Differences in Physiological Response to Exercise in Patients With Different COPD Severity

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BACKGROUND: Patients with 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 subjects (82 males, 9 females, average age 69.7 ± 6.8 y) consecutively underwent incremental cardiopulmonary exercise testing using a cycle ergometer. Arterial blood gases, lactate, and catecholamines were measured during cardiopulmonary exercise testing. RESULTS: The pathophysiology of the COPD differed among the 4 subject groups. Subjects with the most severely reduced exercise capacity (peak oxygen uptake ≤ 623 mL/min) were characterized by exercise-induced steep decrease in P_{aO_2} slope (−78 ± 70 mm Hg/L/min), rapid progression of respiratory acidosis, little change in lactic acidosis, and sympathetic activation at low-intensity work load (plasma norepinephrine 1.41 ± 0.94 ng/mL at 20 watts work load), in addition to the limitation of increase in ventilation and impaired gas exchange. CONCLUSIONS: The mechanisms of exercise intolerance in COPD patients significantly differed among subjects with different exercise capacities. Subjects 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 life-threatening pathophysiological conditions could be improved by medication and/or pulmonary rehabilitation. *Key words: COPD; cardiopulmonary exercise testing; hypoxemia; sympathetic overactivity; acidosis; peak oxygen uptake.* [Respir Care 2014;59(2):252–262. © 2014 Daedalus Enterprises]

Introduction

Patients with COPD have reduced exercise tolerance. Exertional dyspnea (breathlessness) is a symptom that makes COPD patients stop prematurely during exercise. The survival prognosis of COPD patients with severely reduced exercise capacity is extremely poor. While the

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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 gas exchange limitation, cardiovascular factors, skeletal-muscle dysfunction, and other factors.[8,9] Gas-exchange factors involve impaired ventilation-perfusion relationships that lead to hypoxemia, impaired oxygen delivery, and pulmonary hypertension. The severity of dyspnea rapidly increases at work rates above the lactic threshold, and plasma norepinephrine and epinephrine 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 in clinical practice.[12]

Peak oxygen uptake during incremental cardiopulmonary exercise testing, FEV_1, and body mass index (BMI) are predictors of mortality in COPD patients.[13-15] In a previous report,[13] the 5-year survival rate of patients with the most severely reduced peak oxygen uptake (< 654 mL/min) 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 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 to compare these among the quartile groups divided on the basis of peak oxygen uptake, especially in patients with severely reduced exercise capacity whose survival prognosis is extremely poor.

QUICK LOOK

Current knowledge

Patients with COPD have reduced exercise tolerance because of dyspnea, impaired ventilatory mechanics, and hypoxemia. Reduced exercise capacity is associated with poor outcome.

What this paper contributes to our knowledge

Exercise intolerance varied with exercise capacity. Severely reduced exercise capacity was characterized by hypoxemia, sympathetic over-activity, and respiratory acidosis at low-intensity exercise.

Methods

This study was approved by the institutional review board of the National Hospital Organization National Toneyama Hospital and complied with international guidelines for studies involving humans. All subjects gave informed consent.

Subjects

We recruited consecutive, first-visit COPD out-patients who visited our institution and had exertional dyspnea (modified Medical Research Council dyspnea score ≥ 1) between June 2000 and February 2006.[16,17] All subjects had a history of cigarette smoking (at least 40 pack-years), and an FEV_1/FVC of < 0.7, measured 20 min after the inhalation of salbutamol. We excluded patients with: comorbidities (eg, cardiovascular or neuromuscular disease) that could contribute to dyspnea and exercise limitation; history of asthma, allergic rhinitis, or atopy; eosinophil count ≥ 600 cells/μL; on an anti-allergic drug or antihistamine drug; active tuberculosis or definite sequelae of tuberculosis; or history of lung resection. Potential study subjects were monitored for 2 months to determine their eligibility for the study, and were prescribed appropriate medication. We also excluded patients with important contraindications to clinical exercise testing,[9] a history of coronary artery disease, COPD exacerbation within the past 2 months, and patients participating in a pulmonary rehabilitation program.

Pulmonary Function Test and Cardiopulmonary Exercise Testing

Post-bronchodilator spirometry (Autospirometer System 9, Minato Medical Science, Osaka, Japan) was 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 analyses. In the bicycle ergometer exercise testing, all subjects began unloaded pedaling for 2 min, and then progressive increments of 10 watts every 2 min, as previously described.[20,21] Expired gas data were collected breath by breath (Vmax, SensorMedics, Yorba Linda, California). We recorded heart rate, breathing frequency, tidal volume, minute ventilation, oxygen uptake, ventilatory equivalent for oxygen, ventilatory equivalent for carbon dioxide, and oxygen pulse. Progressive incremental exercise testing was discontinued when the subject displayed breathlessness

Table 1. Baseline Data From 91 Subjects With COPD

	Peak Oxygen Uptake Range, mL/min				*P**
	318–623 Group A	665–803 Group B	829–1,037 Group C	1,040–1,487 Group D	
Number of subjects	22	23	23	23	
Age, y	70.8 ± 6.7	68.9 ± 8.3	69.5 ± 6.9	68.9 ± 6.1	.87
Male/female, no.	18/4	20/3	21/2	23/0	
Body weight, kg	47.8 ± 7.8	53.7 ± 7.2	58.6 ± 12.9	62.6 ± 7.8	< .001
Body mass index, kg/m^2	18.8 ± 2.6	20.2 ± 3.1	22.1 ± 4.6	22.9 ± 3	< .001
FEV_1, L	0.76 ± 0.23	1.02 ± 0.28	1.00 ± 0.35	1.54 ± 0.52	< .001
FEV_1, % predicted	31.5 ± 9.1	39.5 ± 10.6	38.8 ± 15.3	57.4 ± 19.3	< .001
FVC, % predicted	82.9 ± 16.0	94.1 ± 12.8	83.1 ± 14.6	105.0 ± 22.2	< .001
Heart rate, beats/min	84.6 ± 14.8	85.5 ± 13.4	85.8 ± 13.8	79.2 ± 14.1	.35
Systolic blood pressure, mm Hg	144 ± 23	141 ± 19	155 ± 24	145 ± 34	.08
Diastolic blood pressure, mm Hg	81 ± 12	81 ± 15	91 ± 12	79 ± 9	.02
pH	7.413 ± 0.031	7.419 ± 0.028	7.406 ± 0.02	7.421 ± 0.032	.31
P_{aO_2}, mm Hg	78.1 ± 10.8	81.2 ± 12.1	85.9 ± 12.4	86.4 ± 9.3	.045
P_{aCO_2}, mm Hg	38.0 ± 4.3	37.3 ± 5.3	38.6 ± 4.4	36.1 ± 3.7	.30
HCO_3^-, mM/L	24.2 ± 2.7	24.0 ± 3.0	24.2 ± 2.3	23.4 ± 1.9	.65
Lactate, mM/L	1.5 ± 0.5	1.7 ± 0.5	1.5 ± 0.6	1.7 ± 0.5	.23
Norepinephrine, ng/mL	0.70 ± 0.3	0.70 ± 0.35	0.66 ± 0.21	0.66 ± 0.34	.84
Epinephrine, ng/mL	0.22 ± 0.2	0.22 ± 0.27	0.18 ± 0.19	0.17 ± 0.11	.83

* Via one-way ANOVA test or Kruskal-Wallis test.
± Values are mean ± SD.

Table 2. *P* Values* for Group Comparisons of Baseline Data

	Group Comparison					
	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
Body weight	.15	.001	< .001	.28	.008	.46
Body mass index	.55	.009	< .001	.22	.041	.87
FEV_1	.08	.12	< .001	.99	< .001	< .001
Percent-of-predicted FEV_1	.23	.31	< .001	.99	< .001	< .001
Percent-of-predicted FVC	.13	1.0	< .001	.13	.14	< .001
Diastolic blood pressure	1.0	.07	.96	.07	.96	.02
P_{aO_2}	.79	.10	.07	.50	.40	.99

* Via Tukey-Kramer honest-significant-difference pair-wise comparison.

and/or leg fatigue, or notable electrocardiogram changes (ST segment depression > 2 mm or a short run of premature ventricular contractions). We subsequently divided the subjects into quartile groups based on peak oxygen uptake: group A ≤ 623 mL/min, group B 665–803 mL/min, group C 829–1,037 mL/min, group D ≥ 1,040 mL/min), as described previously.[13] Arterial blood samples were drawn from an indwelling radial artery cannula, after local anesthesia, before exercise testing, with the subject sitting, during the last 15 s of each exercise stage, and at peak exercise. Arterial blood gases and lactate were immediately measured (ABL-800, Radiometer, Brønshøj, Denmark) in the exercise testing room. Plasma catecholamines (norepinephrine and epinephrine) were measured via high-pressure liquid chromatography. The lactate threshold and norepinephrine threshold were calculated via log-log transform of the lactate-oxygen uptake and norepinephrine-oxygen uptake relationships.[22] We also calculated:

Dyspnea index (%) = minute ventilation (L/min) at peak exercise/maximal voluntary ventilation (L/min) × 100

Breathing reserve (L/min) = maximal voluntary ventilation (L/min) − minute ventilation (L/min) at peak exercise

Heart rate reserve (beats/min) = predicted maximum heart rate − heart rate at peak exercise

P_{aO_2} slope (mm Hg/L) = difference in P_{aO_2}/difference in oxygen uptake between at rest and at peak exercise

Table 3. Peak Exercise Data

	Peak Oxygen Uptake Range, mL/min				*P*
	318–623 Group A	665–803 Group B	829–1,037 Group C	1,040–1,487 Group D	
Oxygen uptake, mL/kg/min	10.8 ± 2	13.8 ± 1.7	16.4 ± 3.5	19.4 ± 2.8	< .001
Work load, watts	28.6 ± 8.3	40.4 ± 11.5	53.9 ± 8.4	67.2 ± 10.1	< .001
Borg dyspnea score	6.1 ± 2.1	5.7 ± 2.1	7.0 ± 2.3	6.8 ± 2.9	.07
Exercise time, s	294 ± 90	432 ± 120	588 ± 114	726 ± 108	< .001
Tidal volume, mL	842 ± 180	1072 ± 147	1129 ± 204	1546 ± 238	< .001
Breathing frequency, breaths/min	31.2 ± 6.7	32.8 ± 6.7	34.7 ± 5.6	32.6 ± 4.3	.28
Minute ventilation, L/min	25.4 ± 5.5	34 ± 5.8	38.1 ± 6.2	49.8 ± 9.9	< .001
Breathing reserve, L/min	1.1 ± 6.7	1.6 ± 7.6	−3.3 ± 8.8	4.1 ± 13.5	0.08
Dyspnea index, %	100.6 ± 26.4	100.3 ± 24.9	117.6 ± 28.1	99 ± 25	0.06
Ventilatory equivalent for O_2	50.4 ± 9.5	46.8 ± 8.2	41.8 ± 8.3	41.4 ± 7.0	< .001
Ventilatory equivalent for CO_2	52.3 ± 8.5	46.5 ± 7.1	39.1 ± 6.8	38.3 ± 5.7	< .001
Heart rate, beats/min	114.1 ± 19.1	114.3 ± 14.4	133.8 ± 18	124.8 ± 15.3	< .001
Heart rate reserve, beats/min	35.1 ± 20.0	36.8 ± 14.5	16.8 ± 17.9	26.3 ± 17.2	< .001
Systolic blood pressure, mm Hg	193 ± 33	196 ± 31	213 ± 37	207 ± 33	.18
Diastolic blood pressure, mm Hg	102 ± 26	98 ± 25	110 ± 17	94 ± 17	.09
pH	7.367 ± 0.034	7.364 ± 0.045	7.329 ± 0.044	7.360 ± 0.045	.02
P_{aO_2}, mm Hg	59.3 ± 7.0	67.4 ± 12.7	68.9 ± 14.8	67.6 ± 11.5	.03
P_{aCO_2}, mm Hg	42.6 ± 4.4	41.4 ± 5.7	43.6 ± 8	38.7 ± 5.2	.043
HCO_3^-, mM/L	24.4 ± 2.3	23.4 ± 2.7	22.7 ± 3.1	21.6 ± 2.2	.005
Lactate, mM/L	2.8 ± 0.8	3.7 ± 1.3	4.7 ± 1.6	4.6 ± 1.3	< .001
Norepinephrine, ng/mL	1.73 ± 1.04	1.99 ± 1.39	2.89 ± 1.76	2.21 ± 1.19	.04
Epinephrine, ng/mL	0.42 ± 0.5	0.35 ± 0.32	0.47 ± 0.49	0.25 ± 0.16	.58
Δ Norepinephrine/Δ oxygen uptake, ng/mL/L/min	0.38 ± 0.33	0.29 ± 0.21	0.34 ± 0.30	0.17 ± 0.12	.04
Δ pH/Δ oxygen uptake, L/min	−0.164 ± 0.108	−0.119 ± 0.066	−0.115 ± 0.056	0.069 ± 0.031	< .001
P_{aO_2} slope, mm Hg/L/min	−78.5 ± 69.7	−30.1 ± 21.0	−26.6 ± 25.1	−20.8 ± 11.0	< .001
Δ P_{aCO_2}/Δ oxygen uptake, mm Hg/L/min	1.82 ± 1.55	0.87 ± 0.78	0.75 ± 0.77	0.30 ± 0.40	< .001

Values are mean ± SD.

Δ Norepinephrine/Δ oxygen uptake (ng/mL/L/min) = change in norepinephrine/difference between oxygen uptake at rest and at peak exercise

Δ P_{aCO_2}/Δ oxygen uptake (mm Hg/L) = change in P_{aCO_2}/difference between oxygen uptake at rest and at peak exercise

Dyspnea was measured with the Borg scale.[23] Before testing, the Borg scale was explained and its end points were anchored: 0 indicates "no difficulty in breathing" and 10 indicates "the most severe difficulty in breathing" that the subject had previously experienced or could imagine. The subjects rated dyspnea at rest, every minute during exercise, and at peak exercise. Immediately after exercise cessation and the completion of mechanical measurements, the subjects were asked for their reason(s) for exercise termination (dyspnea, leg fatigue, both, or other).

Statistical Analysis

Statistical analyses were performed with statistics software (JMP 9, SAS Institute, Cary, North Carolina). Data are reported as mean ± SD. We used parametric one-way analysis of variance for the normally distributed variables, and the non-parametric Kruskal Wallis test for the non-normally distributed variables to determine differences in physiologic parameters between the 4 groups. Differences between pairs of groups were analyzed with the Tukey-Kramer honest significant difference post hoc test. The relationships between norepinephrine and the exercise testing parameters were assessed with Pearson correlation coefficients and linear regression analysis. Differences were considered significant when *P* was < .05.

Results

In general, the 91 subjects were elderly (69.7 ± 6.8 y), slender (BMI 21.0 ± 3.7 kg/m^2), and had emphysematous type COPD, according to the radiographic findings in most cases. Only 12 subjects had chronic bronchitis. These are common features among COPD patients in Japan. The subjects had a range of mild to very severe obstruction (FEV_1 1.06 ± 0.45 L, percent-of-predicted FEV_1

40.8 ± 16.1%, FEV_1/FVC 0.44 ± 0.10), and GOLD stages of 1 (5 subjects), 2 (15 subjects), 3 (49 subjects), and 4 (22 subjects). Subjects stopped cardiopulmonary exercise testing due to breathlessness in 53 tests (59%), leg fatigue in 14 tests (15%), and breathlessness and leg fatigue in 24 tests (26%).

We divided the 91 subjects into quartile groups according to their peak oxygen uptake status:

Group A: ≤ 623 mL/min, 22 subjects
Group B: 665–803 mL/min, 23 subjects
Group C: 829–1,037 mL/min, 23 subjects
Group D: ≥ 1,040 mL/min, 23 subjects

Table 1 shows the baseline physiologic data. FEV_1 and percent-of-predicted FEV_1 were significantly reduced, and BMI was significantly lower among subjects with reduced exercise capacity. Table 2 shows the *P* values for the group comparisons of the baseline data. FEV_1 and percent-of-predicted FEV_1 in group D were significantly higher than in groups A, B, and C. The BMI of group A was significantly lower than that of groups C and D.

Peak Exercise Results

Table 3 shows the peak exercise results.

Ventilation. There were no differences in dyspnea score at peak exercise between 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 incremental exercise (Fig. 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 ($r^2 = 0.64$, $P < .001$, and $r^2 = 0.65$, $P < .001$, respectively).

Table 4 shows the *P* values for the group comparisons of peak exercise results. There were significant differences between all pairs except groups B and C. The expansion of tidal volume during exercise was extremely limited in the subjects with the most severely reduced exercise capacity (group A). On the other hand, the breathing frequency at peak exercise showed no significant differences between the 4 groups. However, it varied among the subjects: 26 subjects (29%) had an elongated expiratory period (breathing frequency < 30 breaths/min), 51 (56%) had normal breathing (30–40 breaths/min), and 14 (15%) had rapid and shallow breathing (> 40 breaths/min). In all groups, breathing reserve was < 10 L/min and dyspnea index was around 100%, which indicates that the exercise limitation was mainly caused by ventilatory disorders.

Gas Exchange. During peak exercise the ventilatory equivalents for oxygen and carbon dioxide remained high 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. The ventilatory equivalent for CO_2 was more impaired in group A than in all other groups, but was also impaired in group B. P_{aO_2} linearly decreased in response to the increase in oxygen uptake during exercise (P_{aO_2} slope). Steep P_{aO_2} slope was also an important feature in group A. While it varied substantially among individuals, the steepest slope was in group A (see Fig. 1).

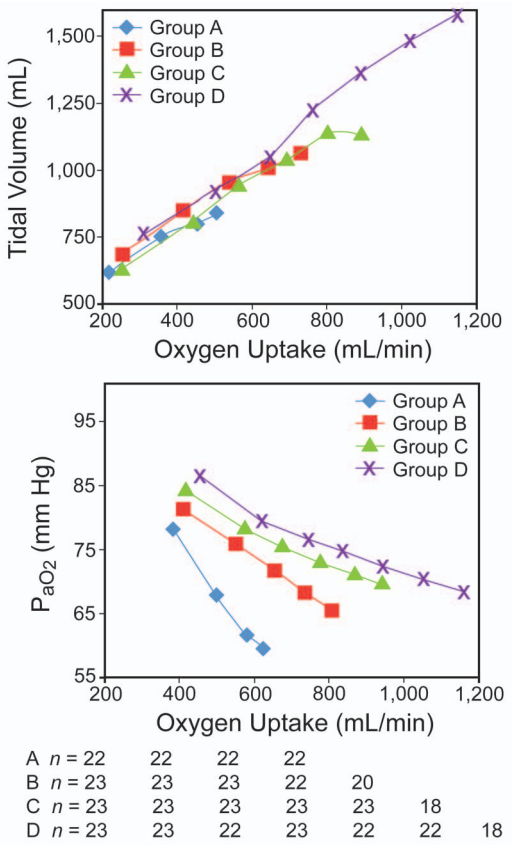

Fig. 1. Oxygen uptake versus tidal volume and P_{aO_2} during incremental exercise testing. *n* = number of subjects in each group at rest and at each exercise stage. P_{aO_2} slope is calculated as the difference in P_{aO_2} divided by the difference between oxygen uptake at rest and at peak exercise. The mean ± SD P_{aO_2} slopes are: group A −78 ± 70 mm Hg L/min, group B −30 ± 21 mm Hg L/min; group C −27 ± 25 mm Hg L/min; group D −21 ± 11 mm Hg L/min. Via Kruskal-Wallis test, $P < .001$. Via Tukey-Kramer honest-significant-difference test (pair-wise comparison), $P < .001$ for group A vs group B, group A vs group C, and group A vs group D.

Exercise-Induced Acidosis and Contributing Factors. We examined the changes in mean plasma lactate, P_{aCO_2}, arterial pH, and standard HCO_3^- from the at-rest stage to the end of each exercise stage (Fig. 2). Lactate was elevated beyond the inflection point (lactic threshold), but the lactate increase was lower in group A than in groups C ($P < .001$) and D ($P < .001$). Moreover, the decrease in HCO_3^- related to lactic acidosis was not detectable in

Table 4. *P* Values for Group Comparisons of Peak Exercise Data

	Group Comparison					
	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
Work load	< .001	< .001	< .001	< .001	< .001	< .001
Exercise time	< .001	< .001	< .001	< .001	< .001	< .001
Tidal volume	< .001	< .001	< .001	.76	< .001	< .001
Minute ventilation	< .001	< .001	< .001	.21	< .001	< .001
Ventilatory equivalent for O_2	.48	.004	.003	.17	.13	.99
Ventilatory equivalent for CO_2	.03	< .001	< .001	.004	.001	.98
Heart rate	1.0	.001	.15	.001	.15	.28
Heart rate reserve	.99	.004	.33	.001	.18	.26
pH	.99	.03	.96	.042	.99	.09
P_{aO_2}	.11	.04	.10	.98	1.0	.98
P_{aCO_2}	.89	.95	.14	.60	.45	.04
HCO_3^-	.64	.16	.003	.79	.08	.46
Lactate	.10	< .001	< .001	.05	.07	.99
Norepinephrine	.92	.029	.65	.12	.95	.34
Δ Norepinephrine/Δ oxygen uptake	.51	.95	.03	.82	.50	.11
Δ pH/Δ oxygen uptake	.14	.10	< .001	.99	.09	.12
P_{aO_2} slope	< .001	< .001	< .001	.99	.84	.95
Δ P_{aCO_2}/Δ oxygen uptake	.007	.002	< .001	.97	.19	.39

groups A and B, which indicates that lactate failed to reach the point that causes lactic acidosis. However, the value of arterial pH steeply decreased and P_{aCO_2} rapidly increased early during exercise in group A.

Table 5 shows the correlations between P_{aCO_2}, lactate, pH, and exercise stage. The pH at rest, and after stages 1 and 2 was significantly correlated with P_{aCO_2}, but not with lactate. Following stage 2 and at peak exercise, pH correlated with both lactate and P_{aCO_2}. The pH decrease resulted from respiratory acidosis at the early stage (work load ~20 watts), and thereafter from combined respiratory and lactic acidosis. In groups A and B, the pH at peak exercise was mainly due to carbon dioxide retention; however, it was influenced by both carbon dioxide retention and arterial lactate in groups C and D (see Table 5), which both had an increase in arterial lactate and a decrease in HCO_3^-, related to the increase in oxygen uptake, but carbon dioxide retention was not detected in group D (see Fig. 2).

Sympathetic Activation During Exercise. Norepinephrine increased rapidly when the ability to increase tidal volume became limited (Fig. 3). The nature of this response was similar to that observed for dyspnea in all 4 groups. The increase in norepinephrine, due to the increase in oxygen uptake (Δ norepinephrine/Δ oxygen uptake) was significantly ($P = .03$) greater in group A than in group D (see Table 3 and Fig. 4). In exercise stage 2 (work load 20 watts) the mean dyspnea score (4.0 ± 2.5) and norepinephrine (1.41 ± 1.0 ng/mL) were significantly ($P < .001$ and $P = .03$) higher in group A than in group D (0.8 ± 1.0 and 0.83 ± 0.41 ng/mL, respectively), and were similar to those during exercise stage 5 (work load 50 watts) in group D (see Fig. 4).

Table 6 shows the correlations between norepinephrine and other variables at peak exercise. In group A norepinephrine at peak exercise significantly negatively correlated with body weight and FEV_1, and positively correlated with diastolic blood pressure and norepinephrine at rest. It also significantly correlated with epinephrine, S_{pO_2}, and diastolic blood pressure at peak exercise. Epinephrine and diastolic blood pressure significantly correlated with FEV_1 ($r = -0.54$, $P = .006$, and $r = -0.68$, $P < .001$) and breathing reserve ($r = -0.41$, $P = .058$, and $r = -0.65$, $P = .003$). On the other hand, norepinephrine at peak exercise in group D was influenced by plasma lactate, heart rate reserve, pH, and dyspnea index at peak exercise. In contrast, the correlation between dyspnea score and the norepinephrine at peak exercise was not significant. Epinephrine during exercise and at peak exercise varied greatly among the individuals, so no significant differences were detected among the 4 groups (see Table 3).

Relationship Between Dyspnea and Norepinephrine. Norepinephrine increased rapidly beyond the inflection point (norepinephrine threshold) during exercise. This response was similar to that of dyspnea score in all the 4 groups. Both factors increased more rapidly in subjects with reduced exercise capacity (see Fig. 4). Moreover, norepinephrine, even in group A, increased to levels similar to those of the other groups. There was a strong linear positive correlation (slope median 4.86, range 0.14–43.39) between norepinephrine and dyspnea score during exer-

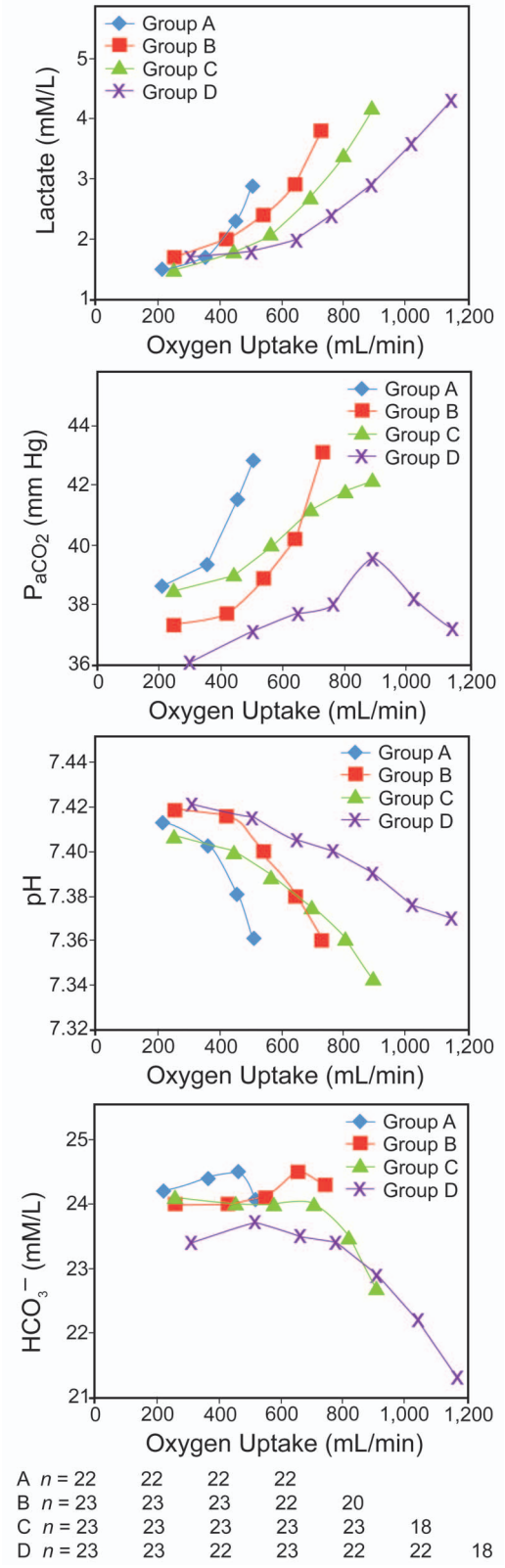

Fig. 2. Changes in mean arterial plasma lactate, P_{aCO_2}, arterial pH, and HCO_3^-, in COPD subjects during incremental exercise. *n* = number of subjects in each group at rest and at each exercise stage.

cise: r^2 median 0.96, range 0.40–0.99. The time points at which the subjects experienced breathing discomfort were also consistent (r^2 0.92, $P < .001$) with the threshold points of norepinephrine, regardless of their exercise capacity (Fig. 5). These findings suggest that exertional dyspnea might be objectively evaluated via norepinephrine level during exercise testing.

Discussion

We divided 91 clinically stable COPD subjects into quartile groups, according to peak oxygen uptake during cardiopulmonary exercise testing, and evaluated the differences in hypoxemia, acidosis, and sympathetic activation. These grouping values were similar to those in a previous study.[13] Peak oxygen uptake was extremely low in group A, whose survival prognosis is poor: peak oxygen uptake < 654 mL/min, 5-year survival rate 45%, peak oxygen uptake < 10 mL/min/kg, 5-year survival rate 35%.[13,14] Group A had severe to very severe obstruction, severe breathlessness at a low work load, and low BMI. On the basis of those results their poor prognosis is also predicted using the BODE (body mass index, air-flow obstruction, dyspnea, exercise capacity) index.[24] Specifically, the subjects with the most severely reduced exercise capacity (group A) had limited ability to increase ventilation; impaired gas exchange, especially exercise-induced rapid decrease in P_{aO_2} (steep P_{aO_2} slope), exercise-induced rapid increase in P_{aCO_2}, and progressive acidosis, but little change in lactic acidosis; and sympathetic activation at a low work load.

Ventilatory Impairment

The ability to increase tidal volume during exercise was limited, which limited exercise capacity in our subjects. O'Donnell et al[25] described the mechanism of this limitation. They showed that dyspnea increases steeply once the inspiratory reserve volume falls to a critical level, preventing further increase of the tidal volume during constant-work-rate exercise. They also revealed that dyspnea increases with the disparity between the respiratory effort and tidal volume response.

Gas-Exchange Abnormality

While P_{aO_2} slope differed substantially among individuals, it steepened with decreasing exercise capacity. It has also been reported that 6-min walk distance and oxygen desaturation (measured as S_{pO_2}) during the 6-min walk test are good predictors of long-term mortality in patients with COPD.[26] However, in a previous study we found that the P_{aO_2} slope was a significant independent prognostic factor for COPD, and was more closely associated with survival

Table 5. Correlation of P_{aCO_2} and Lactate With Exercise Stage and Group

	Number of Subjects	Correlation With P_{aCO_2}		Correlation With Lactate	
Exercise stage		r	*P*	r	*P*
Rest	91	−0.50	< .001		.58
1	91	−0.56	< .001		.32
2	90	−0.61	< .001		.40
3	68	−0.61	< .001	−0.32	.009
4	45	−0.68	< .001	−0.36	.01
5	22	−0.73	< .001	−0.66	< .001
Peak exercise	91	−0.47	< .001	−0.60	< .001
Peak exercise by group					
Group A	22	−0.53	.01		.25
Group B	23	−0.61	.002		.20
Group C	23	−0.64	.001	−0.52	.01
Group D	23	−0.72	< .001	−0.52	.01

time than was peak oxygen uptake or S_{pO_2} slope.[14] Furthermore, the P_{aO_2} slope is a completely objective factor, whereas peak oxygen uptake or 6-min walk distance may be affected by patient motivation and other subjective factors. The results of this study again indicate that the P_{aO_2} slope is a powerful indicator of pathogenetic mechanisms associated with severe exercise limitation and elevated mortality in COPD patients.

Exercise-Induced Acidosis and Contributing Factors

Arterial pH decreased to a similar level regardless of exercise capacity, but the decrease was more rapid in subjects 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 subjects with different exercise capacities. In groups C and D, pH at peak exercise was influenced by both carbon dioxide retention and arterial lactate level, because an increase in lactate and a decrease in HCO_3^-, related to the increase in oxygen uptake, were detected, and carbon dioxide retention was not detected in group D, like that in a healthy subject.[11] However, the arterial pH at peak exercise was mainly due to carbon dioxide retention in groups A and B, which could have been caused by limitation of increase of tidal volume (ie, the decrease in alveolar effective ventilation), and the effect of lactic acidosis was small.

Sympathetic Activation During Exercise

Group A subjects suffered from sympathetic activation at a low-intensity work rate in daily life, such as during 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 lactate, pH, and the heart rate reserve in the other groups.

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

Relationship Between Dyspnea and Arterial Norepinephrine

In the present study, dyspnea score and norepinephrine both increased rapidly after the increase of tidal volume became limited during exercise. One explanation is that the breathlessness during exercise was caused by difficulty in increasing the tidal volume in response to the respiratory motor drive 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 peak norepinephrine was significantly associated with both lactate and dyspnea index, and negatively correlated with pH and S_{pO_2}

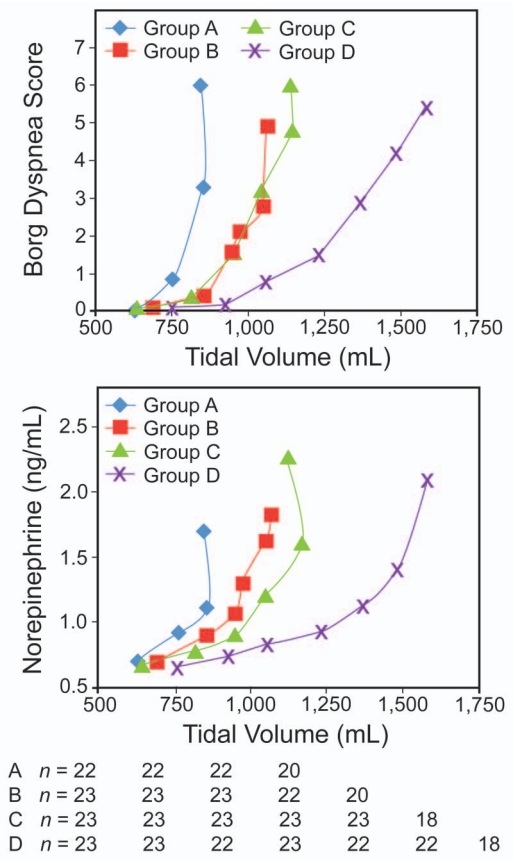

Fig. 3. Tidal volume versus Borg dyspnea score and arterial norepinephrine level during incremental exercise testing. *n* = number of subjects in each group at rest and at each exercise stage.

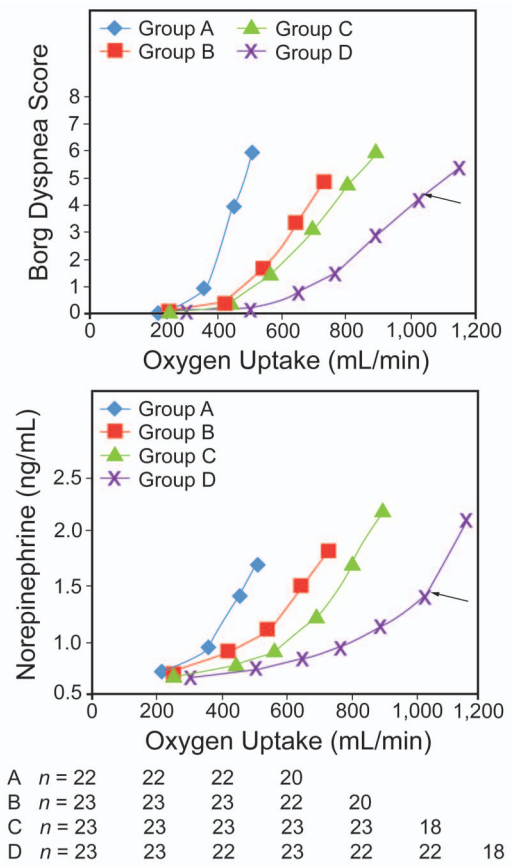

Fig. 4. Oxygen uptake versus Borg dyspnea score and the arterial norepinephrine level during incremental exercise testing. The arrows point to the end point of exercise stage 5 (work load 50 watts). *n* = number of subjects in each group at rest and at each exercise stage. The arrows indicate the end point of exercise stage 5 (50 watts).

(see Table 6). 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, which 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 central nervous system make it difficult to clearly distinguish between cause and effect.

An intimate relationship between the increase in plasma norepinephrine and dyspnea intensity 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] found that the administration of yohimbine increased norepinephrine release in healthy individuals, and this increase was associated with increased ventilatory response and an increased sensation of exertion during steady-state exercise. Thus, the increase in norepinephrine 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 norepinephrine increase, 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 can be objectively evaluated by measuring the plasma norepinephrine during exercise testing in patients with chronic respiratory diseases.

The exercise-induced hypoxemia, respiratory acidosis and sympathetic overactivity during exercise in COPD patients with severely reduced exercise capacity are associated with an elevated risk of mortality. These life-threatening pathophysiological conditions could be improved by medication (eg, tiotropium[34] and ghrelin[35]) and/or pulmonary rehabilitation, including appropriate

Table 6. Correlation of Peak Exercise Norepinephrine Level to Physiologic Variables

	Peak Oxygen Uptake Range, mL/min									
	318–623 Group A $n = 22$		665–803 Group B $n = 23$		829–1,037 Group C $n = 23$		1,040–1,487 Group D $n = 23$		Total $N = 91$	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
Body weight	−0.43	.045	0.01		0.05		−0.2		0.00	
FEV_1	−0.50	.02	−0.12		0.11		−0.35		−0.07	
Diastolic blood pressure	0.66	.001	0.22		0.18		0.36		0.37	< .001
Norepinephrine	0.78	< .001	0.86	< .001	0.39		0.49		0.55	< .001
Dyspnea index	0.35		0.30		0.08		0.55	.007	0.33	.001
Heart rate reserve	−0.34		−0.43	.041	−0.37		−0.73	< .001	−0.5	< .001
Peak heart rate	0.35		0.26		0.32		0.73	< .001	0.46	< .001
Peak diastolic blood pressure	0.47	.03	0.37		0.28		0.05		0.32	.003
Peak pH	−0.38		−0.42	.043	−0.48	.02	−0.45	.03	−0.49	< .001
Peak S_{pO_2}	−0.59	.004	−0.12		−0.35		−0.12		−0.27	.009
Peak lactate	0.13		0.62	.002	0.45	.03	0.73	< .001	0.55	< .001
Peak epinephrine	0.72	< .001	0.67	< .001	0.49	.02	0.29		0.52	< .001

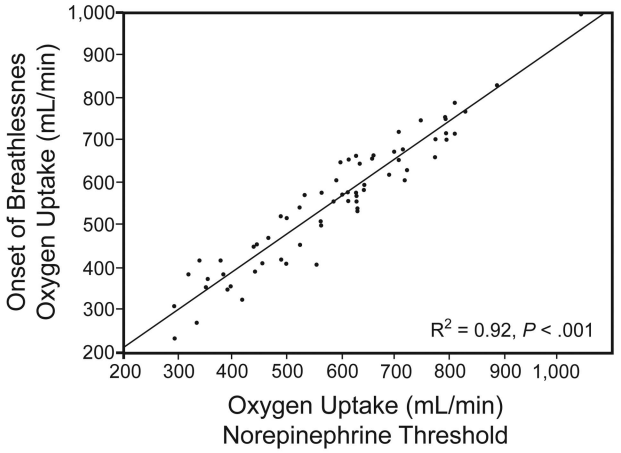

Fig. 5. Norepinephrine threshold versus onset of breathlessness in COPD subjects. Norepinephrine threshold was calculated using the log-log transform of the norepinephrine/oxygen uptake relationship. The time point of breathlessness onset (Borg dyspnea score 0.5–1) and the threshold point are revealed by oxygen uptake.

oxygen supplementation, 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 cardiopulmonary exercise testing 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 subjects 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 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, subjects with the most severely reduced exercise capacity (group A) had the characteristics of life-threatening factors, including impaired gas exchange, especially exercise-induced rapid decrease in P_{aO_2} slopes; exercise-induced rapid increase in P_{aCO_2} and progressive acidosis, but little change in lactic acidosis; and sympathetic activation at low work load. These life-threatening pathophysiological conditions could be improved by medication and/or pulmonary rehabilitation.

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