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Abstract

Background

Spatially resolved (SR) spectroscopy has enabled non-invasive and continuous measurement of muscle oxygen saturation during exercise. In patients with chronic obstructive pulmonary disease (COPD), skeletal muscle dysfunction has been widely studied histochemically and biochemically. However, impairment of muscle oxygenation during exercise has not been elucidated yet.

Methods

We measured oxygen saturation in the vastus lateralis muscle (SmO_2) using SR spectrometry during incremental cycle exercise in 16 COPD patients and 10 age-matched healthy subjects.

Results

Significant decrease in SmO_2 was found at peak exercise compared with warm-up in both groups (56.9±6.0% to 47.3±6.8% in patients with COPD, $p<0.001$; 60.7±5.8% to 49.9±7.7% in healthy subjects, $p<0.01$). The decrease in SmO_2 was linear with respect to increase in work rate, and the slope of SmO_2 was significantly steeper in COPD patients than in healthy subjects (−0.282±0.159 vs −0.107±0.057 %/Watt, $p<0.001$). The slope of SmO_2 in COPD patients significantly correlated with body mass index (BMI) ($p<0.01$), peak percutaneous oxygen saturation ($p<0.05$), and peak pulmonary oxygen consumption ($p<0.05$). Stepwise regression analysis revealed that BMI was a significant determinant of the SmO_2 slope ($p=0.01$).

Conclusions

We conclude that oxygenation of peripheral muscle is impaired during exercise in COPD patients and that BMI contributes independently to the change of muscle oxygen saturation with exercise in COPD patients. SR spectroscopy will provide useful information for the study of the

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dynamics of muscle oxygenation in COPD patients.

Key Words: Near-infrared spectroscopy; Cycle exercise; Vastus lateralis muscle; Oxygen saturation; Body mass index (BMI)

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation and pulmonary gas exchange disorder. In patients with moderate to severe COPD, hypoxemia is often induced by exercise, and tissue oxygenation is therefore impaired during exercise[1]. Exercising muscle is exposed to severely hypoxic conditions since oxygen demand increases greatly with exercise when hypoxemia is induced in patients with COPD.

Loss of body mass plays an important role in exercise intolerance and poor prognosis in COPD[2,3]. This anatomical change is characterized by loss of skeletal muscle mass demonstrable by body composition analysis[2]. Histological change of muscle fiber type and biochemical abnormalities of oxidative metabolism in skeletal muscle are observed in patients with COPD[4-6]. However, it is not yet known whether there is any relationship between change in oxygenation of exercising muscle and clinical manifestations such as decrease in BMI and exercise intolerance in patients with COPD.

Near-infrared (NIR) spectroscopy is a non-invasive means of evaluating the state of oxygenation in skeletal muscle[7]. Recently, spatially resolved (SR) spectroscopy, a newly developed form of NIR spectroscopy, has enabled non-invasive and continuous measurement of muscle oxygen saturation during exercise[8]. The accuracy of SR spectrometry has been proved by measurement of tissue phantoms and has been validated in measurement of human skeletal muscle by comparison with data obtained by time resolved spectroscopy[8]. This new method is extremely attractive for use in study of change in muscle oxygenation during exercise.

To elucidate whether muscle oxygenation is impaired during exercise in patients with COPD compared with healthy subjects, and whether impairment of muscle oxygenation is related to clinical manifestations in patients with COPD, we examined oxygen saturation in the vastus lateralis muscle (SmO_2) using SR spectrometry during incremental cycle exercise in patients with COPD and healthy control subjects.

Materials and Methods

Subjects

Sixteen male patients with stable COPD and 10 age-matched healthy sedentary male subjects were studied. The study was approved by the Institutional Review Board of Osaka City University, and all study subjects gave written informed consent to participate in the study. The diagnosis of COPD was made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[9]. All patients were former cigarette smokers with irreversible airflow limitation. They were clinically stable, and none had a history of acute exacerbation for at least 4 weeks. They were receiving regular treatment with bronchodilators such as inhaled anticholinergic drugs, oral theophylline, and inhaled β_2 agonists. None had received systemic or inhaled corticosteroids. Patients with cardiac disease or peripheral vascular disease were excluded from the study.

Pulmonary function tests and arterial blood gas analysis

Forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_{1.0}$) were measured using a Chestac-25F system (Chest, Tokyo, Japan). The diffusing capacity for carbon monoxide (D_{Lco}) was measured by the single-breath carbon monoxide method. Arterial blood was drawn at rest and examined with a blood gas analyser (ABL™520 Blood Gas System, Radiometer Medical A/S, Copenhagen, Denmark).

Exercise protocol

All study subjects underwent cardiopulmonary exercise testing on an upright cycle ergometer (EM840, SIEMENS, Munich, Germany). The protocol consisted of 0 Watts for 3 min for warm-up and a 10-Watt ramp increment every minute until symptomatic limitation. Pulmonary oxygen consumption ($\dot{V}_{O2}$) was measured continuously using a respiratory monitoring system (Respiromonitor AE-300, Minato Medical Science, Osaka, Japan). Percutaneous oxygen saturation (SpO_2) was measured continuously by pulse oximetry (Pulse oximeter 520-US, Criticare Systems, Inc., Waukesha, WI, USA). Predicted peak $\dot{V}_{O2}$ was calculated from the equations of Wasserman et al[10].

NIR spectroscopy

Oxygen saturation in the vastus lateralis muscle was measured using NIRO200 SR spectrometer (Hamamatsu Hotonics, Hamamatsu, Japan). Its mechanical structure and principle of measurement have been previously described[8]. In brief, the instrument consists of a probe, a measurement unit, and a display unit. The probe has an emitter and a detector. Light of three wavelengths (775, 810, and 850 nm) is irradiated from the emitter and sensed by the detector, which is 4 cm distant from the emitter. The ratio of oxygenated to total concentration of myoglobin and hemoglobin is computed from light attenuation using the photon diffusion equation. NIR spectroscopy is unable to distinguish signals of hemoglobin from those of myoglobin because they have identical spectral characteristics.

The probe was positioned on the lower one-third of the right vastus lateralis muscle. Tissue oxygenation was measured continuously during exercise every 2 seconds. Decrease of oxygen saturation in the vastus lateralis muscle during exercise was evaluated by the slope calculated using linear regression analysis as described previously[11].

Statistical analysis

All values were presented as mean±SD. Statistical analysis was performed using StatView 5.0 software (StatView, Inc., Berkeley, CA, USA). Mann-Whitney's U test was used to compare data between patients with COPD and control subjects. Repeated measurements ANOVA and the Sheffé test were used to compare values of SmO_2 across time. Correlation analysis was performed using Pearson's technique between SmO_2 slope and the variables obtained by pulmonary function tests and exercise testing in patients with COPD. Stepwise regression analysis was performed for patients with COPD using SmO_2 slope as the dependent variable and BMI, peak SpO_2 (SpO_{2peak}), and % predicted of peak $\dot{V}_{O2}$ ($\%\dot{V}_{O2peak}$) as independent variables. The significant level was set at $p<0.05$.

Results

Characteristics of the study subjects are summarized in Table 1. BMI was significantly lower

in patients with COPD than in control subjects. Patients with COPD exhibited limitation of both airflow and diffusion. SpO_2 at rest (SpO_{2rest}) did not differ significantly between the two groups. Results of cardiopulmonary exercise testing are shown in Table 2. Peak $\dot{V}_{O2}$ ($\dot{V}_{O2peak}$), peak work

Table 1. Characteristics of study subjects

	COPD	Controls
N	16	10
Age	70.0±4.9	67.2±4.8
BMI (kg/m^2)	20.5±2.7*	23.7±2.3
$FEV_{1.0}$ (% predicted)	53.1±19.8*	92.6±14.8
$FEV_{1.0}$/FVC (%)	44.4±12.7*	77.9±6.6
$\%D_{Lco}$ (%)	73.2±24.8	NE
PaO_{2rest} (mm Hg)	74.3±9.4	NE
SpO_{2rest} (%)	97.6±1.3	98.4±0.7

Values are mean±SD.
NE: not evaluated.
*: significantly different from control subjects ($p<0.05$).
BMI, body mass index; $FEV_{1.0}$, forced expiratory volume in one second; FVC, forced vital capacity; D_{Lco}, diffusing capacity for carbon monoxide; PaO_{2rest}, arterial partial pressure of oxygen at rest; SpO_{2rest}, percutaneous oxygen saturation at rest.

Table 2. Results of cardiopulmonary exercise testing

	COPD	Controls
W_{peak} (Watt)	73.3±18.8*	112.8±18.7
$\dot{V}_{O2peak}$ (L/min)	0.89±0.23*	1.55±0.24
$\dot{V}_{O2peak}$ (% predicted)	68±12*	96±11
SpO_{2peak} (%)	90.7±6.5*	97.5±0.7

*: significantly different from control subjects ($p<0.05$).
W_{peak}, peak work rate; $\dot{V}_{O2peak}$, peak pulmonary oxygen consumption; SpO_{2peak}, percutaneous oxygen saturation at peak exercise.

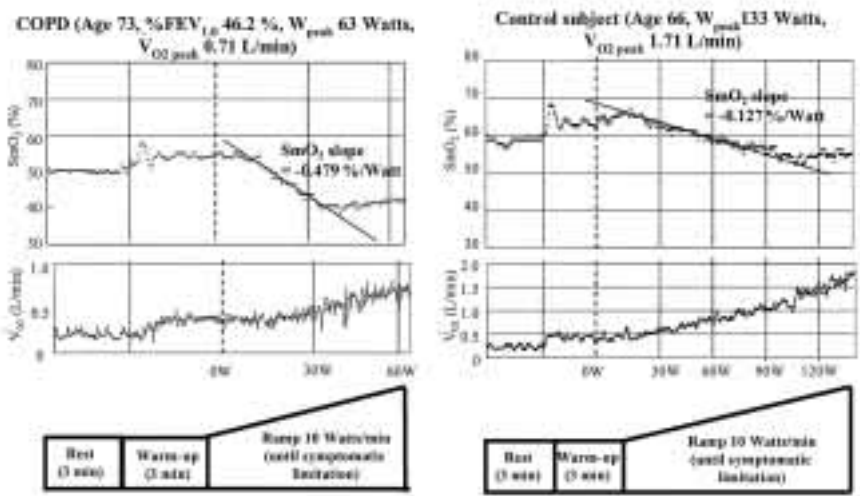

Figure 1. Typical time-trend data of oxygen saturation in the vastus lateralis muscle (SmO_2) during incremental cycle exercise in a patient with COPD (right) and a control subject (left).
$\%FEV_{1.0}$, forced expiratory volume in one second, % predicted; W_{peak}, peak work rate; $\dot{V}_{O2peak}$, peak pulmonary oxygen consumption.

rate (W_{peak}), and peak SpO_2 (SpO_{2peak}) were significantly lower in patients with COPD than in control subjects.

Figure 1 shows results of SmO_2 in a representative case of a patient with COPD and a healthy subject, and Table 3 summarizes values of SmO_2 before and during exercise. SmO_2 began to

Table 3. Changes in oxygen saturation of the vastus lateralis muscle (SmO_2) during exercise

	COPD			Healthy subjects		
	Rest	Warm-up	Peak	Rest	Warm-up	Peak
SmO_2 (%)	54.9±6.2	56.9±6.0	47.3±6.8*†	58.4±8.0	60.7±5.8	49.9±7.7*†

*: significantly different from value at warm-up in the same group ($p<0.05$).
†: significantly different from value at rest in the same group ($p<0.05$).

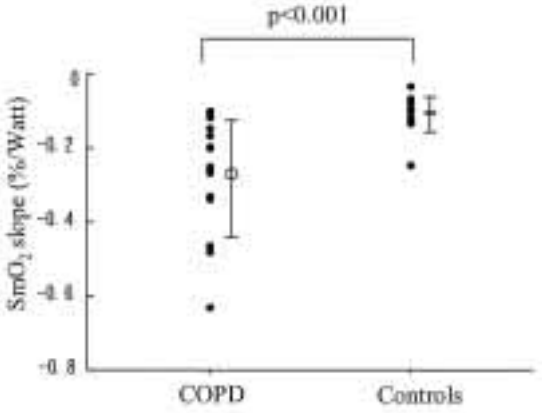

Figure 2. Comparison of SmO_2 slope during exercise between patients with COPD and healthy subjects.
Bars show mean±SD.

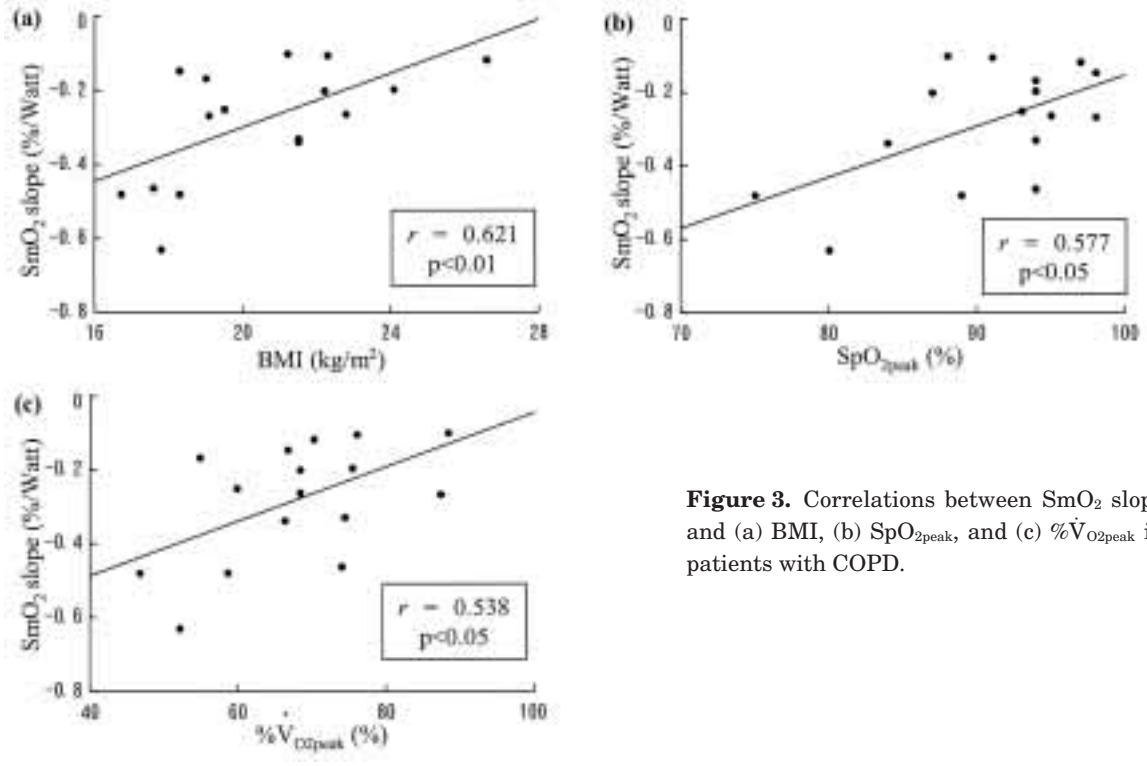

Figure 3. Correlations between SmO_2 slope and (a) BMI, (b) SpO_{2peak}, and (c) $\%\dot{V}_{O2peak}$ in patients with COPD.

decrease with exercise at around 20 Watts in both groups. Decrease in SmO_2 was in linear fashion with respect to increase in work rate (SmO_2 slope), and subsequently SmO_2 reached the nadir. SmO_2 at peak exercise was significantly lower than SmO_2 at warm-up in both patients with COPD and control subjects. No significant difference was found in SmO_2 between patients with COPD and control subjects at rest ($p=0.37$), at warm-up ($p=0.10$), or at the end of peak exercise ($p=0.34$).

SmO_2 slope was much steeper in patients with COPD than that in control subjects (-0.282 ± 0.159 vs -0.107 ± 0.057 %/Watt, $p<0.001$) (Fig. 2). A significant correlation was found between SmO_2 slope and BMI ($r=0.621$, $p<0.01$), SpO_{2peak} ($r=0.577$, $p<0.05$), and $\%\dot{V}_{O2peak}$ ($r=0.538$, $p<0.05$) in patients with COPD (Fig. 3). In stepwise regression analysis, BMI was found to be a significant determinant of SmO_2 slope (Table 4).

Table 4. Stepwise regression analysis for SmO_2 slope in patients with COPD

	B	SE	β	t	p
BMI (kg/m²)	0.036	0.012	0.621	2.961	0.01
(Intercept)	−1.031	0.255	−1.031	−4.045	<0.005

$R^2=0.341$, $F=8.769$.
B, regression coefficient; SE, standard error; β, standardized partial regression coefficient.

Discussion

In this study, we used SR spectroscopy to measure oxygen saturation in the vastus lateralis muscle and found that muscle oxygenation was impaired during exercise in patients with COPD. In addition, we found in stepwise regression analysis that loss of body mass was a significant determinant of SmO_2 slope in patients with COPD.

In patients with COPD, loss of body mass is attributed mainly to loss of skeletal muscle mass[2]. The finding of a significant correlation between SmO_2 slope and BMI suggests that the change in muscle oxygenation with respect to increase in work rate may be associated with loss of skeletal muscle mass. Alteration of muscle fiber type in COPD is characterized by increased proportion of type Ⅱ, ⅡA and ⅡX fibers[4,5]. In biochemical aspects, the activity of oxidative enzymes catalyzing ATP production is decreased in the vastus lateralis muscle in patients with COPD[6]. Thus, impairment of change in oxygenation of exercising muscle may be due to change of muscle fiber type and impairment of oxidative metabolism in patients with COPD. Moreover, oxygen cost of ventilation has been shown to correlate negatively with BMI in patients with COPD[12]. Therefore, impairment of change in oxygenation in the vastus lateralis muscle may also be due to increased oxygen consumption in the respiratory muscle during exercise in patients with COPD.

Decrease in central venous oxygen saturation is greater at maximal exercise in hypoxemic than in normoxemic conditions[13]. Tissue hypoxia is associated with exercise-induced hypoxemia in patients with COPD[1]. In transporting oxygen to the mitochondria, myoglobin plays a fundamental role as a determinant of intracellular oxygen pressure[14]. Since the signals of NIR spectroscopy express mainly myoglobin oxygenation[15], the finding of greater change in muscle oxygenation with lower work rate detected by SR spectroscopy suggests that mitochondrial

oxygen transport of the skeletal muscle may be impaired in patients with COPD.

In this study, the value of SmO_2 at peak exercise was similar in patients with COPD and control subjects, indicating that the decrease in SmO_2 with respect to increase in work rate was greater in patients with COPD with exercise intolerance than in control subjects. We consider that SmO_2 slope rather than the value of SmO_2 may reflect impairment of muscle oxygenation during exercise in COPD. Exercise intolerance in COPD consists of multiple factors such as ventilatory limitation, gas exchange disorder, and skeletal muscle dysfunction. In our study, BMI alone was found to be a significant determinant of SmO_2 slope in stepwise regression analysis in patients with COPD. Simultaneous progression of these multiple disorders in COPD may explain the correlation between $\%\dot{V}_{O2peak}$ and SmO_2 slope in simple correlation analysis without significant correlation in stepwise regression analysis.

NIR spectroscopy is useful because it enables non-invasive and continuous measurement of change in muscle oxygenation during exercise. With the previous method of NIR spectroscopy, Beer-Lambert method, direct measurement of tissue oxygen saturation is impossible[7]. Therefore, clinical application of this method is limited with respect to the study of skeletal muscle dysfunction[16]. SR spectroscopy has enabled measurement of tissue oxygen saturation and comparison of muscle oxygen saturation data between subjects[8]. In our study, oxygen saturation in the vastus lateralis muscle began to decrease with exercise in linear fashion at approximately 20 Watts, and subsequently reached the nadir. This result is consistent with previous finding of time-trend change in oxymyoglobin and oxyhemonglobin detected by Beer-Lambert spectroscopy[17].

The limitation of the present study is that SR spectroscopy can not be used to determine the reason for impairment of oxygen supply to exercising muscle. A recent study using vascular catheterization has shown that oxygen extraction by exercising leg is smaller but oxygen delivery is larger in patients with moderate to severe COPD than in control subjects[5]. Muscle oxygen saturation is determined by oxygen extraction and oxygen delivery. The finding of no significant difference in SmO_2 value at peak exercise between patients with COPD and healthy subjects in the present study may be due to increase in oxygen delivery despite lower oxygen extraction. Another non-invasive technique will be required to be developed to identify the determinants of muscle oxygen consumption.

In conclusion, we have demonstrated using SR spectroscopy that muscle oxygenation is impaired in relation to exercise intolerance in patients with COPD, and that BMI is a strong contributor to the decrease of muscle oxygen saturation with respect to increase in work rate in COPD. SR spectroscopy will aid clinical investigation of the dynamics of muscle oxygenation in research on the pathophysiology of skeletal muscle dysfunction.

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