$ kinetics (Grey et al. 2015; George et al. 2018). Additionally, even though the groups were statistically different in age, participants could still be considered young overall. Moreover, if aging was to have an effect on the $\dot{V}O_2$ kinetics response, the expectation would be that slower $\dot{V}O_2$ kinetics would be observed in the "older" participants, which, in fact, is the opposite response that was observed herein. Additionally, an important aspect to consider is that, although the sample size in our study is in line with previous studies in this field (Murias et al. 2011c), the presence, or lack thereof, of a correlation between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ should be corroborated in a larger sample size including both males and females, such that the results can be generalized across both sexes. In line with this, the current study evaluated this relationship in a subset population of individuals with $\dot{V}O_{2max}$ values ranging from ~ 30 to ~ 70 mL kg^{-1} min^{-1}. Even though this range of fitness levels is wide enough for young healthy participants, further research is needed in order to confirm our findings in deconditioned individuals of even lower fitness levels. Lastly, to maximize the amplitude of the responses, participants performed step-transitions corresponding to 80–90% of GET. This resulted in the amplitude of the responses (i.e., $\dot{V}O_2$, $\dot{Q}$, HR kinetics) being different between groups (see Table 1). However, given the fact that the dynamic changes of $\dot{V}O_2$ are unaffected by the amplitude of the response (Keir et al. 2016) provided that the transition is performed within the moderate intensity domain, as well as the fact that a large component of the change in HR (and thus $\dot{Q}$) at these intensities is mediated by a very fast withdrawal of the parasympathetic activity (Fagraeus and Linnarsson 1976), we believe that these differences had no impact on the temporal differences, or lack thereof, between groups.

Conclusions

This study demonstrated that the strong negative relationship between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ typically assumed and corroborated herein in participants varying in level of fitness, disappears when only trained participants are evaluated. This suggests that there is a "critical" level of fitness (i.e., $\dot{V}O_{2max}$) beyond which no further speeding of $\tau\dot{V}O_2$ is observed. This study also demonstrated that, even in the presence of training induced speeding of the $\dot{V}O_2$ kinetics response, the dynamic adjustment of central delivery of O_2 (as measured by $\dot{Q}$ and HR kinetics) in response to an exercise transition within the moderate intensity domain does not differ amongst trained and untrained participants. Furthermore, as the peripheral redistribution of O_2 (as evaluated by the [HHb]/$\dot{V}O_2$ ratio) seems to be impaired in untrained compared to trained participants, this may be a factor that partly contributes to the slower $\dot{V}O_2$ kinetics observed in untrained participants.

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Author contributions ECI, DI and JMM conceived and designed the research. ECI and DI performed the experiments. ECI and DI analyzed the results. ECI, DI, and JMM interpreted results of the experiment. ECI drafted the manuscript. ECI, DI, and JMM edited and revised the manuscript. ECI, DI, and JMM approved the final version of manuscript.

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Compliance with ethical standards

Conflict of interest None of the authors has any conflict of interest to declare.

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