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Title: Difference in the physiological response to exercise in patients with distinct severity of COPD pathology

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Abstract

Background: Patients with chronic obstructive pulmonary disease (COPD) have reduced exercise tolerance associated with dyspnea. This exercise intolerance is primarily due to impaired ventilatory mechanics, but it is also associated with a combination of factors, including inefficient gas exchange, lactic acidosis at a low work rate, and exercise-induced hypoxemia. The survival prognosis of COPD patients with severely reduced exercise capacity is extremely poor, but the pathophysiology of these patients during exercise remains to be accurately established. The present study aimed to characterize life-threatening factors such as hypoxemia, acidosis, and sympathetic activation during exercise in these patients.

Methods: We monitored changes in life-threatening factors and compared these factors among quartile groups, defined according to their peak oxygen uptake status. Ninety-one COPD patients (82 males, 9 females; average age, 69.7 ± 6.8 years) consecutively underwent incremental cardiopulmonary exercise testing (CPET) using a cycle ergometer. Levels of arterial blood gases, lactate, and catecholamines were measured during CPET.

Results: We found that the pathophysiology of the COPD patients differed among patient groups. Patients with the most severely reduced exercise capacity (peak oxygen uptake ≤ 623 $ml \cdot min^{-1}$) were characterized by exercise-induced steep decrease in arterial oxygen pressure (PaO_2-slope: -78 ± 70 $mmHg \cdot L^{-1} \cdot min^{-1}$), rapid progression of respiratory acidosis, little change in lactic acidosis, and sympathetic activation at low-intensity workload (plasma norepinephrine level, 1.41 ± 0.94 $ng \cdot ml^{-1}$ at 20 W), in addition to the limitation of increase in ventilation and impaired gas exchange.

Conclusions: The mechanisms of exercise intolerance in COPD patients significantly varied among patients with different exercise capacities. Patients with the most severely reduced exercise capacity had the characteristics of exercise-induced hypoxemia, sympathetic overactivity, and progressive respiratory acidosis at low-intensity exercise. These

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life-threatening pathophysiological conditions could be improved by medication and/or pulmonary rehabilitation.

Key Words: COPD, CPET, hypoxemia, sympathetic overactivity, acidosis, peak oxygen uptake

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) have reduced exercise tolerance. Exertional dyspnea (breathlessness) is a symptom that makes COPD patients to stop prematurely during exercise. The survival prognosis of COPD patients with severely reduced exercise capacity is extremely poor. While the reduced exercise capacity is not directly life-threatening, associated factors such as hypoxemia, acidosis, and sympathetic activation can increase the mortality risk in such patients. [1-7] With proper intervention, medication and/or pulmonary rehabilitation, including exercise training and occupational therapy in daily living, survival prognosis can be improved. Unfortunately, the pathophysiology during exercise of COPD patients is not adequately established.

Exercise intolerance in COPD patients is primarily due to impaired ventilatory mechanics, but it is also associated with a combination of several factors, including gas exchange limitation, cardiovascular factors, skeletal-muscular dysfunction, and miscellaneous factors.[8,9] Gas-exchange factors involve impaired ventilation-perfusion relationships that lead to hypoxemia, impaired oxygen delivery, and pulmonary hypertension. It has been established that the severity of dyspnea rapidly increases at work rates above the lactic threshold and that plasma norepinephrine and epinephrine levels also increase in a similar manner during exercise. [10,11] However, we have observed that in some COPD patients with severely reduced exercise capacity, lactic threshold cannot be detected methodologically by estimating the concentration of plasma lactate using the log-log transform of the lactate-oxygen uptake relationships in cardiopulmonary exercise testing (CPET) of clinical practice[12].

Peak oxygen uptake, during incremental CPET, is one of the most important predictors of mortality among the other survival predictors such as forced expiratory volume in one second (FEV_1) or body mass index (BMI) in COPD patients[13-15]. In a previous report[13], the 5-year

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survival rate of patients with the most severely reduced peak oxygen uptake (< 654 $ml \cdot min^{-1}$) was 45% on dividing into quartile groups. The variation among individual COPD patients underpins the need for personalized intervention. However, an improved understanding of COPD pathophysiology is a prerequisite of such intervention and improvement in patients' survival prognosis. The present study aimed to investigate relationships between, and changes in, life-threatening factors such as hypoxemia, acidosis, and sympathetic activation in COPD patients during exercise, and compare these among the divided quartile groups on the basis of peak oxygen uptake status, especially in patients with severely reduced exercise capacity whose survival prognosis is extremely poor.

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Methods

Patients

Patients for this experimental study included consecutively recruited first-visit, COPD outpatients who visited our institution with symptoms of exertional dyspnea (modified Medical Research Council (MRC) dyspnea score ≥ 1) between June 2000 and February 2006.[16,17] All patients had a history of cigarette smoking (at least 40 pack-years), and a ratio of FEV_1 to forced vital capacity (FVC) of less than 0.7, measured 20 min after the inhalation of salbutamol. Patients with the following conditions were excluded: (1) significant diseases (i.e. cardiovascular or neuromuscular diseases) other than COPD that could contribute to dyspnea and exercise limitation; (2) a history of asthma, allergic rhinitis, or atopy; (3) a blood eosinophil count ≥ 600 μL^{-1}; (4) treatment with an anti-allergic drug or anti-histamine drug; (5) tuberculosis (currently active) or definite sequelae of tuberculosis; and (6) history of lung resection. Potential study patients were monitored for 2 months to determine their eligibility for the study and prescribed appropriate medication. In addition, patients with important contraindications to clinical exercise testing,[9] a history of coronary artery disease, acute exacerbation within at least 2 months, and those participating in a pulmonary rehabilitation program were excluded. After obtaining their written informed consent, 91 sedentary outpatients with COPD (82 males and 9 females) were enrolled in this study. The research protocol used in this study was approved by the NHO National Toneyama Hospital institutional review board for experimentation on human subjects and complies with international guidelines for studies involving humans.

Pulmonary function test and CPET

Post-bronchodilator spirometric measurements (FVC and FEV_1) were conducted for all patients by using Autospirometer System 9 (Minato Medical Science, Osaka, Japan)

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according to the recommendations of the American Thoracic Society.[18,19] All spirometric tests were conducted in triplicate, and the highest measurements were used for subsequent analyses. All patients began unloaded pedaling for 2 min and then underwent CPET with progressive increments of 10 W every 2 min by using a bicycle ergometer as previously described.[20,21] Expired gas data were collected breath by breath using a Vmax (Sensor Medics Corporation, Yorba Linda, CA). Measured CPET parameters included heart rate, respiratory frequency, tidal volume, minute ventilation, oxygen uptake, ventilatory equivalent for oxygen and ventilatory equivalent for carbon dioxide, and oxygen pulse. Progressive incremental exercise testing was discontinued when the subjects displayed breathlessness and/or leg fatigue, or notable ECG changes (ST segment depression greater than 2 mm or a short run of premature ventricular contractions). We subsequently divided the enrolled COPD patients into quartile groups (Group A, $\leq$ 623; Group B, 665−803; Group C, 829−1037; Group D, $\geq$1040 ml·min^{-1}) based on their peak oxygen uptake status according to the previous report[12]. Arterial blood samples were drawn from patients through an indwelling radial artery cannula after local anesthesia, before each patient began exercising, when the patient was sitting, during the last 15 s of each exercise stage, and at peak exercise. Arterial blood gases and lactate were immediately measured, in the exercise testing room by using a blood gas analyzer (ABL-800; Radiometer, Tokyo, Japan). The concentrations of arterial plasma catecholamines (norepinephrine and epinephrine) were measured by high-pressure liquid chromatography. The lactate threshold (LT) and norepinephrine threshold (NT) were detected using the log-log transform of the lactate-oxygen uptake and norepinephrine-oxygen uptake relationships.[22]

Dyspnea index(%) = Minute Ventilation (L·min^{-1}) at peak exercise / Maximal Voluntary Ventilation (L·min^{-1}) × 100, Breathing reserve(L/min) = Maximal Voluntary Ventilation (L·min^{-1}) - Minute Ventilation (L·min^{-1}) at peak exercise, HR Reserve (beats·min^{-1}) =

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Predicted maximum HR - HR at peak exercise, PaO_2-slope (mmHg/L) = Difference in PaO_2/ Difference in oxygen uptake between at rest and at peak exercise. ΔNE/Δoxygen uptake ($ng/mL \cdot L^{-1} \cdot min^{-1}$) = Increase in NE/Difference in oxygen uptake between at rest and at peak exercise, $\Delta PaCO_2$ /Δoxygen uptake (mmHg/L) = Difference in $PaCO_2$/Difference in oxygen uptake between at rest and at peak exercise.

The intensity of dyspnea was evaluated during exercise testing using the Borg scale.[23] Before testing, the Borg scale was explained and its endpoints were anchored such that 0 indicated "no difficulty in breathing" and 10 represented "the most severe (maximal) difficulty in breathing that the subject had previously experienced or could imagine." The subjects used this scale to rate dyspnea at rest, every minute during exercise, and at peak exercise. Immediately after exercise cessation and the completion of mechanical measurements, the patients were asked the reason(s) for exercise termination (dyspnea, leg fatigue, both, or other).

Statistical analysis

Statistical analyses were performed using conventional computer analysis (JMP 9, SAS Institute Inc.). Reported values are consistently expressed as mean ± standard deviation. Parametric analyses of variance (One-way ANOVA) for the normally distributed variables and non-parametric test (Kruskal Wallis test) for the non-normally distributed variables were used to determine differences in pathophysiological parameters among the 4 groups of patients. The differences between pairs of groups were analyzed using Tukey-Kramer HSD post hoc comparison. The relationships between the plasma norepinephrine levels and the other parameters obtained from the CPET were assessed using Pearson's correlation coefficients and linear regression analysis. The differences between the groups were considered statistically significant when *P* values were less than 0.05.

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Results

In general, the enrolled patients (n = 91) were elderly (69.7 ± 6.8 years), slender (BMI, 21.0 ± 3.7 $kg \cdot m^{-2}$), and exhibited emphysematous type of COPD, according to the radiographic findings in most cases. Only 12 patients had chronic bronchitis. These are common features among COPD cases in Japan. Furthermore, the pulmonary function of patients showed a mild to very severe obstructive disorder (FEV_1, 1.06 ± 0.45 L; FEV_1 (% predicted), 40.8 ± 16.1; FEV_1/FVC (%), 44.2 ± 10.0) and GOLD stages of 1 (5 patients), 2 (15 patients), 3 (49 patients), and 4 (22 patients). We also found that patients stopped CPET due to breathlessness in 53 cases (59%), leg fatigue in 14 cases (15%), and breathlessness and leg fatigue in 24 cases (26%).

We divided the 91 patients into quartile groups (Group A: 22 patients, Group B: 23 patients, Group C: 23 patients, and Group D: 23 patients) according to their peak oxygen uptake status. The comparison of the static parameters among the 4 COPD groups is shown in Table 1. We found that both FEV_1 and FEV_1 (% predicted) were significantly reduced, and the BMI was significantly lower among patients with reduced exercise capacity. We also tested for differences in factors (FEV_1, FEV_1 (% predicted), and BMI) for which there were originally differences between the pairs of groups. These analyses revealed that the FEV_1 and FEV_1 (% predicted) values in group D were significantly higher than those in groups A, B, and C. Furthermore, we found that the BMI of group A was significantly lower than those of groups C and D.

Comparison of dynamic parameters

Comparison of dynamic parameters among the 4 COPD groups at peak exercise is shown in Table 2.

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1) **Ventilation:** There were no differences in the intensity of dyspnea (Borg scale) at peak exercise among the 4 groups, regardless of their exercise capacity. The 4 groups showed a similar increase in tidal volume in response to the increase in oxygen uptake during an incremental exercise (Figure 1). This increase in tidal volume peaked at a low level with reduced exercise capacity, and the tidal volume and minute ventilation at peak exercise were significantly associated with peak oxygen uptake (r-square =0.64, $P < 0.0001$ and r-square = 0.65, $P < 0.0001$, respectively). Upon comparing the tidal volume at peak exercise for every pair of groups, we found that there were significant differences between all pairs except between groups B and C. The expansion of tidal volume during exercise was extremely limited in COPD patients with the most severely reduced exercise capacity (Group A). On the other hand, the respiratory frequency (f) at peak exercise showed no differences among the 4 groups. However, it varied among the patients; 26 patients (29%) had an elongated expiratory period ($f < 30$ min^{-1}), 51 (56%) had normal breathing ($f = 30-40$ min^{-1}), and 14 (15%) had rapid and shallow breathing ($f > 40$ min^{-1}). In all groups, the breathing reserves were less than 10 L/min and the dyspnea indexes were around 100%. These results represented that the exercise limitation in patients with COPD was mainly caused by ventilatory disorders.

2) **Gas exchange:** During peak exercise, the ventilatory equivalents for oxygen and carbon dioxide remained at a significantly high level in Group A. The ventilatory equivalents for oxygen was more impaired in Group A than in Group C or D, but not more impaired than in Group B; and the ventilatory equivalents for CO_2 was more impaired in Group A than in all other groups, but so was also in Group B. The arterial oxygen pressure linearly decreased in response to the increase in oxygen uptake during exercise (PaO_2-slope). Steep PaO_2-slope was also an important feature among Group A patients. While it varied substantially among individuals, the steepest slope was observed in group A patients (Figure 1).

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3) **Exercise-induced acidosis and contributing factors:** We examined the changes in the mean values of the plasma lactate, $PaCO_2$, arterial blood pH and standard HCO_3 from the at-rest stage to the end of each exercise stage during incremental exercise (Figure 2). The concentrations of lactate were elevated beyond the inflection point (lactic threshold). However, the increase in plasma lactate was lower in Group A than in Groups C ($P < 0.0001$) and D ($P < 0.0001$). Moreover, the decrease in standard HCO_3 related to lactic acidosis was not detectable in Groups A and B. These results indicated that the concentration of lactate in Group A failed to reach a point that result in lactic acidosis. However, the value of arterial pH steeply decreased and $PaCO_2$ rapidly increased at the early stage of exercise in Group A.

The values of arterial pH at rest, and after stages 1 and 2 were significantly correlated with the titers of $PaCO_2$, but not with those of lactate (Table 3). Following stage 2 and at peak exercise, the arterial pH was correlated with both lactate and $PaCO_2$. The decrease in arterial pH resulted from respiratory acidosis at the early stage (~20 W) and, thereafter, from combined respiratory and lactic acidosis. In Groups A and B patients, the arterial pH at peak exercise was mainly due to carbon dioxide retention; however, it was influenced by both carbon dioxide retention and arterial lactate levels among Groups C and D patients (Table 3). In both these groups, an increase in arterial lactate and decrease in standard HCO_3, related to the increase in oxygen uptake, were detected, but the carbon dioxide retention was not detectable in Group D (Figure 2).

4) **Sympathetic activation during exercise:** The plasma norepinephrine levels increased rapidly when the ability to expand tidal volume became limited (Figure 3). The nature of this response was similar to that observed for dyspnea in all the 4 groups. We also determined that the increase in the arterial concentrations of plasma norepinephrine, due to the increase in oxygen uptake ($\Delta NE/\Delta$oxygen uptake), was significantly ($P = 0.033$) greater in Group A than in Group D (Table 2, Figure 4). At a low-intensity work rate (stage 2: 20 W), the

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intensity of dyspnea (Borg scale rating, 4.0 ± 2.5) and the plasma norepinephrine level (1.41 ± 1.0 ng·ml^{-1}) were significantly ($P < 0.0001$ and $P = 0.028$) higher in Group A than those in Group D (0.8 ± 1.0 and 0.83 ± 0.41 ng·ml^{-1}, respectively) and were similar to those at a high-intensity work rate (stage 5: 50 W) in Group D (Figure 4).

Factors correlated with the plasma norepinephrine level at peak exercise were different among the 4 groups (Table 4). In Group A, the plasma norepinephrine level at peak exercise revealed significant negative correlations with body weight and FEV1, and positive correlations with diastolic blood pressure and plasma norepinephrine level at rest. It was also significantly correlated with the plasma epinephrine level, SpO2 and diastolic blood pressure at peak exercise. These plasma epinephrine and diastolic blood pressure were also significantly correlated with FEV1 (r = - 0.54, $P = 0.0061$ and r = - 0.68, $P = 0.0007$) and breathing reserve (r = - 0.41, $P = 0.058$ and r = - 0.65, $P = 0.0025$). On the other hand, the plasma norepinephrine level at peak exercise in Group D was influenced by plasma lactate, the heart rate reserve, pH of arterial blood and dyspnea index at peak exercise. In contrast, the correlation between the Borg scale rating and the plasma norepinephrine level at peak exercise was not significant. The concentrations of plasma epinephrine during exercise and at peak exercise varied greatly among the individuals; therefore, no significant differences were detected among the 4 groups (Table 2).

5) Relationship between dyspnea and arterial norepinephrine levels: The plasma norepinephrine levels increased rapidly beyond the inflection point (norepinephrine threshold) during the incremental exercise. The nature for this response was similar to that observed for Borg scale ratings in all the 4 groups. Both factors increased more rapidly in patients with reduced exercise capacity (Figure 4). Moreover, the plasma norepinephrine levels, even in Group A, increased to levels similar to those of the other groups. In addition, we found a strong linear positive correlation (slope: median = 4.86, range = (0.14, 43.39))

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between the plasma norepinephrine levels and dyspnea (Borg scale ratings) during an incremental exercise, and goodness-of-fit of the data to the linear model was quite high (r-square: median = 0.96, range = (0.40, 0.99)). The time points at which COPD patients experienced breathing discomfort were also consistent (r-square = 0.92, $P < 0.0001$) with the threshold points of plasma norepinephrine, regardless of their exercise capacity (Figure 5). These findings suggested that the degree of exertional dyspnea could be objectively evaluated by measuring plasma norepinephrine levels during CPET.

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Discussion

We divided the 91 clinically stable COPD patients into quartile groups according to their peak oxygen uptake status using CPET and evaluated the differences in life-threatening factors (hypoxemia, acidosis, and sympathetic activation) among the 4 groups. These grouping values were similar to those in the previous report[13]. The peak oxygen uptake was extremely low in Group A patients, whose survival prognosis was predicted to be very poor (peak oxygen uptake < 654 ml/min; 5-year survival rate = 45%[13], peak oxygen uptake <10 $ml \cdot min^{-1} \cdot kg^{-1}$: 5-year survival rate = 35%[14]) on the basis of previous reports. This group consisted of patients who were affected by severe to very severe obstructive disorders, felt severe breathlessness at a low-grade workload, and had low BMI. On the basis of these results, their poor prognosis could be also predicted using the BODE index.[24] Specifically, the pathophysiology of COPD patients with the most severely reduced exercise capacity (Group A) was characterized by several notable impairments, including (i) limited increase in ventilation, (ii) impaired gas exchange, especially, exercise-induced rapid decrease in arterial oxygen pressure (steep PaO_2-slopes), (iii) exercise-induced rapid increase in $PaCO_2$ and progressive acidosis but little change in lactic acidosis, and (iv) sympathetic activation at low-grade workload.

1) **Ventilatory impairment:** The increase in tidal volume during exercise was limited with decreasing exercise capacity of the COPD patients. O'Donnell et al.[25] previously provided a detailed account of the mechanism leading to this result. The authors showed that dyspnea increased steeply once the inspiratory reserve volume fell to a critical level, preventing further expansion of the tidal volume during constant work rate exercise. Furthermore, the authors revealed that dyspnea increased with the disparity between the respiratory effort and tidal volume response.

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2) Gas-exchange abnormality: While exercise-induced rapid decrease in arterial oxygen pressure (PaO_2-slopes) varied substantially among individuals, it was steepened with decreasing exercise capacity. It has also been reported that the 6-min walking distance and oxygen desaturation by pulse oximetry (SpO_2) during the 6-min walking test were good predictors of long-term mortality in patients with COPD.[26] However, in a previous study, we showed that the PaO_2-slope was a significant independent prognostic factor for COPD, and was more closely associated with survival time than peak oxygen uptake or SpO_2-slope.[13] Furthermore, the PaO_2-slope is a completely objective factor, while peak oxygen uptake or 6-min walking distance may be affected by patient motivation and other subjective factors. The results of this study again indicate that the PaO_2-slope is powerful indicator of pathogenetic mechanisms associated with severe exercise limitation and elevated mortality in COPD patients.

3) Exercise-induced acidosis and contributing factors: The arterial pH values decreased to a similar level regardless of the exercise capacity of patients, but the decrease was more rapid in patients with reduced exercise capacity. This progression of arterial acidemia was induced by both lactic acidosis and respiratory acidosis, but the relative contribution of each was different among COPD patients with varying degrees of exercise capacity. In Groups C and D patients, the arterial pH at peak exercise was influenced by both carbon dioxide retention and arterial lactate levels, because an increase in arterial lactate and decrease in standard HCO_3, related to the increase in oxygen uptake, were detected and the carbon dioxide retention was not detectable in Group D, like that in a healthy subject.[11] However, the arterial pH at peak exercise was mainly due to carbon dioxide retention among Groups A and B patients, which could have been caused by limitation of the expansion of tidal volume (i.e., the decrease in alveolar effective ventilation), and the effect of lactic acidosis was small.

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4) Sympathetic activation during exercise: Group A patients were suffering from the sympathetic activations at a low-intensity work rate in daily life, such as eating, morning care, defecation, dressing, and bathing. These levels of sympathetic activation were similar to those at a high-intensity work rate in Group D. The sympathetic nerve activity was largely related to obstructive and ventilatory disorders in group A, whereas it was mainly influenced by plasma lactate, pH of arterial blood and the heart rate reserve in the other groups.

It has been recognized that COPD is a systemic disease that negatively affects the cardiovascular and autonomic nerve systems.[5] The presence of cardiovascular disease and COPD are also intertwined.[27,28] The cardiac event including sudden death is a common cause of death in patients with COPD.[29] It is well known that enhanced sympathetic nerve activity, evidenced by elevated plasma norepinephrine level, is deleterious for the pathophysiology of chronic heart failure.[6,30] We consider that the sympathetic overactivity, which can be objectively evaluated by measuring the plasma norepinephrine level during exercise, is one of the life-threatening factors for COPD. However, the implication of sympathetic activation for COPD during exercise is inconclusive in this study and requires further investigation in detail.

5) Relationship between dyspnea and arterial norepinephrine levels: In the present study, dyspnea (Borg scale) and the concentration of norepinephrine, both increased rapidly after the expansion of the tidal volume became limited during exercise. One explanation is that the breathlessness experienced by the COPD patients during exercise was caused by difficulty in increasing the tidal volume in response to the respiratory motor drives resulting from lactic acidosis, hypercapnia, and/or hypoxemia. This, in turn, would likely necessitate greater breathing effort, which might stimulate the central sympathetic outflow in the brainstem. This hypothesis is supported by the fact that the peak level of plasma norepinephrine was significantly associated with both the concentration of plasma lactate and the dyspnea index,

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and was negatively correlated with the pH of arterial blood and SpO_2 (Table 4). Dyspnea, respiratory motor drive, and autonomic control are tightly linked, both anatomically and functionally, in the brainstem. Specifically, the perception of respiratory discomfort is represented in the sensorimotor integration area of the limbic system that governs autonomic control,[31] and the central respiratory motor drive is associated with the central sympathetic outflow in the brainstem.[32] These central interactions indicate that dyspnea and the increased respiratory drive in COPD may be pathophysiologically linked to heightened sympathetic activation, although the complexity of these interactions within the CNS make it difficult to clearly distinguish between cause and effect.

An intimate relationship between the increase in plasma norepinephrine and the intensity of dyspnea during exercise has also been observed in patients with other respiratory diseases, including idiopathic pulmonary fibrosis[20] and sequelae of pulmonary tuberculosis.[21] Also, Clark et al.[33] demonstrated that the administration of yohimbine caused increased norepinephrine release in healthy individuals. This increase was associated with both an increased ventilatory response and an increase in the sensation of exertion during steady-state exercise. Thus, the increase in norepinephrine in the plasma, induced by exercise, could also contribute to the increase in both ventilation and the sensation of breathlessness. Here, we only demonstrate that sympathetic activation, which was estimated by the increase in plasma norepinephrine, was closely correlated with dyspnea during incremental exercise. Further investigations are necessary to clarify whether the increase in dyspnea causes an increase in plasma norepinephrine, or whether the increase in plasma norepinephrine induces exertional dyspnea. However, regardless of the cause, our results demonstrate that exertional dyspnea could be objectively evaluated by measuring the plasma norepinephrine level during exercise testing in patients with chronic respiratory diseases.

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The exercise-induced hypoxemia, respiratory acidosis and sympathetic overactivity during exercise, observed in COPD patients with severely reduced exercise capacity are associated with an elevated risk of mortality among patients with COPD. These life-threatening pathophysiological conditions could be improved by medication (e.g., tiotropium[34]and ghrelin[35]) and/or pulmonary rehabilitation, including (1) appropriate oxygen supplementation, and (2) energy conservation and work simplification using occupational therapy in addition to improvements in ventilation and exercise capacity. However, our results (variation in the appearance of hypoxemia, respiratory acidosis, and/or sympathetic overactivity during exercise) highlight the importance of conducting CPET when determining the appropriate prescription for medication and pulmonary rehabilitation. On the basis of such evaluations, appropriate pulmonary rehabilitation, including exercise training and occupational therapy in daily living, can be prescribed.[36] These interventions could be shown to improve the survival prognosis of COPD patients.

Conclusions

We divided the stable COPD patients into quartile groups according to their peak oxygen uptake status and investigated relationships between, and changes in, life-threatening factors such as hypoxemia, acidosis, and sympathetic activation in COPD patients during exercise, especially in those with most severely reduced exercise capacity (Group A). The survival prognosis of these patients could be predicted to be very poor.

The mechanisms of exercise intolerance in COPD patients significantly varied among patients with different exercise capacities. Specifically, patients with the most severely reduced exercise capacity (Group A) had the characteristics of life-threatening factors, including (1) impaired gas exchange, especially exercise-induced rapid decrease in arterial oxygen pressure (PaO_2-slopes), (2) exercise-induced rapid increase in arterial carbon dioxide

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pressure and progressive acidosis but little change in lactic acidosis and (3) sympathetic activation at low-grade workload. These life-threatening pathophysiological conditions could be improved by medication and/or pulmonary rehabilitation.

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Figure legends

Figure 1. Comparisons of a) the increase in tidal volume and the decrease in arterial oxygen pressure response (PaO_2-slope) to the increase in oxygen uptake during exercise by the groups.

n = number of cases for each group at rest and at each stage.

PaO_2-slope (mm Hg $L^{-1}min^{-1}$) = Difference in PaO_2/Difference between oxygen uptake at rest and at peak exercise.

PaO_2-slope mean (SD) ; -78(70) mm Hg $L^{-1}min^{-1}$ in Group A, -30(21) mm Hg $L^{-1}min^{-1}$ in Group B, -27(25) mm Hg $L^{-1}min^{-1}$ in Group C and -21(11) mm Hg $L^{-1}min^{-1}$ in Group D. Kruskal-Wallis test, $P < 0.0001$, Turkey-Kramer HSD (pair-wise comparison): A-B* $P = 0.0003$, A-C** $P = 0.0001$, A-D*** $P < 0.0001$.

Figure 2. Changes in mean values of the arterial plasma lactate levels, $PaCO_2$, arterial blood pH, and HCO_3 in COPD patients at each stage during an incremental exercise.

n = number of cases for each group at rest and at each stage.

Figure 3. Increase in the Borg scale rating and the arterial norepinephrine level in response to the increase of tidal volume during exercise.

n = number of cases for each group at rest and at each stage.

Figure 4. Increase in the Borg scale rating and the arterial norepinephrine level at each stage during incremental exercise of 10 W every 2 min .

n = number of cases for each group at rest and at each stage. (→)； shows the endpoint of stage 5 (50 W).

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Figure 5. Relationship between onset of breathlessness and norepinephrine threshold (NT). NT was detected using the log-log transform of norepinephrine-oxygen uptake relationships. The time point of breathlessness onset at which COPD patients experienced breathing discomfort (Borg scale: 0.5 or 1) and the threshold point are revealed by oxygen uptake (ml min^{-1}).

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Table 1. **Comparison of static parameters among the four COPD groups and between two groups**

	Group : Peak oxygen uptake (mL/min)				Group
Patient	A	B	C	D	comparison
characteristics	318-623	665-803	829-1037	1040-1487	*p* value #
Number	22	23	23	23	—
Age (y)	70.8 (6.7)	68.9 (8.3)	69.5(6.9)	68.9 (6.1)	ns
Gender (male/ female)	18 / 4	2 0 / 3	21 / 2	23 / 0	
Body weight (kg)	47.8 (7.8)	53.7 (7.2)	58.6 (12.9)	62.6 (7.8)	<0.0001
BMI (kg/m^2)	18.8 (2.6)	20.2 (3.1)	22.1 (4.6)	22.9 (3)	0.0004
FEV1 (L)	0.76 (0.23)	1.02 (0.28)	1.00 (0.35)	1.54 (0.52)	<0.0001
%FEV1 (% predicted)	31.5 (9.1)	39.5 (10.6)	38.8 (15.3)	57.4 (19.3)	<0.0001
%VC (% predicted)	82.9 (16.0)	94.1 (12.8)	83.1 (14.6)	105.0 (22.2)	<0.0001
Heart rate (beats/min)	84.6 (14.8)	85.5 (13.4)	85.8 (13.8)	79.2 (14.1)	ns
Systolic Blood Pressure (mmHg)	144 (23)	141 (19)	155 (24)	145 (34)	ns
Diastolic Blood Pressure (mmHg)	81 (12)	81 (15)	91 (12)	79 (9)	0.0173
Arterial Blood Gases					
pH	7.413 (0.031)	7.419 (0.028)	7.406 (0.02)	7.421 (0.032)	ns
PaO_2 (mmHg)	78.1 (10.8)	81.2 (12.1)	85.9 (12.4)	86.4 (9.3)	0.0447

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$PaCO_2$ (mmHg)	38.0 (4.3)	37.3 (5.3)	38.6 (4.4)	36.1 (3.7)	ns
HCO_3 (mM/L)	24.2 (2.7)	24.0 (3.0)	24.2 (2.3)	23.4 (1.9)	ns
Lactate (mM/L)	1.5 (0.5)	1.7 (0.5)	1.5 (0.6)	1.7 (0.5)	ns
Norepinephrine (NE: ng/mL)	0.70 (0.3)	0.70 (0.35)	0.66 (0.21)	0.66 (0.34)	ns
Epinephrine (ng/mL)	0.22 (0.2)	0.22 (0.27)	0.18 (0.19)	0.17 (0.11)	ns

Tukey-Kramer HSD pair-wise comparison; group comparison: *p* value

	A-B	A-C	A-D	B-C	B-D	C-D
Body weight (kg)	*	0.001	<0.0001	*	0.0083	*
BMI (kg/m^2)	*	0.0088	0.0008	*	0.0408	*
FEV1 (L)	*	*	<0.0001	*	<0.0001	<0.0001
%FEV1 (L)	*	*	<0.0001	*	0.0003	0.0002
%VC (% predicted)	*	*	0.0002	*	*	0.0002
Diastolic Blood Pressure (mmHg)	*	*	*	*	*	0.0183
PaO_2 (mmHg)	*	*	*	*	*	*

BMI: body mass index, FEV1: forced expiratory volume in one second, VC: vital capacity

Mean (SD), #: One-way ANOVA test or Kruskal Wallis test, *: *p* value > 0.05

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Table 2. Comparison of dynamic parameters at peak exercise

	Group : Peak oxygen uptake (mL/min)				Group
Dynamic parameters	A: 318-623	B: 665-803	C: 839-1037	D: 1040-1487	Comparison#
Oxygen uptake (ml/kg/min)	10.8(2)	13.8(1.7)	16.4(3.5)	19.4(2.8)	*<0.0001*
Watt	28.6(8.3)	40.4(11.5)	53.9(8.4)	67.2(10.1)	<0.0001
Borg scale	6.1(2.1)	5.7(2.1)	7.0(2.3)	6.8(2.9)	ns
Exercise time (s)	294(90)	432(120)	588(114)	726(108)	<0.0001
Tidal volume (ml)	842 (180)	1072(147)	1129(204)	1546(238)	<0.0001
Respiratory frequency	31.2(6.7)	32.8(6.7)	34.7(5.6)	32.6(4.3)	ns
Minute Ventilation (L/min)	25.4(5.5)	34(5.8)	38.1(6.2))	49.8(9.9)	<0.0001
Breathing reserve (L/min)	1.1(6.7)	1.6(7.6)	- 3.3(8.8)	4.1(13.5)	ns
Dyspnoea index (%)	100.6(26.4)	100.3(24.9)	117.6(28.1)	99(25)	ns
Ventilatory equivalent for O_2	50.4(9.5)	46.8(8.2)	41.8(8.3)	41.4(7.0)	0.0009
Ventilatory equivalent for CO_2	52.3(8.5)	46.5(7.1)	39.1(6.8)	38.3(5.7)	<0.0001
Heart rate (beats/min)	114.1(19.1)	114.3(14.4)	133.8(18)	124.8(15.3)	0.0002
HR reserve (beats/min)	35.1(20.0)	36.8(14.5)	16.8(17.9)	26.3(17.2)	0.0006
Systolic Blood Pressure (mmHg)	193 (33)	196(31)	213(37)	207(33)	ns
Diastolic Blood Pressure (mmHg)	102 (26)	98(25)	110(17)	94(17)	ns
Arterial Blood Gases					
pH	7.367(0.034)	7.364(0.045)	7.329(0.044)	7.360(0.045)	0.0166
PaO_2 (mmHg)	59.3(7.0)	67.4(12.7)	68.9(14.8)	67.6(11.5)	0.0333
$PaCO_2$ (mmHg)	42.6(4.4)	41.4(5.7)	43.6(8)	38.7(5.2)	0.0433

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HCO_3 (mM/L)	24.4(2.3)	23.4(2.7)	22.7(3.1)	21.6(2.2)	0.0054
Lactate (mM/L)	2.8(0.8)	3.7(1.3)	4.7(1.6)	4.6(1.3)	<0.0001
Norepinephrine (NE: ng/mL)	1.73(1.04)	1.99(1.39)	2.89(1.76)	2.21(1.19)	0.0356
Epinephrine (ng/ml)	0.42 (0.5)	0.35 (0.32)	0.47 (0.49)	0.25 (0.16)	ns
ΔNE/Δoxygen uptake(ng/mL•L^{-1}•min^{-1})	0.38(0.33)	0.29(0.21)	0.34(0.30)	0.17(0.12)	0.0362
ΔpH/Δoxygen uptake(L^{-1}•min^{-1})	-0.164(0.108)	-0.119(0.066)	-0.115(0.056)	0.069(0.031)	0.0003
PaO_2-slope (mmHg•L^{-1}•min^{-1})	- 78.5(69.7)	- 30.1(21.0)	- 26.6(25.1)	- 20.8(11.0)	<.0001
ΔPaCO2/Δoxygen uptake(mmHg•L^{-1}•min^{-1})	1.82(1.55)	0.87(0.78)	0.75(0.77)	0.30(0.40)	<.0001

#: One-way ANOVA test or Kruskal-Wallis test

2) Comparison between two groups: Tukey-Kramer HSD pair-wise comparison; Group comparison: *p* value

	A-B	A-C	A-D	B-C	B-D	C-D
Watt	0.0005	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Exercise time (s)	0.0002	<0.0001	<0.0001	<0.0001	<0.0001	0.0003
Tidal volume (ml)	0.0009	<0.0001	<0.0001	*	<0.0001	<0.0001
Minute Ventilation (L/min)	0.0006	<0.0001	<0.0001	*	<0.0001	<0.0001
Ventilatory equivalent for O_2	*	0.0041	0.0027	*	*	*
Ventilatory equivalent for CO_2	0.0321	<0.0001	<0.0001	0.0039	0.001	*
Heart rate (beats/min)	*	0.001	*	0.001	*	*
HR reserve (beats/min)	*	0.0038	*	0.0011	*	*

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pH	*	0.0261	*	0.0422	*	*
PaO_2 (mmHg)	*	0.0397	*	*	*	*
$PaCO_2$ (mmHg)	*	*	*	*	*	0.0363
HCO_3 (mM/L)	*	*	0.0034	*	*	*
Lactate (mM/L)	*	<0.0001	<0.0001	*	*	*
Norepinephrine (NE: ng/mL)	*	0.0287	*	*	*	*
ΔNE/Δoxygen uptake ($ng/mL \cdot L^{-1} \cdot min^{-1}$)	*	*	0.033	*	*	*
ΔpH /Δoxygen uptake (L-1•min-1)	*	*	0.0001	*	*	*
PaO_2-slope ($mmHg \cdot L^{-1} \cdot min^{-1}$)	0.0003	0.0001	<0.0001	*	*	*
$\Delta PaCO_2$ /Δoxygen uptake ($mmHg \cdot L^{-1} \cdot min^{-1}$)	0.0073	0.0019	<0.0001	*	*	*

Dyspnoea index (%) = Minute Ventilation (L/min) at peak exercise / Maximal Voluntary Ventilation (L/min) X 100,

Breathing reserve (L/min) = Maximal Voluntary Ventilation (L/min) - Minute Ventilation (L/min) at peak exercise,

HR Reserve (beats/min) = Predicted maximum HR - HR at peak exercise,

ΔNE/Δoxygen uptake($ng/mL \cdot L^{-1} \cdot min^{-1}$) = Increase in NE/Difference in oxygen uptake between at rest and at peak exercise,

ΔpH /Δoxygen uptake(L-1•min-1) = Decrease in pH/Difference in oxygen uptake between at rest and at peak exercise,

PaO_2-slope ($mmHg \cdot L^{-1} \cdot min^{-1}$) = Decrease in PaO_2/Difference in oxygen uptake between at rest and at peak exercise,

$\Delta PaCO_2$ /Δoxygen uptake = Difference in $PaCO_2$/Difference in oxygen uptake between at rest and at peak exercise.

Values are presented as mean (SD), *: *p* value > 0.05

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Table 3 Correlation of $Paco_2$ and lactate with arterial pH by exercise stage and Group

a) Stages	Number	$PaCO_2$	Lactate
rest	91	r = -0.50, $P < 0.0001$	ns
stage 1	91	r = -0.56, $P < 0.0001$	ns
stage 2	90	r = -0.61, $P < 0.0001$	ns
stage 3	68	r = -0.61, $P < 0.0001$	r = -0.32, $P = 0.0087$
stage 4	45	r = -0.68, $P < 0.0001$	r = -0.36, $P = 0.0139$
stage 5	22	r = -0.73, $P < 0.0001$	r = -0.66, $P = 0.0008$
peak exercise	91	r = -0.47, $P < 0.0001$	r = -0.60, $P < 0.0001$

b) Peak exercise	Number	$PaCO_2$	Lactate
Group A	22	r = - 0.53, $P = 0.0108$	ns
Group B	23	r = - 0.61, $P = 0.0021$	ns
Group C	23	r = - 0.64, $P = 0.0011$	r = - 0.52, P = 0.0105
Group D	23	r = - 0.72, $P = 0.0001$	r = - 0.52, $P = 0.0105$

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Table 4 Correlation coefficients to the Norepinephrine level at peak exercise by group

Group : Peak oxygen uptake (mL/min)

	A: 318-623	B: 665-803	C: 839-1037	D: 1040-1487	Total
Number	22	23	23	23	91
a) Static Parameters					
BW	-0.43, $P = 0.0453$	ns	ns	ns	ns
FEV1	-0.50, $P = 0.0190$	ns	ns	ns	ns
DBP	0.66, $P = 0.0010$	ns	ns	ns	0.37, $P = 0.0004$
Norepinephrine	0.78, $P = 0.0001$	0.86, $P = 0.0001$	ns	ns	0.55, $P = 0.0001$
b) Dynamic Parameters					
Dyspnea index	ns	ns	ns	0.55, $P = 0.0074$	0.33, $P = 0.0013$
Heart rate reserve	ns	-0.43, $P = 0.0412$	ns	-0.73, $P = 0.0001$	-0.5, $P = 0.0001$
Peak-HR	ns	ns	ns	0.73, $P = 0.0001$	0.46, $P = 0.0001$
Peak-DBP	0.47, $P = 0.0338$	ns	ns	ns	0.32, $P = 0.0028$
Peak-pH	ns	-0.42, $P = 0.0433$	-0.48, $P = 0.0203$	-0.45, $P = 0.0316$	-0.49, $P = 0.0001$
Peak-SpO_2	-0.59, $P = 0.0038$	ns	ns	ns	-0.27, $P = 0.0086$
Peak-Lactate	ns	0.62, $P = 0.0016$	0.45, $P = 0.0325$	0.73, $P = 0.0001$	0.55, $P = 0.0001$
Peak-epinephrine	0.72, $P = 0.0002$	0.67, $P = 0.0005$	0.49, $P = 0.0170$	ns	0.52, $P = 0.0001$

(r-value and p-value)

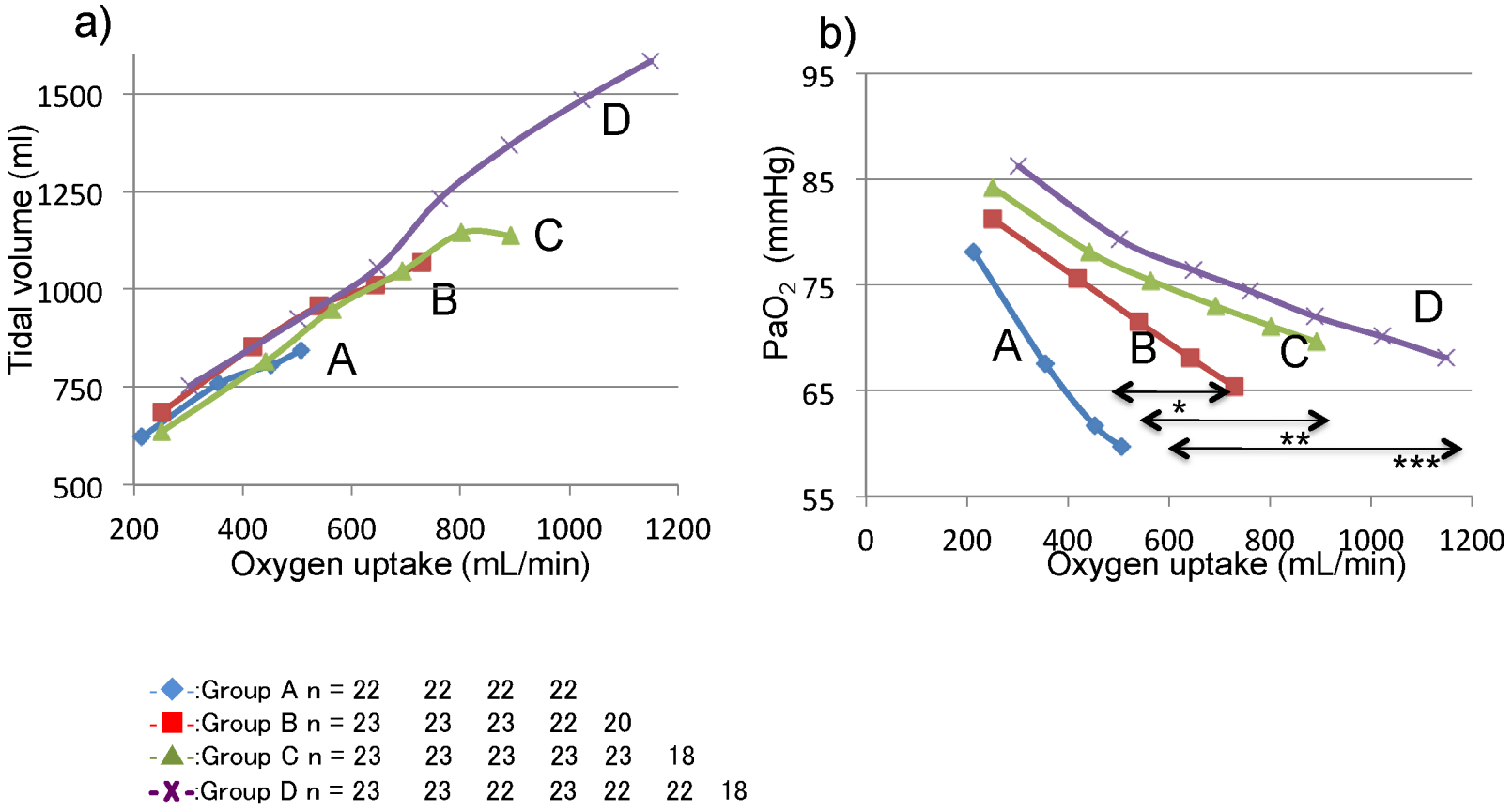
a)
Tidal volume (ml)
1500
1250
1000
750
500
200
400
600
800
1000
1200
Oxygen uptake (mL/min)
A
B
C
D
b)
PaO2 (mmHg)
95
85
75
65
55
0
200
400
600
800
1000
1200
Oxygen uptake (mL/min)
A
B
C
D
*
**
***
-◆-:Group A n = 22 22 22 22
-■-:Group B n = 23 23 23 22 20
-▲-:Group C n = 23 23 23 23 23 18
-✕-:Group D n = 23 23 22 23 22 22 18

Figure 1

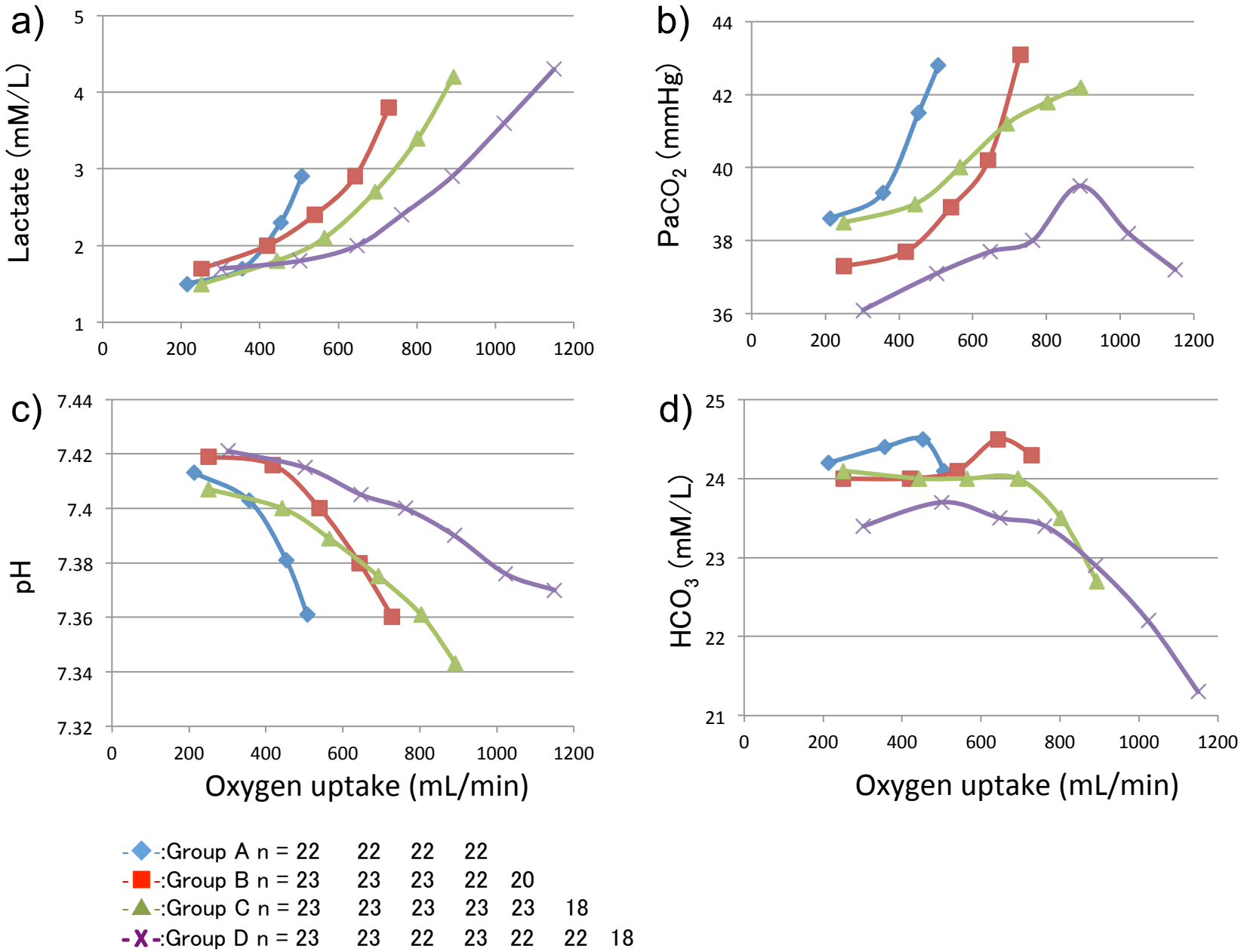
a)
Lactate (mM/L)
5
4
3
2
1
0
200
400
600
800
1000
1200
b)
PaCO2 (mmHg)
44
42
40
38
36
c)
pH
7.44
7.42
7.4
7.38
7.36
7.34
7.32
Oxygen uptake (mL/min)
d)
HCO3 (mM/L)
25
24
23
22
21
Oxygen uptake (mL/min)
-◆-:Group A n = 22 22 22 22
-■-:Group B n = 23 23 23 22 20
-▲-:Group C n = 23 23 23 23 23 18
-X-:Group D n = 23 23 22 23 22 22 18

Figure 2.

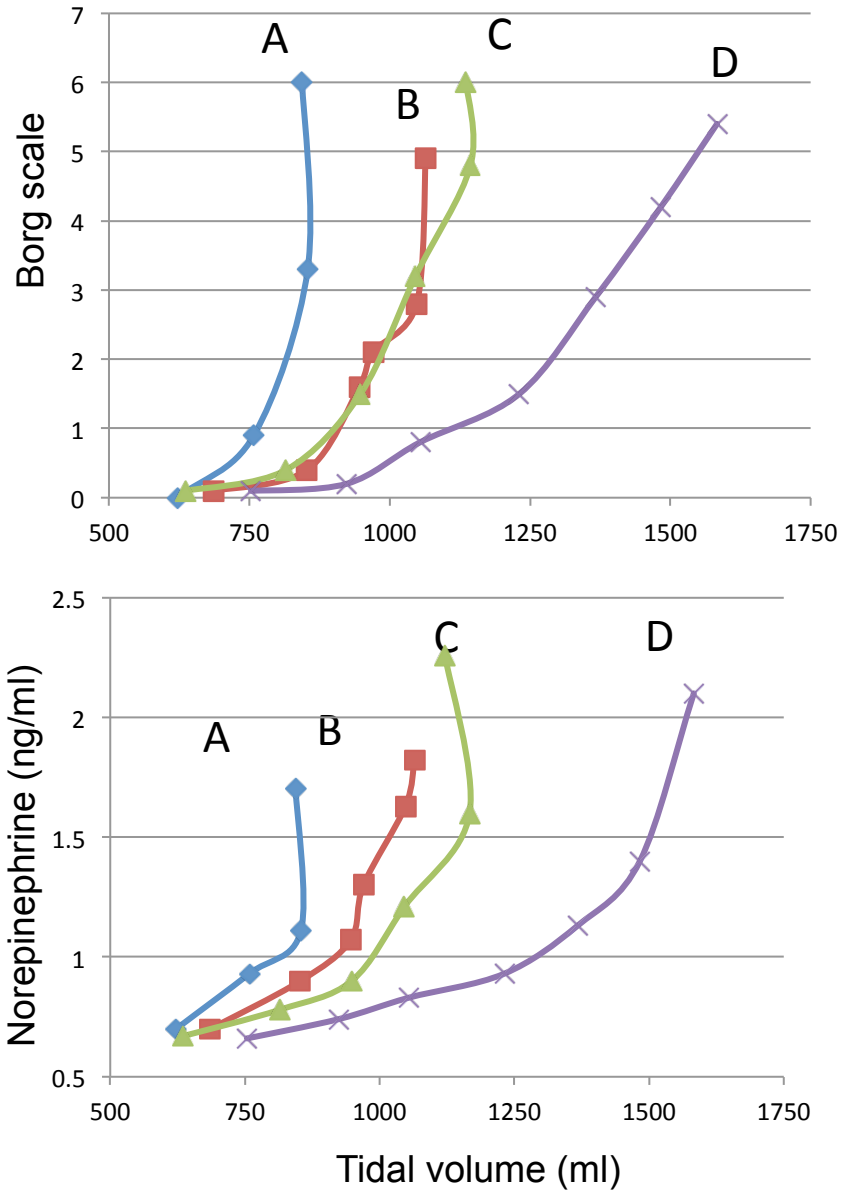
Borg scale
7
6
5
4
3
2
1
0
500
750
1000
1250
1500
1750
A
B
C
D
Norepinephrine (ng/ml)
2.5
2
1.5
1
0.5
Tidal volume (ml)
-◆-:Group A n = 22 22 22 20
-■-:Group B n = 23 23 23 22 20
-▲-:Group C n = 23 23 23 23 23 18
-✕-:Group D n = 23 23 22 23 22 22 18

Figure 3

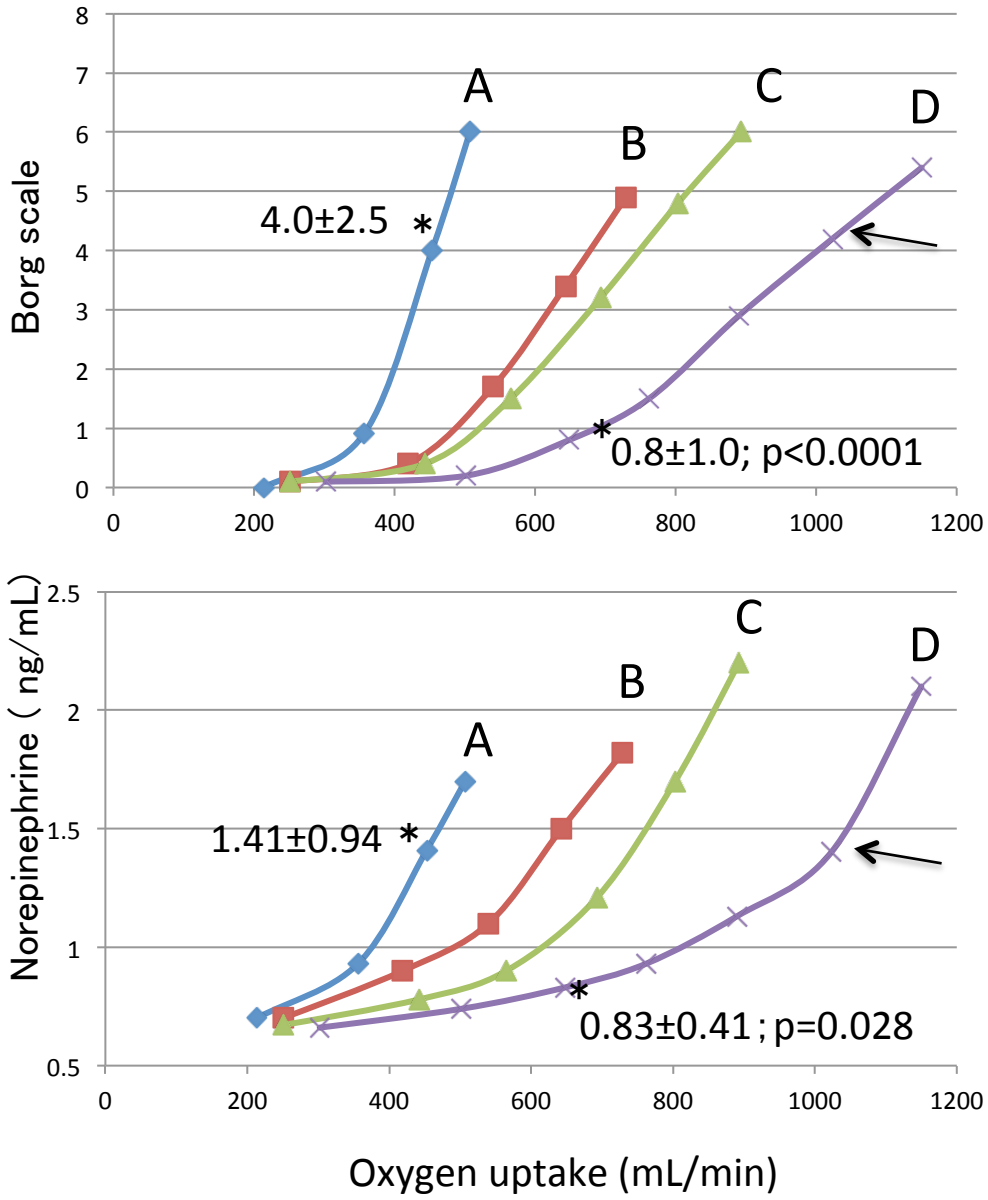
Borg scale
A
B
C
D
4.0±2.5 *
* 0.8±1.0; p<0.0001
Norepinephrine (ng/mL)
1.41±0.94 *
* 0.83±0.41 ; p=0.028
Oxygen uptake (mL/min)
-◆-:Group A n = 22 22 22 20
-■-:Group B n = 23 23 23 22 20
-▲-:Group C n = 23 23 23 23 23 18
-X-:Group D n = 23 23 22 23 22 22 18

Figure 4

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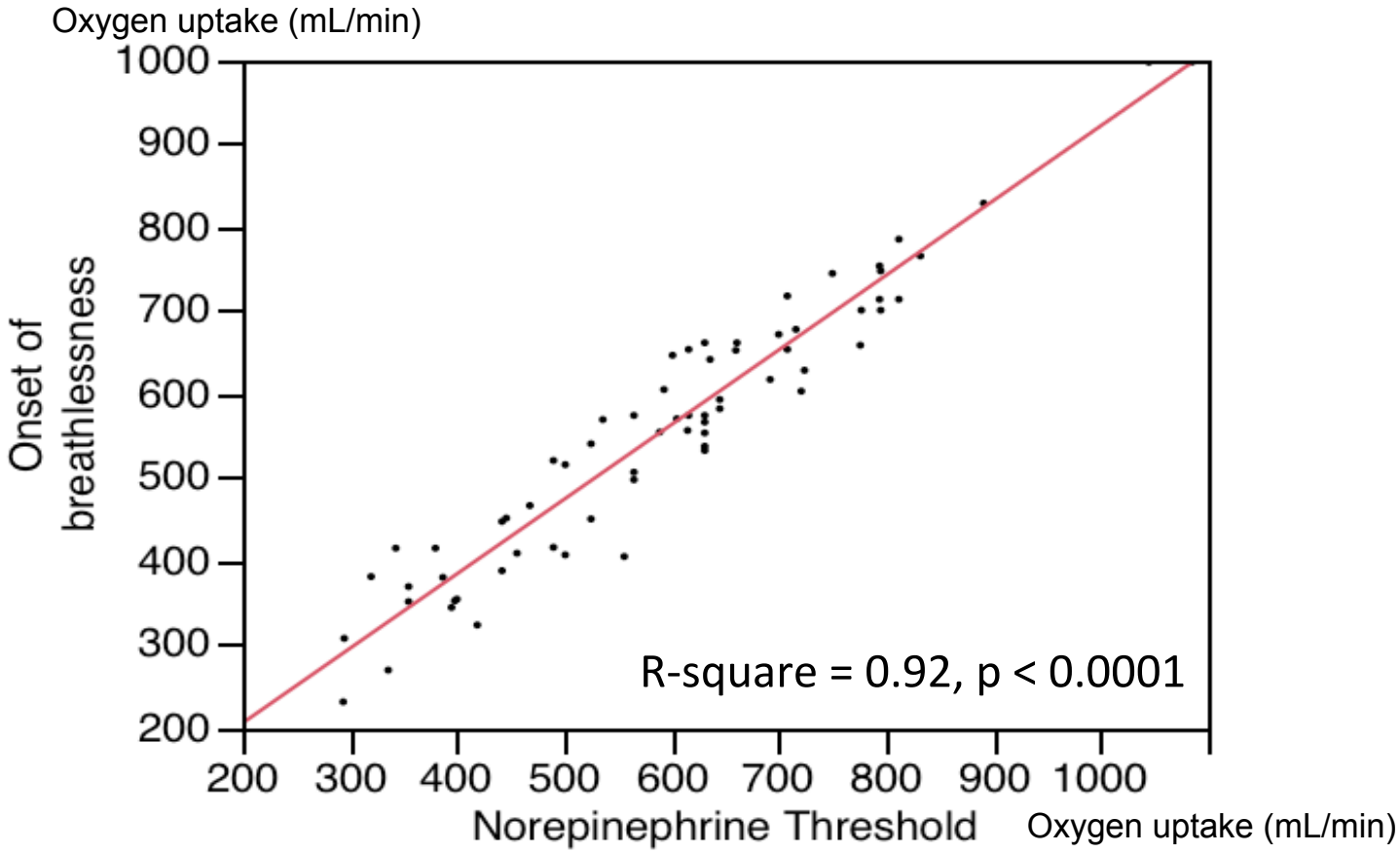

Figure 5.