

The Relationship Between Skeletal Muscle Oxygenation and Systemic Oxygen Uptake During Exercise in Subjects With COPD: A Preliminary Study

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BACKGROUND: Muscle oxygenation correlates with systemic oxygen uptake (\dot{V}_{O_2}) in normal subjects; however, whether this relationship exists in COPD patients remains unclear. The purpose of this study was to investigate the influence of skeletal muscle oxygenation on \dot{V}_{O_2} during exercise in patients with COPD. **METHODS:** Eight subjects performed an incremental cycle ergometer exercise test. We measured ventilation and pulmonary gas exchange with a metabolic measurement system. We also continuously monitored S_{pO_2} , and measured tissue oxygen saturation (S_{tO_2}) in the vastus lateralis with continuous-wave near-infrared spectroscopy. We calculated the muscle oxygen extraction rate (MOER) based on S_{pO_2} and S_{tO_2} . In addition, we calculated Pearson correlation coefficients to examine the relationships between the \dot{V}_{O_2} obtained during exercise testing and the mean values of S_{pO_2} , S_{tO_2} , heart rate (HR), and MOER for each 30-second interval of the tests. Finally, we analyzed the relationships between the peak \dot{V}_{O_2} and the slopes of HR/\dot{V}_{O_2} , S_{pO_2}/\dot{V}_{O_2} , S_{tO_2}/\dot{V}_{O_2} , and $MOER/\dot{V}_{O_2}$. **RESULTS:** With the increasing exercise intensity, many subjects showed a gradual decrease in S_{tO_2} and S_{pO_2} , but a gradual increase in HR and MOER. \dot{V}_{O_2} was negatively correlated with S_{tO_2} and S_{pO_2} , and was positively correlated with HR and MOER. However, peak \dot{V}_{O_2} was not correlated with any of the slopes. **CONCLUSIONS:** \dot{V}_{O_2} is highly influenced by oxygen utilization in exercising muscles, as well as by blood oxygenation levels and cardiac function. However, the impact of skeletal muscle utilization during exercise on peak \dot{V}_{O_2} varied greatly among the subjects. *Key words:* COPD; oxygen uptake; oxygen utilization; skeletal muscle oxygenation; near-infrared spectroscopy; muscle oxygen extraction rate; rehabilitation; exercise test. [Respir Care 2012;57(10):1602–1610. © 2012 Daedalus Enterprises]

Introduction

The exercise tolerance of COPD patients is limited by ventilation and gas exchange, and by cardiac, skeletal muscle, and respiratory muscle dysfunctions.^{1,2} Early dyspnea and ventilatory insufficiency have traditionally been viewed

as the main causes of such exercise intolerance.¹ Many studies have shown that hyperinflation typically worsens air-flow obstruction and decreases exercise capacity.^{1–3} However, some patients are capable of performing many exercises despite having severe air-flow limitations.⁴ Leg

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fatigue is also commonly experienced during peak exercise in patients with COPD.⁵ These observations indicate that peripheral muscle alterations, such as poor oxidative capacity, atrophy, and weakness, increase the susceptibility to contractile fatigue and are common in patients with COPD.^{6–9}

In 1997 the American Association of Cardiovascular and Pulmonary Rehabilitation, and the American College of Chest Physicians published the first evidence-based guidelines on pulmonary rehabilitation.¹⁰ Since this report, several additional guidelines on pulmonary rehabilitation have been published.^{11–13} These guidelines recommend lower extremity exercise training for improving the exercise tolerance of patients with COPD. It has been shown that unsupported endurance training of the upper extremities is beneficial for patients with COPD and should be included in pulmonary rehabilitation programs. In contrast, the existing evidence does not support the routine use of inspiratory muscle training, anabolic drugs, or nutritional supplementation for pulmonary rehabilitation.^{12,13} Collectively, these publications^{11–13} indicate that skeletal muscle function is important for improving exercise tolerance.

Recent developments in near-infrared spectroscopy (NIRS) have made it possible to noninvasively measure *in vivo* changes in oxygenated hemoglobin (oxy-Hb), deoxygenated Hb (deoxy-Hb), and total Hb of tissues.¹⁴ NIRS has previously been used to assess changes in blood volume, the balance between oxygen delivery (D_{O_2}) and O_2 consumption in skeletal muscles, and tissue oxygenation during exercise. A number of studies have used NIRS to evaluate skeletal muscle in patients with heart and muscular diseases, diabetes mellitus, as well as lung disease.¹⁵ Patients with COPD have faster dynamics of muscle deoxygenation than their age-matched controls.^{16,17} Studies have also shown that muscle oxygenation in patients with COPD during exercise can be improved by bronchodilators,¹⁸ heliox (mixture of 79% He and 21% O_2),¹⁹ and proportional assist ventilation.²⁰ These NIRS-based observations suggest that a relationship exists between respiratory muscle work and peripheral muscle oxygenation in patients with COPD. It has been reported that NIRS-generated muscle oxygenation measurements correlate with systemic oxygen uptake (\dot{V}_{O_2}) levels in normal subjects.²¹ However, whether this relationship exists in COPD patients with skeletal muscle dysfunction remains unclear. Accordingly, the purpose of this study was to better understand the influence of skeletal muscle oxygenation, heart rate (HR), and S_{pO_2} on \dot{V}_{O_2} during exercise in patients with COPD.

Methods

Subjects

Eight male subjects with moderate to very severe COPD participated in this study. Individuals were diagnosed with

QUICK LOOK

Current knowledge

Muscle oxygenation correlates with systemic oxygen consumption in normal subjects, but the relationship between muscle oxygenation and oxygen consumption in patients with COPD is not well described.

What this paper contributes to our knowledge

In patients with COPD, oxygen consumption is highly influenced by oxygen utilization in exercising muscles, blood oxygenation level, and cardiac function. The relationship between muscle oxygenation and peak oxygen consumption varies widely in this population.

COPD according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria ($FEV_1/FVC < 70\%$ and FEV_1 percent predicted $< 80\%$).¹³ The related COPD symptoms were stable at the time of the study, and no participants suffered from any cardiovascular, neurological, skeletal muscle, or other conditions that could alter their capacity to perform or influence the exercise test. The medical ethics committee at Kio University, Koryo-cho, Japan, approved the design of this study. All participants provided written informed consent. The characteristics of the subjects included in the study are shown in Table 1.

Study Design

Body anthropometry was performed, and measurements of resting lung function were obtained. Dyspnea was assessed using the Medical Research Council (MRC) breathlessness scale, consisting of 5 statements that describe nearly the entire range of respiratory disabilities, from no disability (grade 1) to complete incapacity (grade 5).²² All subjects were subjected to a symptom-limited incremental cycle ergometry test. A flow chart of this study is shown in Figure 1.

Pulmonary Function Tests

Spirometry was performed using a hand-held spirometer (AS-502, Minato Medical Science, Osaka, Japan), according to published recommendations.²³ The data evaluated consisted of FVC, FEV_1 , and the Tiffeneau index (FEV_1/FVC). Recorded values were compared with the values predicted for the adult Japanese population.²⁴

Exercise Test

We carried out all tests on subjects under close medical supervision, and monitored the subjects' cardiac activities

Table 1. Characteristics of 8 Male Subjects With COPD

Subject Number	Age (y)	Height (cm)	BMI (kg/m ²)	MRC Dyspnea Score	FVC (% predicted)	FEV ₁ (% predicted)	FEV ₁ /FVC	Peak \dot{V}_{O_2} (mL/kg/min)
1	71	154.0	22.4	3	69.3	36.1	39.6	16.99
2	74	160.5	19.0	3	65.5	38.2	47.3	10.94
3	63	156.6	19.7	2	88.5	20.6	19.6	14.83
4	68	154.0	16.2	2	68.0	23.6	29.0	13.79
5	75	159.0	17.3	2	110.0	58.3	42.9	12.67
6	77	156.0	19.1	2	84.9	69.0	65.2	17.61
7	87	150.0	22.4	2	37.6	31.0	63.4	11.09
8	55	168.0	20.3	3	86.0	52.4	52.6	23.21
Mean \pm SD	71.3 \pm 10.4	157.7 \pm 5.7	19.1 \pm 2.0	NA	76.2 \pm 21.3	41.9 \pm 18.4	45.7 \pm 16.9	14.9 \pm 4.3

BMI = body mass index

MRC = Medical Research Council dyspnea score

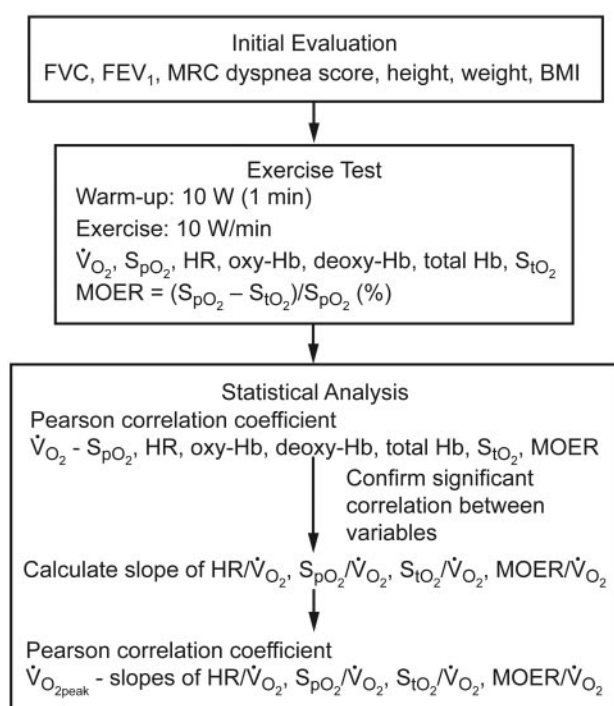
Peak \dot{V}_{O_2} = peak oxygen uptake

Fig. 1. A flow diagram of this study. BMI = body mass index. MRC = Medical Research Council dyspnea score. \dot{V}_{O_2} = oxygen uptake. HR = heart rate. Oxy-Hb = oxyhemoglobin. Deoxy-Hb = deoxyhemoglobin. S_{tO_2} = tissue oxygen saturation. MOER = muscle oxygen extraction rate.

with electrocardiogram. We used an electromagnetically braked cycle ergometer (232CXL, Combi, Tokyo, Japan), with a pedal revolution rate of 50 revolutions/min. The subjects performed incremental exercises using the modified protocol of the American Thoracic Society/American College of Chest Physicians guidelines,²⁵ which consisted of exercising at 10 W for 1 min, with the exerted work

load increased thereafter by an additional 10 W every min until the subject reached voluntary exhaustion. We determined the subjects' \dot{V}_{O_2} levels (expressed as the mean mL/kg/min) breath by breath with a computerized metabolic cart (AE280S, Minato Medical Science, Osaka, Japan). Moreover, the peak \dot{V}_{O_2} was defined as the mean during the last 30 s of the highest work load achieved by the subject. We continuously estimated S_{pO_2} (every 30 s) via pulse oximetry (Pulsox-M24, Konika-Minolta, Tokyo, Japan). We continuously measured HR of subjects with electrocardiogram.

Kinetics of Peripheral Muscle Oxygenation

During the exercise test we measured the kinetics of peripheral muscle oxygenation in the right vastus lateralis muscle of subjects, using a laser tissue blood oxygen monitor (BOM-L1TRW, Omegawave, Tokyo, Japan). Specifically, the NIRS probe was placed on the muscle approximately 14–20 cm from the knee joint. This instrument uses 3 light emitting diodes (wavelengths 780, 810, and 830 nm) and calculates the relative tissue levels of oxy-Hb, deoxy-Hb, and total Hb, according to the Beer-Lambert law. The absorption coefficients of Hb were based on previously reported data.²⁶ The individual values were proportional to the Hb levels, which suggests that oxy-Hb, deoxy-Hb, and total Hb were mostly expressed in $\mu\text{mol/L}$.

We expressed the Hb concentrations in arbitrary units because they do not represent actual physical volumes. We calculated tissue blood oxygen saturation (S_{tO_2}) from the oxy-Hb and total Hb values with the following formula:

$$S_{tO_2} (\%) = \text{oxy-Hb} / \text{total Hb} \times 100$$

For measurements, the distances between the incident point and the 2 detectors were 30 mm and 15 mm, which

were selected because a previous study showed that the maximum measuring depth for the tissue blood volume and its oxygenation of the intra-soft tissue were approximately 15 mm and 30 mm from the surface of the skin, respectively.²⁷ To demonstrate that subcutaneous fatty tissue had little influence on the intramuscular hemodynamics and oxygenation measurements, we performed a differential calculation from the measurements of the detectors. The detectors were fixed with tape after being shielded with a rubber sheet and vinyl. These data were imported into a personal computer at a sampling frequency of 10 Hz via an analog-to-digital converter (NR500, Keyence, Osaka, Japan). The integrated and mean values from 30-second intervals were calculated using the analog-to-digital converter's software (Wave Logger 1.03, Keyence, Osaka, Japan). The mean was calculated by dividing these values by the integral time.

Muscle Oxygen Extraction Rate

Oxygen transport variables included \dot{D}_{O_2} , \dot{V}_{O_2} , and the oxygen extraction rate (OER). It has been established that \dot{D}_{O_2} is determined by arterial oxygen content (C_{aO_2}) and cardiac output, whereas \dot{V}_{O_2} is determined by C_{aO_2} , venous oxygen content (C_{vO_2}), and differences in cardiac output. OER is determined by the ratio of \dot{D}_{O_2} to \dot{V}_{O_2} .²⁸ In this study, C_{aO_2} and C_{vO_2} were calculated from S_{pO_2} , venous blood saturation (S_{vO_2}), P_{aO_2} , and mixed venous oxygen pressure (P_{vO_2}) with the following formulas:

$$C_{aO_2} = (1.34 \times \text{Hb} \times S_{pO_2}) + (0.003 \times P_{aO_2})$$

$$C_{vO_2} = (1.34 \times \text{Hb} \times S_{vO_2}) + (0.003 \times P_{vO_2})$$

The terms $(0.003 \times P_{aO_2})$ and $(0.003 \times P_{vO_2})$ are typically negligibly small, particularly because OER is calculated using the following formula:

$$\text{OER} = (C_{aO_2} - C_{vO_2})/C_{aO_2} \approx (S_{pO_2} - S_{vO_2})/S_{pO_2}$$

Moreover, in this study we calculated the MOER using the formula:

$$\text{MOER} = (S_{pO_2} - S_{tO_2})/S_{pO_2}$$

Statistical Analysis

Data analysis was performed using statistics software (SPSS 19.0, SPSS, Chicago, Illinois). The Kolmogorov-Smirnov test was used to evaluate the data distribution. We performed analyses with Pearson correlation coefficients (r) to examine the relationships between the \dot{V}_{O_2}

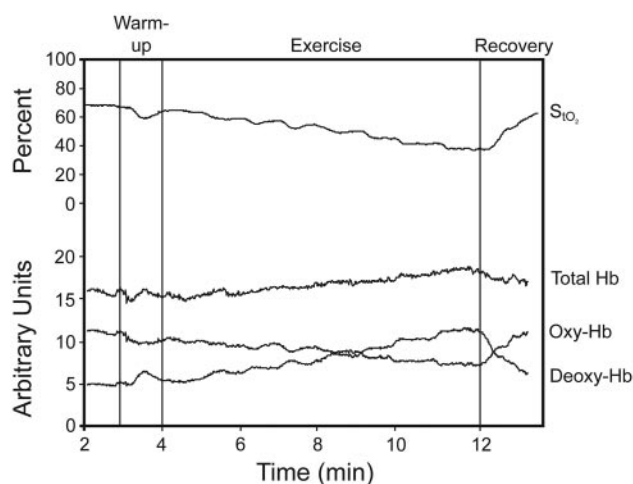


Fig. 2. Typical tracing of changes in tissue oxygen saturation (S_{tO_2}), oxyhemoglobin (oxy-Hb), deoxyhemoglobin (deoxy-Hb), and total Hb during exercise.

values from the exercise test and the means of oxy-Hb, deoxy-Hb, total Hb, S_{tO_2} , S_{pO_2} , HR, or MOER for each 30-second interval during the test. After we confirmed significant correlations between \dot{V}_{O_2} and HR, S_{pO_2} , S_{tO_2} , or MOER, we obtained the slopes of HR/\dot{V}_{O_2} , S_{pO_2}/\dot{V}_{O_2} , S_{tO_2}/\dot{V}_{O_2} , and $\text{MOER}/\dot{V}_{O_2}$ from the regression analysis. In some subjects, S_{pO_2} was not normally distributed, but we performed the same analysis in order to estimate regression slopes in this study. We also analyzed the relationships between the peak \dot{V}_{O_2} and the slopes of HR/\dot{V}_{O_2} , S_{pO_2}/\dot{V}_{O_2} , S_{tO_2}/\dot{V}_{O_2} , and $\text{MOER}/\dot{V}_{O_2}$ using Pearson correlation coefficients. A P value of less than .05 was considered statistically significant.

Results

Kinetics of Peripheral Muscle Oxygenation During an Exercise Test

In many of the subjects in this study, both the deoxy-Hb and total Hb levels gradually increased with exercise intensity, either immediately or during the test. In contrast, the levels of both oxy-Hb and S_{tO_2} gradually decreased during the test (Fig. 2). However, the oxy-Hb, deoxy-Hb, and S_{tO_2} levels changed somewhat during the test in subjects 2 and 6.

Relationships Between \dot{V}_{O_2} and Peripheral Muscle Oxygenation, Heart Rate, and S_{pO_2}

We calculated the relationships between \dot{V}_{O_2} and oxy-Hb, deoxy-Hb, total Hb, S_{tO_2} , MOER, HR, and S_{pO_2} per

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Table 2. Correlation Coefficients Between \dot{V}_{O_2} and Muscle Oxygenations, Heart Rate, and S_{pO_2}

Subject Number	Oxy-Hb	Deoxy-Hb	Total Hb	S_{tO_2}	MOER	Heart Rate	S_{pO_2}
1	-0.977†	0.978†	0.952†	-0.979†	0.965†	0.962†	-0.977†
2	0.068	0.722†	0.840†	-0.624*	0.557*	0.927†	-0.625*
3	-0.811†	0.947†	0.755†	-0.942†	0.894†	0.983†	-0.599*
4	-0.667*	0.809†	0.641*	-0.734†	0.625*	0.975†	-0.927†
5	-0.840†	0.819†	0.598*	-0.898†	0.817†	0.903†	-0.810†
6	-0.209	0.706†	0.825†	-0.473*	0.594*	0.981†	-0.908†
7	-0.655†	0.767†	0.860†	-0.727†	0.825†	0.972†	-0.913†
8	-0.835†	0.973†	0.930†	-0.941†	0.937†	0.991†	-0.875†

* Correlation is significant at the .05 level (2-tailed).

† Correlation is significant at the .01 level (2-tailed).

Oxy-Hb = oxyhemoglobin

Deoxy-Hb = deoxyhemoglobin

S_{tO_2} = tissue oxygen saturation

MOER = muscle oxygen extraction rate = $(S_{pO_2} - S_{tO_2})/S_{pO_2} \times 100$ (%)

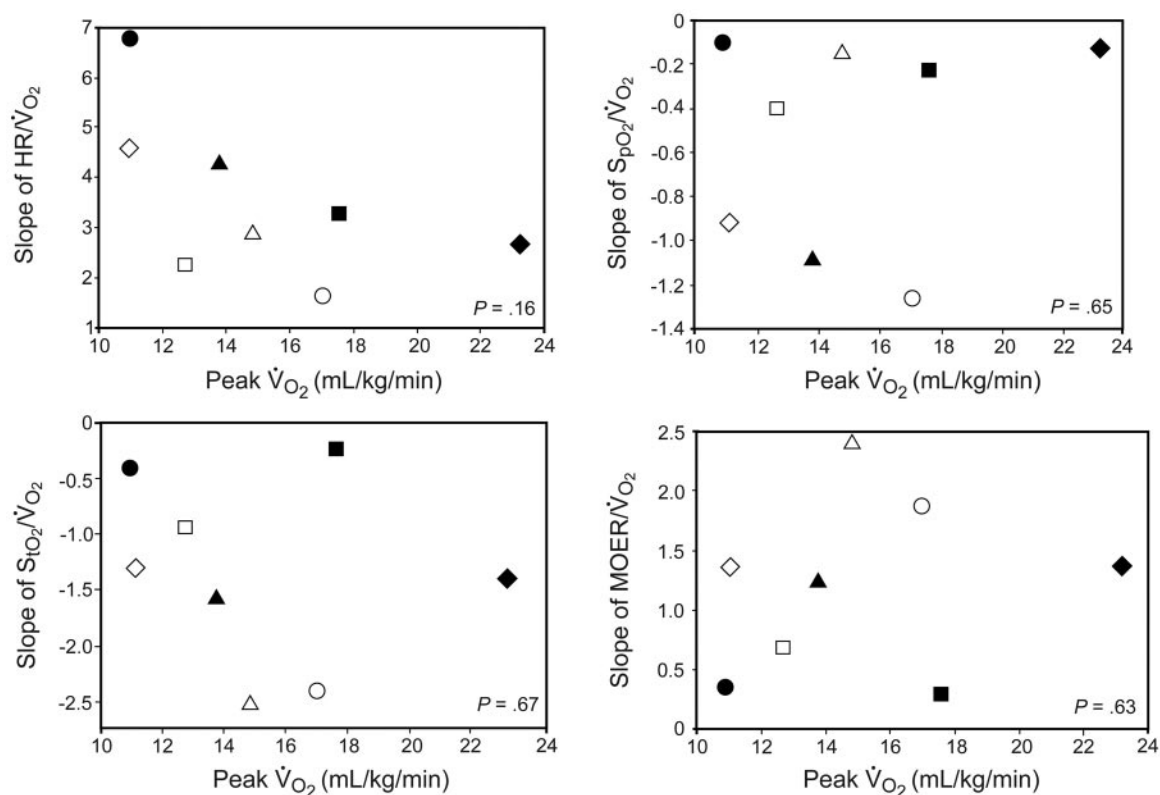


Fig. 3. Relationships between peak oxygen uptake (\dot{V}_{O_2}) and the slope of heart rate/ \dot{V}_{O_2} , S_{pO_2}/\dot{V}_{O_2} , S_{tO_2}/\dot{V}_{O_2} , and MOER/ \dot{V}_{O_2} . The muscle oxygen extraction rate (MOER) was calculated as $(S_{pO_2} - S_{tO_2})/S_{pO_2} \times 100$ (%). S_{tO_2} = tissue oxygen saturation. ○ Subject 1. ● Subject 2. △ Subject 3. ▲ Subject 4. □ Subject 5. ■ Subject 6. ◇ Subject 7. ◆ Subject 8.

30 seconds during the exercise test for each subject, using primary regression. \dot{V}_{O_2} was negatively correlated with S_{tO_2} ($r = -0.473$ to -0.979 , $P = .001$ to $.047$) and S_{pO_2} ($r = -0.599$ to -0.977 , $P = .001$ to $.029$). In contrast, \dot{V}_{O_2} was positively correlated with deoxy-Hb ($r = 0.706$ to 0.978 , $P < .001$), total Hb ($r = 0.598$ to 0.952 , $P = .001$ to $.039$), MOER ($r = 0.557$ to 0.965 ,

$P = .001$ to $.047$), and HR ($r = 0.903$ to 0.991 , $P < .001$) of subjects. We found no obvious relationship between \dot{V}_{O_2} and oxy-Hb; in some individuals, there was a marked negative correlation in these parameters ($r = -0.655$ to -0.977 , $P = .001$ to $.029$), but there was no apparent correlation in subjects 2 ($r = 0.068$) or 6 ($r = -0.209$) (Table 2).

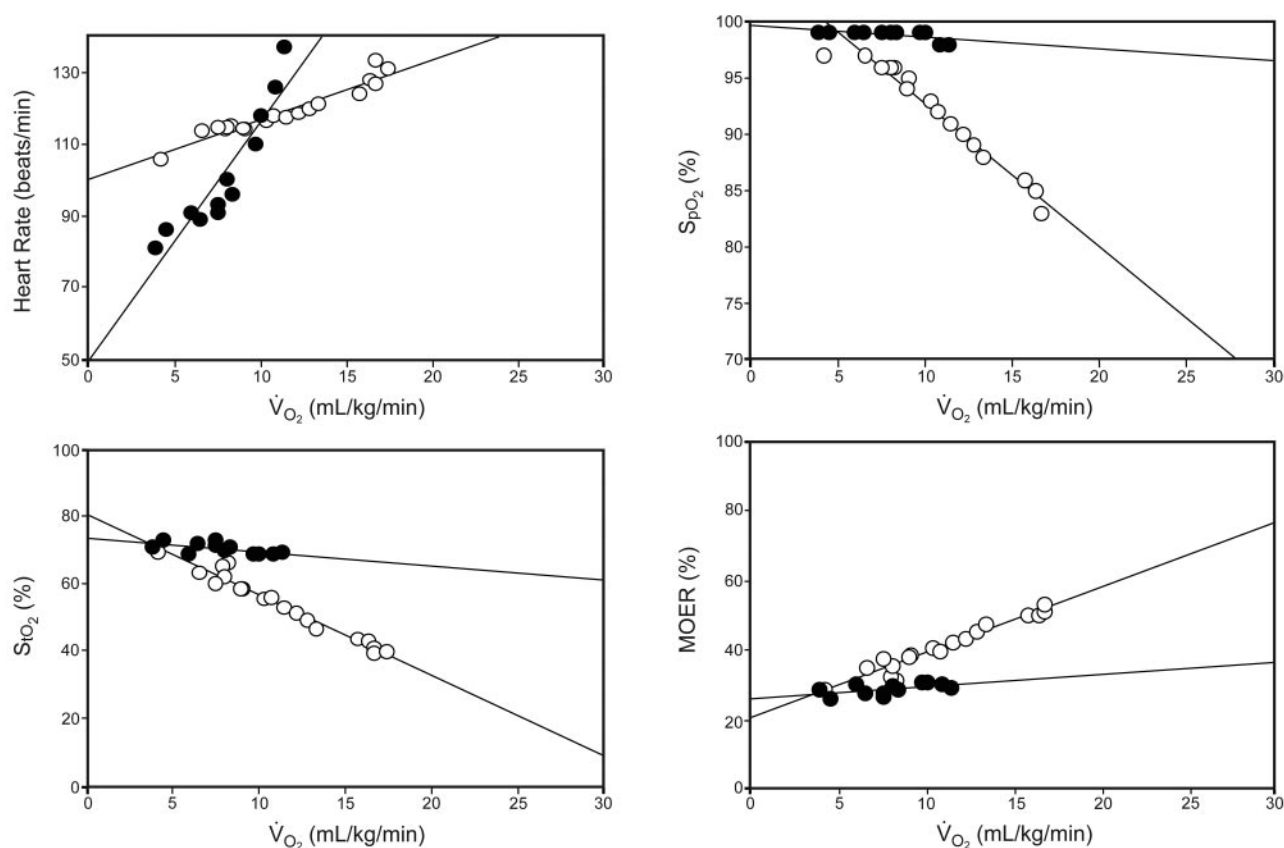


Fig. 4. Relationships between oxygen uptake (\dot{V}_{O_2}) and heart rate (HR), S_{pO_2} , tissue oxygen saturation (S_{tO_2}), and muscle oxygen extraction rate (MOER) for typical subjects. ○ Subject 1: age 71 y, % predicted FVC 69.3%, % predicted FEV₁ 36.1%, peak \dot{V}_{O_2} 17.0 mL/kg/min. ● Subject 2: age 74 y, % predicted FVC 65.5%, % predicted FEV₁ 38.2%, peak \dot{V}_{O_2} 10.9 mL/kg/min. The MOER was calculated as $(S_{pO_2} - S_{tO_2})/S_{pO_2} \times 100$ (%). The severity of air-flow limitation was similar in both subjects, but peak \dot{V}_{O_2} was greater in Subject 1 than in Subject 2. The slopes of HR/\dot{V}_{O_2} , S_{pO_2}/\dot{V}_{O_2} and S_{tO_2}/\dot{V}_{O_2} were lower, but $MOER/\dot{V}_{O_2}$ was relatively higher in Subject 1 than in Subject 2.

Relationships Between Peak \dot{V}_{O_2} and the Slopes of HR/\dot{V}_{O_2} , S_{pO_2}/\dot{V}_{O_2} , S_{tO_2}/\dot{V}_{O_2} , and $MOER/\dot{V}_{O_2}$

We also examined the relationships between \dot{V}_{O_2} and the slopes of HR/\dot{V}_{O_2} , S_{pO_2}/\dot{V}_{O_2} , S_{tO_2}/\dot{V}_{O_2} , and $MOER/\dot{V}_{O_2}$. The influence of \dot{V}_{O_2} on the HR/\dot{V}_{O_2} slope is partially expressed in the cardiac response, the S_{pO_2}/\dot{V}_{O_2} slope in the respiratory response, and the S_{tO_2}/\dot{V}_{O_2} and $MOER/\dot{V}_{O_2}$ slopes in the muscle response. peak \dot{V}_{O_2} did not correlate with any of the slopes (Fig. 3). In subject 1 the HR/\dot{V}_{O_2} , S_{pO_2}/\dot{V}_{O_2} , and S_{tO_2}/\dot{V}_{O_2} slopes were high and the $MOER/\dot{V}_{O_2}$ slope was low, compared with most of the other subjects. However, in subject 2 the HR/\dot{V}_{O_2} , S_{pO_2}/\dot{V}_{O_2} , and S_{tO_2}/\dot{V}_{O_2} slopes were low and the $MOER/\dot{V}_{O_2}$ slope was high. Figure 4 displays the relationships between \dot{V}_{O_2} and HR, S_{pO_2} , S_{tO_2} , and MOER for the different types of subjects (subjects 1 and 2). We determined that the severity of air-flow limitation was similar in both subjects, but peak \dot{V}_{O_2} was greater in subject 1 than in subject 2 (see Table 1). The slopes of HR/\dot{V}_{O_2} and S_{pO_2}/\dot{V}_{O_2} were lower, but $MOER/\dot{V}_{O_2}$ was relatively higher in subject 1 than in subject 2.

Discussion

Kinetics of Peripheral Muscle Oxygenation During an Exercise Test

The work rate of normal subjects is increased during exercise, and muscle oxygenation either remains constant near resting levels initially or decreases.²⁹ With an increasing work rate, tissue oxygenation decreases linearly or exponentially below the resting value, followed by a leveling off as the person reaches exhaustion.³⁰ These changes indicate there is a larger increase in oxygen extraction than in arterial blood flow during ramp load. In this study, most subjects with COPD exhibited similar changes (see Fig. 2). These results indicate that the balance between D_{O_2} and O_2 utilization in exercising muscle in subjects with COPD is similar to that in normal subjects. However, in 2 of the 8 subjects with COPD (subjects 2 and 6) there was little change in muscle oxygenation during exercise, and these subjects also had low MOERs (see Fig. 3).

Patients with COPD have been reported to have faster dynamics of muscle deoxygenation than their age-matched controls.^{16,17} Chiappa et al¹⁷ reported that the time constant ratio of O_2 uptake to mean response time of deoxy-Hb concentration was significantly greater in patients with COPD after the performance of heavy-intensity exercise. It has been suggested that patients with COPD have slower kinetics of microvascular O_2 delivery and impaired cardiovascular adjustments. Studies have also shown that muscle oxygenation in patients with COPD during exercise can be improved by bronchodilators,¹⁸ heliox,¹⁹ and proportional assist ventilation,²⁰ all of which reduced the rate of onset of dynamic hyperinflation and diminished respiratory muscle work. These findings suggest that a fraction of the available cardiac output can be redirected from respiratory muscles to the peripheral muscles, as a consequence of respiratory muscle unloading; and that decreased muscle oxygenation during exercise may be due to insufficient D_{O_2} in patients with COPD.

Some studies, however, show that blood flow in respiratory muscle is progressively reduced with increasing exercise intensity³¹; that blood flow redistribution from respiratory muscle to exercising muscle does not occur with heliox³²; and that supplemental O_2 does not improve muscle oxygenation, despite improved central O_2 delivery in patients with COPD.³³ These observations suggest that factors other than insufficient D_{O_2} cause decreased muscle oxygenation during exercise in patients with COPD.

Another study showed that muscle oxygenation was decreased after endurance training³⁴ and tapering,³⁵ due to improved oxygen utilization in exercising muscle. Thus, it is important to differentiate between decreasing muscle oxygenation that is caused either by decreasing D_{O_2} or increasing oxygen utilization.

In this study we found little change in the muscle oxygenation of subjects with COPD during exercise, and subjects 2 and 6 had low MOERs. These changes likely reflect the presence of an increased oxygen supply for covering decreased muscle oxygen extraction during the ramp load. Since there was little decrease in S_{pO_2} in these subjects, we concluded that the oxygen supply may have been mostly provided by the arterial blood flow for increased oxygen uptake during exercise. This might compensate for the insufficient muscle oxygen utilization during exercise in these subjects.

Relationships Between \dot{V}_{O_2} and Peripheral Muscle Oxygenation

It has been reported that \dot{V}_{O_2} positively correlates with deoxy-Hb and total Hb, whereas it negatively correlates with oxy-Hb and S_{IO_2} , during cycle ergometry in normal subjects.^{21,36} Furthermore, \dot{V}_{O_2} is reportedly negatively correlated with exercise muscle oxygenation during running.³⁷

In this study we observed a similar relationship between \dot{V}_{O_2} and NIRS data in subjects with COPD (see Table 1), which suggests that the kinetics of muscle oxygenation reflect \dot{V}_{O_2} in both COPD and normal subjects.

\dot{V}_{O_2} is dependent upon the difference between arterial and venous oxygenation levels, as well as blood flow. Since a higher percentage of total blood flow is diverted to skeletal muscles during maximum exercise,³⁸ it appears that the MOER is related to the OER. Thus, we found \dot{V}_{O_2} was significantly correlated with HR, S_{pO_2} , and MOER for each subject in this study.

Relationships Between peak \dot{V}_{O_2} and the Slopes of $\text{HR}/\dot{V}_{\text{O}_2}$, $\text{S}_{\text{pO}_2}/\dot{V}_{\text{O}_2}$, $\text{S}_{\text{IO}_2}/\dot{V}_{\text{O}_2}$, and $\text{MOER}/\dot{V}_{\text{O}_2}$

Many studies have examined skeletal muscle dysfunction in patients with COPD.^{6,9,39} Peripheral muscle dysfunction may be attributed to deconditioning induced by inactivity, systemic inflammation, oxidative stress, blood gas disturbances, corticosteroid use, or reductions in muscle mass. In this study we found that peak \dot{V}_{O_2} was not correlated with any of the slopes of $\text{HR}/\dot{V}_{\text{O}_2}$, $\text{S}_{\text{pO}_2}/\dot{V}_{\text{O}_2}$, $\text{S}_{\text{IO}_2}/\dot{V}_{\text{O}_2}$, and $\text{MOER}/\dot{V}_{\text{O}_2}$ (see Fig. 3). It is likely that the slopes were limited by ventilation due to arterial desaturation, because they had low peak \dot{V}_{O_2} with a low slope of $\text{S}_{\text{pO}_2}/\dot{V}_{\text{O}_2}$ in subjects 4 and 7. However, subject 2 had low peak \dot{V}_{O_2} without a low slope of $\text{S}_{\text{pO}_2}/\dot{V}_{\text{O}_2}$. The relationship between peak \dot{V}_{O_2} and the $\text{MOER}/\dot{V}_{\text{O}_2}$ slope varied greatly. This relationship varied with the severity of skeletal muscle dysfunction in the subjects. Because they had low $\text{MOER}/\dot{V}_{\text{O}_2}$ slopes, subjects 2 and 6 apparently had severely impaired muscle oxygenation dysfunction. In contrast, subjects 1 and 3 had high $\text{MOER}/\dot{V}_{\text{O}_2}$ slopes, and therefore most likely had no or lightly impaired dysfunction.

Previous studies revealed muscle oxygen utilization was greater in patients with COPD than in unaffected subjects.^{40–42} This increase may be a compensatory mechanism for insufficient muscle oxygen supply during exercise in patients with severe COPD. It has been reported that peripheral skeletal muscle oxygenation is not compromised in patients with COPD during submaximal exercise, and suggested that limitations in exercise capacity are most likely a result of muscle disuse and poor lung function.⁴³ Puente-Maestu et al reported that high-intensity training improves muscle oxygen capacity and oxygenation recovery kinetics, due to the increased presence of oxidative enzymes in patients with COPD.⁴⁴

In the present study the $\text{MOER}/\dot{V}_{\text{O}_2}$ slope varied greatly, which may indicate that various activity levels exist in patients with COPD. As shown in Figure 4, the $\text{HR}/\dot{V}_{\text{O}_2}$ and $\text{S}_{\text{pO}_2}/\dot{V}_{\text{O}_2}$ slopes were lower, but $\text{MOER}/\dot{V}_{\text{O}_2}$ was relatively higher, in subject 1 than in subject 2. However, peak \dot{V}_{O_2} was greater in subject 1 than in subject 2 (see

Table 1). These results suggest that \dot{V}_{O_2} was influenced by muscle oxygen utilization rather than cardiac function in subject 1, whereas subject 2 showed the opposite trend. Thus, the major factor of the cardiopulmonary response during exercise that differs between these subjects is possibly the muscle oxygen utilization function.

If a patient exhibits a decline in \dot{V}_{O_2} due to skeletal muscle dysfunction (eg, subject 2), skeletal muscle training may be the better management strategy from a rehabilitation standpoint. However, if a patient exhibits a decline in \dot{V}_{O_2} due to oxygen desaturation (eg, subject 1), supplemental oxygen may be the better management strategy, in addition to instructions for breathing control and relaxation techniques for improving exercise endurance.

We recognize that our study has limitations. We evaluated muscle oxidative function using S_{tO_2} and MOER for NIRS in the regional skeletal muscles, not in all exercising muscles, which is not ideal, since it has been shown that the oxidative response of muscles during exercise differs between exercising muscles.⁴⁵ We could not accurately analyze muscle oxygenation dynamics and calculate MOER, because S_{pO_2} is not equivalent to oxygen saturation measured from an arterial blood sample (S_{aO_2}); S_{tO_2} is not an adequate expression of S_{VO_2} ; and local blood flow, cardiac output, and respiratory muscle \dot{V}_{O_2} were not measured.

Conclusions

Our findings indicate that \dot{V}_{O_2} is highly influenced by oxygen utilization in the exercising muscles, as well as by blood oxygenation levels and cardiac function, in subjects with COPD. However, the impact of skeletal muscle utilization during exercise on peak \dot{V}_{O_2} varied greatly for each subject.

REFERENCES

1. Pepin V, Saey D, Laviolette L, Maltais F. Exercise capacity in chronic obstructive pulmonary disease: mechanisms of limitation. *COPD* 2007;4(3):195-204.
2. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;173(12):1390-1413.
3. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164(5):770-777.
4. Jones NL, Killian KJ. Limitation of exercise in chronic airway obstruction. In: Cherniack NS, editor. *Chronic obstructive pulmonary disease*. Philadelphia: WB Saunders; 1991.
5. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJ. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992;146(4):935-940.
6. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society. *Am J Respir Crit Care Med* 1999;159(4 Pt 2):S1-S40.
7. Palange P, Wagner PD. The skeletal muscle in chronic respiratory diseases, summary of the ERS research seminar in Rome, Italy. February 11-12 1999. *Eur Respir J* 2000;15(4):807-815.
8. Bernard S, LeBlanc P, Whittom F, Carrier G, Jobin J, Belleau R, et al. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158(2):629-634.
9. Maltais F, LeBlanc P, Whittom F, Simard C, Marquis K, Belanger M, et al. Oxidative enzyme activities of the vastus lateralis muscle and the functional status in patients with COPD. *Thorax* 2000;55(10):848-853.
10. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. *Chest* 1997;112(5):1363-1396.
11. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest* 2007;131(5 Suppl):4S-42S.
12. British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation. Pulmonary rehabilitation. *Thorax* 2001;56(11):827-834.
13. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for diagnosis, management, and prevention of COPD. Updated December 2011. <http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html>. Accessed July 17, 2012.
14. Jobis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 1977;198:1264-1267.
15. Hamaoka T, McCully KK, Quaresima V, Yamamoto K, Chance B. Near-infrared spectroscopy/imaging for monitoring muscle oxygenation and oxidative metabolism in healthy and diseased humans. *J Biomed Opt* 2007;12(6):062105.
16. Kutsuzawa T, Shioya S, Kurita D, Haida M. Deoxygenated hemoglobin/myoglobin kinetics of forearm muscles from rest to exercise in patients with chronic obstructive pulmonary disease. *Tohoku J Exp Med* 2009;217(1):9-15.
17. Chiappa GR, Borghi-Silva A, Ferreira LF, Carrascosa C, Oliveira CC, Maia J, et al. Kinetics of muscle deoxygenation are accelerated at the onset of heavy-intensity exercise in patients with COPD: relationship to central cardiovascular dynamics. *J Appl Physiol* 2008;104(5):1341-1350.
18. Berton DC, Barbosa PB, Takara LS, Chiappa GR, Siqueira AC, Bravo DM, et al. Bronchodilators accelerate the dynamics of muscle O_2 delivery and utilisation during exercise in COPD. *Thorax*;65(7):588-593.
19. Chiappa GR, Queiroga F, Jr., Meda E, Ferreira LF, Diefenthaler F, Nunes M, et al. Heliox improves oxygen delivery and utilization during dynamic exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;179(11):1004-1010.
20. Borghi-Silva A, Oliveira CC, Carrascosa C, Maia J, Berton DC, Queiroga F Jr, et al. Respiratory muscle unloading improves leg muscle oxygenation during exercise in patients with COPD. *Thorax* 2008;63(10):910-915.
21. Kawaguchi K, Tabusadani M, Sekikawa K, Hayashi Y, Onari K. Do the kinetics of peripheral muscle oxygenation reflect systemic oxygen intake? *Eur J Appl Physiol* 2001;84(1-2):158-161.
22. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *BMJ* 1959;2(5147):257-266.
23. American Thoracic Society; Medical Section of the American Lung Association. Future directions for research on diseases of the lung. This report was approved by the ATS Board of Directors in November 1994. *Am J Respir Crit Care Med* 1995;152(5 Pt 1):1713-1735.

24. Japan Society of Chest Diseases. The predicted values of pulmonary function testing in Japanese. *Jpn J Thorac Dis* 1993;31(Appendix). *Article in Japanese*.
25. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167(2):211-277.
26. Mather SJ, Elwell CE, Cooper CE, Cope M, Delpy DT. Performance comparison of several published tissue near-infrared spectroscopy algorithms. *Anal Biochem* 1995;227(1):54-68.
27. Kashima S. Spectroscopic measurement of blood volume and its oxygenation in a small volume of tissue using red laser lights and differential calculation between two point detections. *Optics Laser Technol* 2003;35:485-489.
28. Wasserman K. Pathophysiology of disorders limiting exercise. In: Wasserman K, Hansen J, Sue D, Whipp B, editors. *Principles of exercise testing and interpretation including pathophysiology and clinical applications*. Philadelphia: Lea and Febiger; 2005:111-125.
29. Belardinelli R, Barstow TJ, Porszasz J, Wasserman K. Changes in skeletal muscle oxygenation during incremental exercise measured with near infrared spectroscopy. *Eur J Appl Physiol Occup Physiol* 1995;70(6):487-492.
30. Bhambhani YN. Muscle oxygenation trends during dynamic exercise measured by near infrared spectroscopy. *Can J Appl Physiol* 2004;29(4):504-523.
31. Vogiatzis I, Athanasopoulos D, Habazettl H, Aliverti A, Louvaris Z, Cherouveim E, et al. Intercostal muscle blood flow limitation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*;182(9):1105-1113.
32. Vogiatzis I, Habazettl H, Aliverti A, Athanasopoulos D, Louvaris Z, LoMauro A, et al. Effect of helium breathing on intercostal and quadriceps muscle blood flow during exercise in COPD patients. *Am J Physiol Regul Integr Comp Physiol* 2011;300(6):R1549-R1559.
33. Siqueira AC, Borghi-Silva A, Bravo DM, Ferreira EM, Chiappa GR, Neder JA. Effects of hyperoxia on the dynamics of skeletal muscle oxygenation at the onset of heavy-intensity exercise in patients with COPD. *Respir Physiol Neurobiol* 2010;172(1-2):8-14.
34. Neary JP, McKenzie DC, Bhambhani YN. Effects of short-term endurance training on muscle deoxygenation trends using NIRS. *Med Sci Sports Exerc* 2002;34(11):1725-1732.
35. Neary JP, McKenzie DC, Bhambhani YN. Muscle oxygenation trends after tapering in trained cyclists. *Dyn Med* 2005;4(1):4.
36. Demarie S, Quaresima V, Ferrari M, Sardella F, Billat V, Faina M. VO_2 slow component correlates with vastus lateralis de-oxygenation and blood lactate accumulation during running. *J Sports Med Phys Fitness* 2001;41(4):448-455.
37. Hiroyuki H, Hamaoka T, Sako T, Nishio S, Kime R, Murakami M, et al. Oxygenation in vastus lateralis and lateral head of gastrocnemius during treadmill walking and running in humans. *Eur J Appl Physiol* 2002;87(4-5):343-349.
38. Rowell LB. *Human cardiovascular control*. New York: Oxford University Press; 1993.
39. Casaburi R. Skeletal muscle function in COPD. *Chest* 2000;117(5 Suppl 1):267S-271S.
40. Sala E, Roca J, Marrades RM, Alonso J, Gonzalez D-S-J, Moreno A, et al. Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159(6):1726-1734.
41. Richardson RS, Leek BT, Gavin TP, Haseler LJ, Mudaliar SR, Henry R, et al. Reduced mechanical efficiency in chronic obstructive pulmonary disease but normal peak VO_2 with small muscle mass exercise. *Am J Respir Crit Care Med* 2004;169(1):89-96.
42. Sekikawa K, Tabira K, Sekikawa N, Kawaguchi K, Takahashi M, Kuraoka T, et al. Muscle blood flow and oxygen utilization measured by near-infrared spectroscopy during handgrip exercise in chronic respiratory patients. *J Phys Ther Sci* 2009;21(3):231-238.
43. Austin KG, Mengelkoch L, Hansen J, Shahady E, Sirithienthad P, Panton L. Comparison of oxygenation in peripheral muscle during submaximal aerobic exercise, in persons with COPD and healthy, matched-control persons. *Int J Chron Obstruct Pulmon Dis* 2006;1(4):467-475.
44. Puente-Maestu L, Tena T, Trascasa C, Perez-Parra J, Godoy R, Garcia MJ, et al. Training improves muscle oxidative capacity and oxygenation recovery kinetics in patients with chronic obstructive pulmonary disease. *Eur J Appl Physiol* 2003;88(6):580-587.
45. Azuma K, Homma S, Kagaya A. Oxygen supply-consumption balance in the thigh muscles during exhausting knee-extension exercise. *J Biomed Opt* 2000;5(1):97-101.