Activation of the Prefrontal Cortex Is Associated with Exertional Dyspnea in Chronic Obstructive Pulmonary Disease

Yuji Higashimoto^a Noritsugu Honda^a Toshiyuki Yamagata^b Toshiki Matsuoka^d
Kazushige Maeda^a Rhyuji Satoh^b Osamu Nishiyama^b Hiroyuki Sano^b
Takashi Iwanaga^b Takayuki Miyara^b Masato Muraki^b Katsuyuki Tomita^b
Hiroaki Kume^b Ichiro Miyai^c Yuji Tohda^b Kanji Fukuda^a

Departments of ^aRehabilitation Medicine and ^bRespiratory Medicine and Allergology, Kinki University, Faculty of Medicine, and ^cNeurorehabilitation Research Institute, Morinomiya Hospital, and Department of Neurology, Osaka University Graduate School of Medicine, Osaka, Japan; ^dBiomedical Engineering University of Michigan, Ann Arbor, Mich., USA

Key Words

Chronic obstructive pulmonary disease • Dyspnea • Exercise • Near-infrared spectroscopy

Abstract

Background: Exertional dyspnea is the primary symptom that limits exercise in patients with chronic obstructive pulmonary disease (COPD). It is unknown which activated brain area is associated with this symptom in COPD patients. **Objectives:** To investigate the activation of cortical areas associated with dyspnea during exercise in COPD patients. **Methods:** COPD patients (n = 10) and age-matched controls (n = 10) performed mild-intensity constant work rate cycle exercise (40% of their symptom-limited peak work rates) for 10 min, while cerebral hemodynamics and oxygenation were measured by near-infrared spectroscopy (NIRS). Ventilatory responses (breathing pattern and pulmonary gas exchange) and Borg scale ratings of dyspnea and leg fatigue were measured during exercise. Three NIRS probes were placed over the prefrontal and temporoparietal cortical regions of the subjects' heads. Changes in cortical oxyhemoglobin (oxy-Hb), deoxyhemoglobin (deoxy-Hb), and total hemoglobin

(total Hb) concentrations from baseline recordings were measured. Increased oxy-Hb (oxygenation) was assumed to reflect cortical activation. **Results:** Oxy-Hb concentration was significantly increased in the prefrontal region during exercise in both groups but not in the temporoparietal regions. The change in prefrontal oxy-Hb concentration of COPD patients was not different from that of controls. Dyspnea scores were positively correlated with changes in oxy-Hb concentrations of the prefrontal regions in both groups. Multivariate analysis showed that oxy-Hb concentration in the prefrontal region was the best predictor of dyspnea in both groups. **Conclusions:** Exertional dyspnea was related to activation (oxygenation) of the prefrontal cortex in COPD patients and control subjects. Copyright © 2011 S. Karger AG, Basel

Introduction

Patients with chronic obstructive pulmonary disease (COPD) are often limited in their activities due to the sensation of dyspnea. Reductions in overall functional status, quality of life, and disability are frequently conse-

quences of this symptom. Patients' 'fear of dyspnea' may lead to further avoidance of otherwise achievable physical activities and cause additional debility. Thus, alleviating dyspnea with an overall objective of improving activity levels is an important goal of treatment [1].

Dyspnea is a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. This experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses [2]. The Borg category scale is increasingly being used to measure the intensity of dyspnea during cardiopulmonary exercise testing of COPD patients [3–5]. With some recent methodological improvements, this subjective scale remains the most frequently used measure of exertional dyspnea perception [4].

Recent reports using functional magnetic resonance imaging (fMRI) show that activation of the limbic system, amygdala and anterior insula is essential for dyspnea perception [6, 7]. Evans et al. [6] reported activation of the anterior insula, anterior singulate, operculum, cerebellum, amygdala, thalamus and basal ganglia associated with 'air hunger' evoked by lower tidal volume ventilation. Von Leupoldt et al. [7] demonstrated that resistive-load breathing activated the sensory motor cortex, supplementary motor cortex and insular cortex associated with the intensity (sensory aspect) of dyspnea. They also evaluated the affective aspect (unpleasantness) of dyspnea induced by viewing a standardized emotional picture series; this aspect of dyspnea was related to the activation of the limbic system (right anterior insula and right amygdala). However, in these previous studies, dyspnea was induced by resistive-load breathing, CO₂ inhalation, or reduced tidal volume with mechanical ventilation in healthy subjects at rest. In contrast, little is known about brain activation in COPD patients during exercise or the areas of the cortex that are related to dyspnea in these patients.

Positron emission tomography scanning and fMRI have been used in a wide variety of investigative contexts. Both methods can measure regional and global cerebral blood flows, which are increased during neural activity. However, the experimental contexts in which these techniques are used are quite different from normal daily environments, require strict motion restrictions and may be stressful to subjects [8]. A recent advance in the multichannel near-infrared spectroscopy (NIRS) technique, NIR optical topography, has provided functional brain imaging with improved spatial resolution and greater temporal resolution in both adults and infants [9, 10].

NIRS is a noninvasive method for detecting dynamic changes in the concentrations of oxyhemoglobin (oxy-Hb), deoxyhemoglobin (deoxy-Hb) and total hemoglobin (total Hb). NIRS is based on the assumption that an increase in Hb concentration represents an increase in blood flow, which in turn reflects neural activation. Thus, neural activation of cortical regions can be continuously monitored, even during exercise [11]. In particular, increased oxy-Hb concentrations have been assumed to indicate cortical activation [12]. A number of papers have provided detailed descriptions of the principles underlying NIRS [10, 13, 14]. Previous studies have suggested that vascular response properties measured using NIRS are comparable to those described for the blood oxygen level dependence (BOLD) effect in fMRI [15, 16].

In this study, we monitored cortex activity (as mirrored by hemodynamic responses) with multichannel NIRS during cycle exercise to determine which areas of cortex activation in COPD patients were associated with the perception of exertional dyspnea.

Methods

Subjects

Ten right-handed, stable symptomatic male patients with COPD were recruited from patients seen at the Department of Respiratory Medicine and Allergology at Kinki University Hospital. Patients were excluded if they had (1) other unstable medical conditions that could cause or contribute to breathlessness (i.e. metabolic, cardiovascular or other respiratory diseases) or (2) other disorders that could interfere with exercise testing, such as neuromuscular diseases or musculoskeletal problems. We also recruited 10 age-matched healthy male volunteers. Each subject was seen three times over a 5-day time period. At visit 1, spirometry was performed to ensure that the subject met the inclusion criteria. At visit 2, incremental exercise testing was conducted. At visit 3, constant work rate exercise (CWRE) was performed on a cycling ergometer. All participants gave signed informed consent and the protocol was approved by the Committee for Ethics at Kinki University School of Medicine.

Multichannel NIRS

We used an NIRS instrument (ETG-7100, Hitachi Medical Corporation, Tokyo, Japan) that measured the time course of relative changes in the concentrations of oxy-Hb and deoxy-Hb with multiple channels, 0.1 s time resolution, and 2 wavelengths of NIR light (780 and 830 nm). Data analyses were based on the modified Lambert-Beer law [17]. During cortical activity, a neurovascular process occurs whereby changes occur in cerebral blood flow, volume and metabolic rate of oxygen consumption. This primarily manifests as an increased demand for oxygen, with the local vasculature responding by flooding the cortical area and surrounding tissue with oxy-Hb, and is usually accompanied by a corresponding drop in deoxy-Hb [8]. Because base-

line hemoglobin oxygenation varied among subjects, we evaluated the relative changes in oxy-Hb and deoxy-Hb from baseline values determined at the start of the measurement period. Also, as baseline hemoglobin oxygenation may be affected by arterial oxygen saturation, the baseline was adjusted for 10 s just before recording.

Because the precise optical path length was unknown, the unit of measurement used was molar concentration multiplied by length (mM·mm). Detailed descriptions of the principles underlying NIRS have been published previously [10, 14, 18]. We placed 3 arrays mounted on a flexible cap over the prefrontal (3 × 5 array; 8 incident and 7 detection optical fibers) and temporoparietal regions (4 × 4 array; 8 incident and 8 detection optical fibers) of each hemisphere. The distance between incident and detection positions was 3 cm. Each pair of adjacent incident and detection fibers defined a single measurement channel, which enabled us to simultaneously measure the time courses of oxy-Hb and deoxy-Hb signals across 70 measurement channels (24 channels in each temporoparietal probe and 22 channels in the prefrontal probe). The measured area of each hemisphere of each subject was correctly positioned by using the nasion, vertex (Cz), inion, and tragus as skull landmarks. The prefrontal probe was placed just above the nasion. Two temporoparietal probes were placed symmetrically on both sides of Cz. The overall average changes from baseline in concentrations of oxy-Hb, deoxy-Hb, and total Hb were calculated for each probe (prefrontal probe and 2 temporal probes) each minute. An increased concentration of oxy-Hb was assumed to indicate cortex activation, increased deoxy-Hb indicated deactivation and increased total Hb, total cortex blood flow [9].

With regard to the NIRS measurements, the exact probe positions may not always have accurately corresponded to the targeted underlying brain regions. However, Okamoto and Dan [16] and Okamoto et al. [19] showed that the locations of 10–20 cortical projection points for the standard Montreal Neurological Institute (MNI) or Talairach space could be estimated with an average standard deviation of 8 mm. Based on this estimation, the prefrontal probe was targeted near Brodmann areas 9 and 10 in the prefrontal cortex.

Mild Cycling CWRE

Symptom-limited exercise tests used an electronically braked cycle ergometer (Aerobike75XLII, Combi Wellness, Tokyo, Japan) and breath-by-breath gas analysis was done using an AE-310S (Minato Medical Science, Osaka, Japan) in a temperature-controlled room. Mild cycling CWRE with NIRS recording was performed at a working intensity corresponding to 40% of a subject's symptom-limited peak work rate achieved during the incremental exercise test at visit 3. To avoid the interfusion of the effects of exercise intensity and perceived exertion on prefrontal activation, the exercise intensity was set to a stable level (constant work rate) [20]. Ide et al. [21] reported that arterial lactate accumulation did not change significantly during mild exercise (30% of maximum oxygen consumption, $\text{VO}_{2\text{max}}$), but it increased during maximal exercise (60% of $\text{VO}_{2\text{max}}$). Accordingly, the arterial pH did not change during mild exercise, but it decreased at a higher work rate. Thus, we used a mild level of exercise (40% of a subject's symptom-limited peak work rate); most patients could continue exercising for 10 min without significant leg fatigue, although they still exhibited some degree of dyspnea. The intensities of dys-

pnea and leg fatigue were determined each minute during both exercise and resting periods using the 10-point Borg scale [3, 22]. Cardiopulmonary and breathing pattern parameters were continuously measured during exercise.

Statistical Analysis

Results are given as the means $\pm$ standard errors of the means. All variables, including oxy-Hb, deoxy-Hb, total Hb, blood pressures (BPs), oxygen saturation and ventilation measurements, were evaluated as averages at each minute during CWRE (10 measuring points in each subject). The data of figure 1 (time course of hemoglobin concentrations) were analyzed using repeated-measures ANOVA, followed by individual contrasts (Dunnett's method). Correlation analyses were performed using Pearson's correlation (fig. 2) and partial correlation coefficients adjusted for age. We also used standard least-squares fitting with the restricted maximum likelihood method for multiple-regression analyses. The F ratio is equal to the square of a t test statistic. A large F ratio indicated that the group of regressors should be included in the model. Analyses were performed using JMP 80.1 (SAS Institute, Inc.) and SPSS 15.0 (SPSS Japan, Inc., Tokyo, Japan).

Results

Subjects' Characteristics

The clinical characteristics and the main results of incremental cardiopulmonary exercise testing are shown in table 1. Mild CWRE was performed with average watt loads of 35.9 ± 3.6 and 25.0 ± 2.2 in controls and COPD patients, respectively (40% of the subjects' symptom-limited peak work rates).

During CWRE, peak dyspnea (Borg scale) was higher in COPD patients (3.9 ± 0.6) than in controls (1.3 ± 0.4 ; $p < 0.05$, unpaired t test), while peak leg fatigue was similar in both groups.

Time Courses of Oxy-Hb, Deoxy-Hb and Total Hb Concentrations

Overall averages of oxy-Hb, deoxy-Hb and total Hb concentrations were calculated at each minute of CWRE in the prefrontal region (fig. 1a, b), left temporoparietal region (fig. 1c, d), and right temporoparietal region (fig. 1e, f). With regard to the prefrontal probe, oxy-Hb increased during CWRE. The changes in oxy-Hb were significant at each exercise time point between 8 and 10 min compared to the rest period in controls, and between 9 and 10 min in COPD patients ($p < 0.05$) (fig. 1a, b). The deoxy-Hb concentrations tended to decrease and total Hb tended to increase during CWRE, but these changes were not significant in either group. These results suggest that the prefrontal cortex was activated, but that cortex blood flow did not change during CWRE.

Fig. 1. Time courses of oxy-Hb (●), total-Hb (○), and deoxy-Hb (▲) during CWRE. Prefrontal region (average of 22 channels) in control (a) and COPD (b) subjects; left temporoparietal region (average of 24 channels) in control (c) and COPD (d) subjects, and right temporoparietal region (average of 24 channels) in control (e) and COPD (f) subjects. Results are the means (with standard error bars) of 10 subjects/group. * $p < 0.05$, significant difference from rest.

Fig. 2. Correlations of dyspnea scale ratings with prefrontal area oxy-Hb concentrations at peak perception of dyspnea. When subjects perceived strongest exertion (peak dyspnea), the changes in oxy-Hb concentration were significantly correlated with dyspnea in both the control group (**a**, $n = 10$) and the COPD group (**b**, $n = 10$).

Table 1. Subjects' characteristics

Characteristics	Control ($n = 10$)	COPD ($n = 10$)	P value
Age, years	70.6 ± 2.7	69.0 ± 1.8	NS
Male	10	10	
Smoking status			
Current smoker	0	4	
Nonsmoker	7	6	
Never smoker	3	0	
Smoking history, pack-years	11.5 ± 5.3	82.0 ± 21.1	<0.01
BMI	22.8 ± 0.4	22.3 ± 1.3	NS
FEV ₁ /FVC ratio	82.1 ± 2.5	51.3 ± 7.1	<0.001
FEV ₁ , liters	2.6 ± 0.1	1.5 ± 0.2	<0.001
FEV ₁ , % predicted	91.7 ± 3.7	54.4 ± 7.2	<0.001
FVC, liters	3.1 ± 0.2	2.9 ± 0.3	NS
SaO ₂ , %	98.0 ± 0.3	96.3 ± 0.5	<0.01
COPD stage			
I		1	
II		6	
III		2	
IV		1	
MRC dyspnea scale	0.2 ± 0.1	2.0 ± 0.1	<0.0001
Peak work rate, W	96.9 ± 12.5	70.3 ± 6.8	NS
Peak VO ₂ , ml/min	998 ± 117	927 ± 89	NS
Anaerobic threshold, W	58.9 ± 5.5	44.6 ± 4.0	NS

Results are means $\pm$ SEMs; NS = not significant.

The changes in oxy-Hb and total-Hb were smaller in COPD patients than in controls throughout CWRE, although these differences were not significant. In the left and right temporoparietal regions, oxy-Hb and total Hb tended to increase during CWRE, but these changes did not achieve statistical significance in either group (fig. 1c–f). The changes in deoxy-Hb were not significant during CWRE, with the exception of a significant reduction during the recovery time. Thus, the prefrontal region was activated during CWRE, whereas the temporoparietal regions were not.

Correlations between Borg Scale Ratings for Dyspnea and Leg Fatigue with Ventilatory Parameters and Concentrations of Oxy-Hb, Deoxy-Hb, and Total Hb

The peak ratings of dyspnea (Borg scale) were significantly correlated with the changes in oxy-Hb concentration in both groups (fig. 2, Pearson's correlation). Peak Borg scale ratings of leg fatigue were also correlated with oxy-Hb concentrations (control: $r = 0.691$, $p < 0.05$, $n = 10$, and COPD: $r = 0.814$, $p < 0.01$, $n = 10$).

For all measured points ($n = 100$ for each group; 10 measured points for each subject), correlations of dyspnea and leg fatigue scores with ventilatory parameters, oxygen saturations, BPs and oxy-Hb concentrations were calculated using adjustments for subjects' ages (table 2). Again, dyspnea and leg fatigue scores showed significant positive correlations with changes in oxy-Hb concentrations in the prefrontal region.

Table 2. Age-adjusted correlation coefficients for dyspnea Borg scores with ventilatory parameters and concentration changes in oxy-Hb during CWRE

	Control				COPD			
	dyspnea		leg fatigue		dyspnea		leg fatigue	
	r value ¹	p value	r value ¹	p value	r value ¹	p value	r value ¹	p value
Prefrontal oxy-Hb	0.68	<0.01	0.61	<0.01	0.78	<0.01	0.74	<0.01
Leg fatigue	0.93	<0.01	–	–	0.92	<0.01	–	–
SaO ₂	–0.35	<0.01	–0.43	<0.01	–0.05	0.72	0.01	0.93
VO ₂	0.32	<0.01	0.33	<0.01	–0.02	0.88	–0.16	0.23
VCO ₂	0.29	<0.05	0.29	<0.05	0.10	0.48	–0.04	0.79
Systolic BP	0.45	<0.001	0.51	<0.01	0.30	<0.05	0.42	<0.01
Diastolic BP	0.27	<0.05	0.24	<0.05	0.39	<0.01	0.39	<0.01
Respiratory rate	0.19	0.09	0.05	0.65	–0.03	0.85	0.05	0.72
VE	0.19	0.09	0.14	0.23	0.48	<0.01	0.36	<0.05
VD/VT	–0.17	0.12	–0.23	<0.05	0.09	0.54	0.28	<0.05
VT/T _i	0.07	0.53	0.04	0.72	0.30	<0.05	0.12	0.37
T _i /T _{tot}	0.27	<0.05	0.24	<0.05	0.00	0.99	0.14	0.30
PETCO ₂	0.17	0.13	0.28	<0.05	–0.27	<0.05	–0.22	0.10
PETO ₂	–0.19	0.08	–0.30	<0.05	0.44	<0.01	0.43	<0.01
VT	0.04	0.72	0.10	0.38	0.32	<0.05	0.18	0.20
Heart rate	–0.01	0.93	0.07	0.52	0.09	0.52	0.12	0.40

¹ Age-adjusted correlation coefficient for dyspnea or leg fatigue. Prefrontal = Prefrontal probe, VT/T_i = mean inspiratory flow; T_i/T_{tot} = inspiratory duty cycle; VD/VT = dead space/tidal volume ratio.

Regarding ventilation parameters in the control group, oxygen consumption (VO₂), rate of elimination of carbon dioxide (VCO₂), inspiratory time/total time ratio (T_i/T_{tot}), systolic BP and diastolic BP had significant positive correlations with dyspnea, while oxygen saturation (SaO₂) was negatively correlated with dyspnea. In COPD patients, there were significant positive correlations between dyspnea and ventilation (VE), tidal volume/inspiratory time ratio (VT/T_i), end-tidal oxygen tension (PETO₂), VT, systolic BP, and diastolic BP, while dyspnea and PETO₂ were negatively correlated. In addition, dyspnea and leg fatigue scores were highly correlated with each other in both groups. Prefrontal region oxy-Hb concentration was negatively correlated with SaO₂ (control: $r = -0.45$, $p < 0.0001$; COPD: $r = -0.39$, $p < 0.01$), and positively correlated with both systolic BP (control: $r = 0.37$, $p < 0.001$; COPD: $r = 0.30$, $p < 0.05$) and diastolic BP (control: $r = 0.29$, $p < 0.01$; COPD: $r = 0.29$, $p < 0.05$).

Multiple-Regression Analysis

Physiological contributors to exertional dyspnea were determined by multiple-regression analysis for each group (table 3). Candidate independent variables that showed

statistically significant correlations with dyspnea by univariate analysis (table 2) were included in a least-squares regression analysis to determine the final variables for the model. In control subjects, the variables identified as significant by the least-squares model for dyspnea were prefrontal region oxy-Hb concentration, VCO₂ and SaO₂. In COPD patients, systolic BP and prefrontal region oxy-Hb concentration were identified as independent variables for dyspnea. Prefrontal region oxy-Hb concentration was the best predictor of dyspnea in both groups.

Next, we examined which factors affected the changes of oxy-Hb concentrations (cortical activation) in the prefrontal area. Multiple regression analysis showed that VO₂, PETCO₂, PETO₂, SaO₂, and dyspnea scores were significantly correlated with prefrontal region oxy-Hb concentrations in control subjects. In contrast, only the dyspnea score, but not leg fatigue, was identified as a significant variable for prefrontal region oxy-Hb concentrations in COPD patients (table 4).

In summary, oxy-Hb concentration was significantly increased in the prefrontal region during exercise and the change in oxy-Hb concentration in COPD patients was not different from that of controls. Dyspnea scores were

Table 3. Least-squares regression model: relationships of prefrontal region oxy-Hb concentrations and ventilatory parameters to dyspnea scores

Factors	Dyspnea in controls			Dyspnea in COPD		
	d.f.	F	p value	d.f.	F	p value
VT/T _i	–	–	–	1	2.71	0.10
V _E	–	–	–	1	0.06	0.80
V _T	–	–	–	1	0.64	0.43
T _i /T _{tot}	1	0.00	0.94	–	–	–
V _{O₂}	1	0.20	0.65	–	–	–
V _{CO₂}	1	10.3	<0.01	–	–	–
PETCO ₂	–	–	–	1	0.14	0.71
PETO ₂	–	–	–	1	0.03	0.87
Systolic BP	1	0.14	0.71	1	15.8	<0.001
Diastolic BP	1	0.13	0.72	1	0.72	0.40
SaO ₂	1	5.71	<0.05	–	–	–
Age	1	0.76	0.41	1	0.51	0.51
Prefrontal region oxy-Hb	1	73.4	<0.0001	1	76.4	<0.0001

Results refer to mixed models (whole model: control $r^2 = 0.87$, COPD $r^2 = 0.92$) that further included patients as a random factor, which explained 82.6 and 80.2% of the variance (restricted maximum likelihood estimates) for dyspnea scores of controls and COPD patients, respectively.

d.f. = Degrees of freedom, F = F ratio. Other abbreviations as in table 2. Figures in bold type show significant correlations.

Table 4. Least-squares regression model: relationships of dyspnea score, leg fatigue and ventilatory parameters to prefrontal region oxy-Hb concentrations

Factors	Oxy-Hb in control			Oxy-Hb in COPD		
	d.f.	F	p value	d.f.	F	p value
VD/VT	–	–	–	1	2.16	0.15
VT/T _i	1	0.03	0.86	–	–	–
V _E	1	0.45	0.50	–	–	–
V _T	1	0.52	0.47	1	0.53	0.48
V _{O₂}	1	6.97	<0.05	1	0.00	0.92
V _{CO₂}	1	2.85	0.10	1	0.29	0.59
PETCO ₂	1	10.2	<0.01	1	0.02	0.89
PETO ₂	1	8.17	<0.01	1	0.10	0.76
Systolic BP	1	0.00	0.97	1	1.94	0.17
Diastolic BP	1	0.11	0.74	1	0.38	0.54
Heart rate	1	1.10	0.30	–	–	–
SaO ₂	1	5.60	<0.05	1	3.17	0.08
Age	1	0.04	0.85	1	0.68	0.45
Leg fatigue	1	0.00	0.98	1	0.12	0.73
Dyspnea	1	19.3	<0.0001	1	14.7	<0.001

Results refer to mixed models (whole model: control $r^2 = 0.92$, COPD $r^2 = 0.84$) that further included patients as a random factor, which explained 83.1 and 42.6% of the variance (restricted maximum likelihood estimates) for the changes in oxy-Hb concentrations in controls and COPD patients, respectively.

d.f. = Degrees of freedom, F = F ratio. Other abbreviations as in table 2. Figures in bold type show significant correlations.

positively correlated with changes in oxy-Hb concentrations in the prefrontal regions in both groups. Multivariate analysis showed that oxy-Hb concentration in the prefrontal region was the best predictor of dyspnea.

Discussion

This study examined cortical activation in relation to exertional dyspnea using NIRS in COPD patients and control subjects. The results showed that cortical activation in the prefrontal area, as indicated by increased oxy-Hb concentrations, corresponded to the levels of exertional dyspnea and that the change in oxy-Hb concentration in COPD patients was not different from that of controls. This is the first report to compare cortical oxygenation between COPD patients and control subjects during exercise.

The changes in oxy-Hb concentrations tended to be lower in COPD patients than in control subjects, while peak dyspnea intensity was higher in COPD patients than

in controls. This discrepancy might be related to differences in SaO₂ because baseline SaO₂ levels were lower in COPD patients than controls. However, we evaluated relative changes in oxy-Hb and deoxy-Hb from baseline levels recorded at the start of the measurement period. In fact, there were negative correlations between oxy-Hb concentrations and SaO₂ levels in both the control and COPD groups. Small decreases in SaO₂ may enhance respiratory drive and dyspnea perception, although SaO₂ was not significantly altered during exercise. More pronounced Hb desaturation could decrease cerebral oxygenation [23].

Subudhi et al. [24] evaluated the prefrontal cortex oxygenation of healthy volunteers during incremental cycle exercise with normoxic (117 torr oxygen pressure, PaO₂) and hypoxic (79 torr PaO₂) conditions; cerebral oxygenation was decreased with hypoxic conditions. Jensen et al. [25] reported that cerebral oxygenation decreased as deoxy-Hb increased during exercise, while oxy-Hb concentration remained unchanged, which caused desaturation in patients with terminal lung diseases. Further research

is needed to examine cortical oxygenation in patients with exercise-induced hypoxemia.

In our study, oxy-Hb concentration increased only in the prefrontal region during exercise in both groups but not in the temporoparietal regions. Two major pathways have been suggested to process respiratory sensations to the cortex [26]. The first pathway arises predominantly from respiratory muscle afferents, is relayed in the brainstem medulla and projects to the ventroposterior thalamus area, from where thalamocortical projections ascend to the primary and secondary somatosensory cortex. Along with other interoceptive sensations, these structures might process the sensory or intensity aspects of dyspnea.

The second pathway includes mainly vagal afferents from the lungs and airways, which are relayed in the brainstem medulla. Brainstem projections ascend to the amygdala and medial dorsal areas of the thalamus, and further to the insula and cingulate cortex. This predominantly limbic pathway might additionally include the hippocampus, operculum, putamen and other prefrontal areas, and might be more associated with the affective components of the experience of breathlessness. This second pathway (sensory aspect of dyspnea) might have been activated and resulted in cortical oxygenation of prefrontal areas in COPD patients and control subjects during exercise.

Nybo et al. [27] reported that the rating of perceived exertion (Borg scale) was correlated with brain activity in the frontal cortex measured by electroencephalogram (EEG) in healthy subjects. They placed EEG electrodes at 1 cm in front of Cz, at the F3, and Oz positions (10–20 system) and measured EEG and rating of perceived exertion during submaximal exercise (60% of VO_2max). Stepwise regression analysis identified the EEG frequency index over the frontal cortex as the best predictor of rating of perceived exertion. Nielsen et al. [28] measured oxy-Hb concentrations in healthy subjects using NIRS probes placed on the forehead just below the hairline during 150-watt exercise with or without resistive breathing. Resistive breathing increased oxy-Hb concentrations; however, they did not measure exertion scores. Our results are consistent with these reports.

In contrast, Shibuya et al. [20] measured prefrontal cortex oxygenation levels of healthy subjects during elbow flexion CWRE with or without muscle spindle stimulation, which can decrease perceived exertion. Cerebral oxygenation increased with exercise, but oxy-Hb concentration was not changed by muscle spindle stimulation. They concluded that perceived exertion was not associated with prefrontal cortex activation. Cortical activation and dyspnea perception may be different when evalua-

tions are made during upper limb exercises and lower limb exercises because upper limb exercises may affect movement of the thorax. Further study is needed to clarify the differences in dyspnea perception and cortical activation associated with upper- and lower-limb exercises.

Increased oxy-Hb concentration might simply be due to increased global cerebral blood flow (gCBF) during exercise. However, gCBF is thought to be regulated in order to remain stable for as long as PaCO_2 is stable and BP stays within the range for cerebral autoregulation [11]. Cycle exercise does not increase gCBF or oxygen uptake by the brain, even though BP increases [29]. In this study, CWRE did not change total Hb concentrations corresponding to cortex blood volumes, and oxy-Hb increased only in the prefrontal area. However, some previous studies reported that gCBF and oxygenation were increased with exercise.

Ide et al. [21] showed that cerebral oxy-Hb and total Hb increased in parallel with increased mean blood velocity in the middle cerebral artery, while mean arterial pressure increased during cycle exercise, even with mild-intensity exercise (30% of VO_2max). By comparison, Nielsen et al. [28] reported that oxy-Hb, deoxy-Hb and total Hb in the prefrontal area were not increased during submaximal exercise (150 W), while these hemoglobin concentrations were increased by resistive-load breathing using a narrow tube [28]. These studies did not examine dyspnea or leg fatigue, and cerebral oxygenation (cortical activation) may be affected by these sensations. In COPD patients, oxy-Hb concentration was correlated with BP, whereas it was not in control subjects. BP may affect cerebral blood volume during exercise in COPD patients. BP did not change during CWRE, and multiple regression analysis showed that BP was not an independent factor correlated with oxy-Hb. However, we cannot neglect the effect of BP on oxy-Hb concentration.

Dyspnea is not a single sensation, as it has multiple qualitative descriptors [30]. The sensory and affective dimensions of dyspnea can be differentiated [31, 32]. Von Leupoldt et al. [32] showed that increasing dyspnea led to higher sensations of unpleasantness (affective dimension of dyspnea) compared to intensity (sensory dimension of dyspnea), which, in turn, under more natural conditions, might motivate adaptive behaviors to change this unpleasant condition. In this study, we did not differentiate between these dimensions. Additional research is clearly required to assess the different dimensions of dyspnea and their relationships to cortical activation in COPD patients.

There are some limitations in the present study. NIRS does not measure the absolute blood flow or absolute ox-

ygenation of the cortex; rather, changes from baseline were measured. Therefore, it is best suited for within-subject comparisons. We could not investigate whole brain activity because NIRS only detects cortical hemodynamics. As positron emission tomography and fMRI are excellent for spatial analysis, these methods are ideal for localizing brain activity. By comparison, NIRS is an excellent tool for temporal analysis. We could easily monitor brain activity during exercise without restrictions.

In conclusion, our study using NIRS demonstrates that there is a correlation between increased prefrontal blood flow and a dyspnea index in both healthy subjects and COPD patients, although this response appears to be attenuated in COPD patients. NIRS could be a new method for exploring the cortical contributions to perceptions of dyspnea in COPD patients and for monitoring changes of this sensation. Further research will be necessary to determine how cortical activation is attenuated in COPD.

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