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Relationships of Pulmonary Oxygen Uptake Kinetics with Skeletal Muscle Fatigue Resistance and Peak Oxygen Uptake in Healthy Young Adults

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Abstract. [Purpose] The objective of this study was to determine the validity of pulmonary oxygen uptake kinetics in assessment of the ability of skeletal muscles to utilize oxygen. [Subjects] We evaluated 12 young, healthy males. [Methods] The subjects completed a series of tests to determine their peak oxygen uptake, pulmonary oxygen uptake kinetics at the onset of moderate-intensity treadmill exercise, and the rate of decline in electromyographic (EMG) mean power frequency (MPF) (EMG MPF_{rate}) during one continuous, fatiguing, isometric muscle action of the plantar flexors until exhaustion at approximately 60% maximum voluntary contraction. We discussed the relationships between pulmonary oxygen uptake kinetics and EMG MPF_{rate} reflecting the ability of skeletal muscles to utilize oxygen and between pulmonary oxygen uptake kinetics and peak oxygen uptake reflecting the ability to deliver oxygen to skeletal muscles. We hypothesized that pulmonary oxygen uptake kinetics may be more highly correlated with EMG MPF_{rate} than peak oxygen uptake. [Results] Pulmonary oxygen uptake kinetics (33.9 ± 5.9 s) were more significantly correlated with peak oxygen uptake (50.6 ± 5.5 mL/kg/min) than EMG MPF_{rate} (−14.7 ± 8.7%/s). [Conclusion] Pulmonary oxygen uptake kinetics is a noninvasive index that is mainly usable for evaluation of the ability of cardiovascular system to deliver oxygen to skeletal muscles in healthy young adults with slower pulmonary oxygen uptake kinetics (>20 s).
Key words: Pulmonary oxygen uptake kinetics, Oxygen utilization capacity, Oxygen delivery capacity

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INTRODUCTION

In patients with cardiac disease, it is becoming increasingly clear that peripheral (skeletal muscle) factors, in addition to central (cardiac) factors, play an important role in the determination of exercise tolerance, clinical status, and quality of life[1)]. Recently, cardiac rehabilitation programs have focused on skeletal muscles[2, 3)]. It is clinically important to evaluate oxidative metabolism in skeletal muscles and establish a conventional index that can be widely used in routine clinical practice. This approach should interest clinicians who need noninvasive tools, allowing quantitative and longitudinal evaluation of metabolic impairment, which can be used for patient follow-up and assessment of therapies or other interventions.

At exercise onset, the fundamental adjustment of pulmonary oxygen uptake (VO_2) kinetics during moderate-intensity exercise [i.e., exercise performed below the intensity corresponding to the anaerobic threshold (AT)] may be considered to represent a functional evaluation tool of oxidative metabolism at the skeletal muscle level. The rate of this adjustment, given by the VO_2 time constant (τVO_2), provides a useful insight into the integrated functioning of the cardiovascular, pulmonary, and muscular systems. Aerobic fitness may be defined as the ability to deliver O_2 to skeletal muscles and utilize it to generate energy during exercise. In healthy individuals, it is largely accepted that τVO_2 is determined by sluggish activation of enzymes and provision of substrates for mitochondrial oxidative phosphorylation (i.e., oxidative inertia hypothesis and O_2 utilization limitation hypothesis)[4–6)], but it may be constrained by the rate of O_2 delivery to active muscle fibers (i.e., O_2 delivery limitation hypothesis)[7, 8)]. Doria et al[9)]. recently reported that an improvement in τVO_2 is highly correlated with percent increase in mitochondrial protein following exercise training, but this occurs without improvement in the dynamics of O_2 delivery. This investigation indicates that τVO_2 may be an evaluation index capable of reflecting the ability of skeletal muscle to utilize O_2.

However, further investigation relevant to the relationship between τVO_2 and skeletal muscle fatigue resistance is required. Skeletal muscle fatigue resistance was evaluated by the rate of decline in electromyographic (EMG) mean power frequency (MPF) (EMG MPF_{rate}) as an index for evaluating muscle fatigue during sustained isometric mus-

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cle actions[10, 11]. Several studies have suggested that when fatiguing isometric contractions are performed at low levels [<30% maximal voluntary contraction (MVC)], fatigue assessed by EMG changes is primarily due to neural changes, whereas at higher levels (>45% MVC), fatigue is primarily caused by metabolic factors[12, 13]. EMG MPF_{rate}, measured at higher contraction levels, is an evaluation index reflecting the ability of skeletal muscle to utilize O_2.

In this report, we discussed the relationships of τVO_2 with skeletal muscle fatigue resistance (EMG MPF_{rate}) and peak oxygen uptake (VO_{2peak}) in healthy young adults, which reflect the ability to deliver O_2 to skeletal muscle[14] and determined the validation of τVO_2 in assessing the ability of skeletal muscle to utilize O_2. We hypothesized that τVO_2 may be more highly correlated with EMG MPF_{rate} than VO_{2peak}.

SUBJECTS AND METHODS

Subjects

In this study, 12 healthy male subjects volunteered and gave written consent to participate. The ages, heights, masses, and body fat percentages of the subjects (mean ± SD) were 20 ± 1.7 years, 1.70 ± 0.05 m, 62.2 ± 7.0 kg, and 21.6 ± 2.1%, respectively. All procedures were approved by the Ethics Committee of Seirei Christopher University (approval No. 09007). All participants were recreationally active and nonsmokers. No participant was taking medications that would affect the cardiorespiratory response to exercise.

Methods

Participants visited the laboratory for physiological testing on four occasions within a 10-day period. To allow adequate recovery and minimize circadian/diurnal variations, each test was separated by at least 48 h and was performed at approximately the same time of the day. On day one, a maximal treadmill ramp test (0% grade; 1 km/h/min) was performed (AR-200, Minato Medical Science Co., Ltd., Osaka, Japan) to determine VO_{2peak} and AT. VO_{2peak} was arbitrarily defined as the highest VO_2 value attained during two consecutive 20-s periods. AT was defined as the VO_2 at which CO_2 production (VCO_2) began to increase out of proportion in relation to VO_2 with a systematic rise in the minute ventilation-to-VO_2 ratio and end-tidal partial pressure of O_2, whereas the minute ventilation-to-VO_2 ratio and end-tidal partial pressure of CO_2 were stable. From the results of this ramp test, a moderate-intensity running speed was selected to elicit a VO_2 equivalent to approximately 80−90% of the VO_2 at AT. In each of the subsequent two visits to the laboratory, subjects performed two-step transitions at a moderate-intensity running speed. Exercise was performed continuously, the duration of each step transition was 6 min, and each transition was preceded by a baseline of 4 km/h/min walking that lasted for 6 min. Changes in the treadmill speed were initiated as a step function without warning the subjects. During the last day of testing, MVC was determined, and one continuous, fatiguing, isometric muscle action was performed until voluntary exhaustion at approximately 60% MVC. All isometric ankle flexion testing was performed on the dominant leg (based on kicking preference). The isokinetic dynamometer (Biodex System 3, Sakai Medical Co., Ltd., Tokyo, Japan) was adjusted at an ankle joint angle of 15° of plantar flexion in the sitting position with the hip and knee at 90°. Subjects performed three 5 s MVCs, that were interspersed with 5 s of rest. The highest torque developed during the three attempts was used as the individual's MVC. After 10 min rest, 60% MVC was set as the marker on the dynamometer screen, and each subject performed one continuous, fatiguing, isometric muscle action of the plantar flexors at approximately 60% MVC until exhaustion (through visual feedback). We defined the exhaustion level as a drop in torque greater than 50% MVC.

During all treadmill exercise sessions, pulmonary gas exchange was measured breath-by-breath using a metabolic measurement system (A-E 300S, Minato Medical Science Co., Ltd., Osaka, Japan). Inspired and expired gas volumes were measured using a hot-wire respiratory flow system. The expired fractions of O_2 and CO_2 were analyzed using a paramagnetic O_2 analyzer and an infrared CO_2 analyzer, respectively. The system was calibrated prior to each exercise test according to the manufacturer's instructions. The volume was calibrated before each exercise test by manually pumping a 2-L syringe. The O_2 and CO_2 analyzers were calibrated by gases of known concentration before each exercise test. Breath-by-breath VE, VO_2, and VCO_2 were determined, and the results were stored on a hard disk for subsequent analyses. VO_2 values were filtered by removing aberrant values that were more than 4 SD of the local mean. Further, each transition value was linearly interpolated to 1-s intervals and time aligned so that time zero represented the onset of exercise. Each transition value was ensemble averaged to yield a single, average response for each subject. This transition was further time averaged into 5-s bins to provide a single time-averaged response for each subject. The on-transient response for VO_2 was fitted using a monoexponential model of the form

$$Y_{(t)} = Y_{Bsln} + Amp\ (1 - e^{-(t-TD)/\tau}),$$

where Y (t) represents VO_2 at any time (t); Y Bsln is the baseline VO_2 during 4 km/h/min walking; Amp is the steady-state increase in VO_2 above the baseline value; τ is the time constant defined as the duration of time for VO_2 to increase to 63% of the steady-state increase; and TD is the time delay (so that the model is not constrained to pass through the origin.) After excluding the initial 20 s of values, while still allowing TD to vary freely (to optimize the accuracy of parameter estimates), VO_2 values were modeled from 20 s to 4 min (240 s) of the step transition; this ensured that each subject had attained a VO_2 steady-state, yet did not bias the model fit during the on-transient15, 16). Model parameters were estimated by least-squares nonlinear regression (Microsoft Office Excel 2010, Microsoft Japan Co., Ltd., Tokyo, Japan) in which the best fit was defined by minimization of the residual sum of squares and minimal residual variations around the Y-axis (Y=0).

EMG (Noraxon) of the soleus was continuously recorded at a sampling frequency of 1,500 Hz using bipolar 34-mm

diameter Ag-AgCl electrodes (Blue Sensor, Ambu A/S, Ballerup, Denmark) placed 2/3rd of the way along a line between the medial condyle of the femur and the medial malleolus (according to Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles recommendations). Electrode sites were prepared by shaving, gently abrading, and cleaning them with an alcohol-ether-acetone solution. Myoelectric signals were relayed from the bipolar electrodes to a TeleMyo device (TeleMyo 2400T, Noraxon U.S.A. Inc., Scottsdale, AZ, USA). The raw EMG signal was rectified, band-pass-filtered and integrated using commercially available software (MyoResearch XP, Noraxon U.S.A. Inc., Scottsdale, AZ, USA). EMG MPF_{rate} was then derived from the following equation:

$$\text{EMG } MPF_{rate}\ (\%/s) = [(\text{first MPF} - \text{final MPF}) / \text{first MDF} \times 100\ (\%)] / ET\ (s) \times 10^5,$$

where first and final MPF represent the mean of the first 5 s and final 5 s, respectively, during the fatigue resistance test; ET is the endurance time until exhaustion.

All analyses were performed using a statistical software package (IBM SPSS Statistics 19, IBM Corp., Armonk, NY, USA). Descriptive statistics (mean ± SD) were calculated for each physiological measure during all tests. Quantitative variables were tested for normal distribution by a Shapiro-Wilk test. Relationships between physiological measures were determined using Pearson's product moment correlation coefficient. Significance at the level of $p<0.05$ was used to determine the statistical significance.

RESULTS

We found that τVO_2 was 33.9 ± 5.9 s, EMG MPF_{rate} was −14.7 ± 8.7%/s, VO_{2peak} was 50.6 ± 5.5 mL/kg/min, and MVC was 126.3 ± 25.2 Nm. Table 1 shows interrelationships between τVO_2, EMG MPF_{rate}, and VO_{2peak} (All $p<0.05$). τVO_2 was more highly correlated with VO_{2peak} ($r = -0.744$) than EMG MPF_{rate} ($r = -0.670$). There was no significant relationship between MVC and other measures ($p>0.05$).

Table 1. Interrelationship between τVO_2, EMG MPF_{rate}, and VO_{2peak}

Measure	τVO_2 (s)	EMG MPF_{rate} (%/s)	VO_{2peak} (ml/min/kg)
τVO_2 (s)	–	−0.670*	−0.744*
EMG MPF_{rate} (%/s)	–	–	0.715*

*$p<0.05$

DISCUSSION

The primary finding of the present study is that, in healthy young adults at exercise onset, the τVO_2 measured at the alveolar level is dependent more on the ability to deliver O_2 to skeletal muscles (VO_{2peak}) than on the utilization of O_2 in skeletal muscle (skeletal muscle fatigue resistance; EMG MPF_{rate}). Our results indicate that τVO_2 offers promise as a noninvasive index to mainly evaluate the ability of the cardiovascular system to deliver O_2 to skeletal muscles in healthy young adults.

The present finding does not support our initial hypothesis that τVO_2 is more highly correlated with EMG MPF_{rate} than VO_{2peak} or the findings from other studies showing no effect of O_2 delivery on τVO_2[4–6, 9]. This may reflect that τVO_2 is limited because of the ability to deliver O_2 to skeletal muscles; i.e., our result may support the O_2 delivery limitation hypothesis.

This discrepancy may be due to the fact that the limiting factor in τVO_2 (O_2 utilization or O_2 delivery limitation) has not been fully revealed. The O_2 utilization limitation hypothesis was based on the representative experiments, which showed that in older adults, but not younger adults, τVO_2 during the transition from a priming bout of heavy-intensity exercise to moderate-intensity exercise accelerated[17, 18], and this τVO_2 acceleration in the older adults was attributed either to an attenuation of muscle perfusion or O_2 delivery limitation. The finding that τVO_2 was not affected by a previous bout of heavy-intensity exercise in young adults agrees with earlier findings[19, 20], and it is consistent with the suggestion that muscle blood flow and O_2 delivery do not limit τVO_2 in younger adults. However, a consistent observation among these experiments was that τVO_2 was significantly faster (approximately 20−30 s)[19–21] in young adults compared with that in older adults (approximately 40−60 s)[17, 18, 22]. Thus it is unclear from these experiments whether the apparent lack of τVO_2 acceleration during moderate-intensity exercise in young adults compared with older adults is a consequence of age-dependent differences between groups or physiological differences contributing to slower τVO_2 in older adults compared with younger adults.

Gurd et al.[23] recently demonstrated that the τVO_2 acceleration during moderate-intensity exercise after heavy-intensity warm-up exercise was not restricted to older adults and may be related to the physiological processes that control τVO_2. In young adults exhibiting slower VO_2 kinetics (τVO_2 >30 s), it was observed that τVO_2 acceleration was associated with improvement in local muscle oxygenation, whereas this was not seen in young adults exhibiting inherently faster VO_2 kinetics (i.e., τVO_2, approximately 20 s). Thus, τVO_2 acceleration was due to, in part, an increase in local muscle O_2 delivery. More recently, this observation was supported by Murias et al.[24], who reported that at the onset of exercise, the rate of adjustment of near-infrared spectroscopy (NIRS)-derived muscle deoxygenation [change in deoxyhomoglobin (HHb) concentration (Δ[HHb]), or [HHb], depending on the NIRS system used (a proxy for tissue O_2 extraction)] during moderate-intensity exercise was faster than VO_2 without heavy-intensity warm-up exercise, causing a period of greater reliance on O_2 extraction for a given VO_2. Thus, there was a transient mismatch in local muscle O_2 delivery to O_2 utilization [represented as a transient "overshoot" in the normalization of the Δ[HHb] to VO_2 (Δ[HHb]/VO_2) ratio]; τVO_2 was significantly reduced, and this transient overshoot in the Δ[HHb]/VO_2 ratio was abolished with heavy-intensity warm-up exercise. In addition to this experiment, Murias et al.[25] demonstrated in a group of young men that those

with the highest τVO_2 values presented with the largest mismatch between microvascular O_2 delivery and O_2 utilization, which was again represented as the highest Δ[HHb]/VO_2 overshoot. Furthermore, no Δ[HHb]/VO_2 overshoot was observed when values from subjects with τVO_2 <21 s were grouped. Most recently, it was suggested that τVO_2 is primarily limited by O_2 provision when τVO_2 exceeds approximately 20 s in young, healthy men[26]. According to the above observations, it seems that when τVO_2 > 20 s, τVO_2, even in healthy young adults, is primarily limited by the ability to deliver O_2 to skeletal muscles.

In the present study, τVO_2 may reflect the ability to deliver O_2 to skeletal muscles because this value was found to be 33.9 ± 5.9 s (>20 s). Therefore, τVO_2 was more highly correlated with VO_{2peak} than EMG MPF_{rate}.

In conclusion, this study demonstrated that, in healthy young adults at exercise onset, pulmonary VO_2 kinetics during the transition to moderate-intensity exercise is dependent more on the ability to deliver O_2 to skeletal muscles than utilization of O_2 in skeletal muscle. This suggests that O_2 delivery could be a possible factor regulating τVO_2 during the onset of moderate-intensity exercise in young adults having slower VO_2 kinetics (τVO_2 >20 s).

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