



Early View

Research letter

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Research Letter

Exertional multidimensional dyspnoea predicts exacerbation in stable outpatients with COPD

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‘Take home’ message

This study assessed the sensory and emotional aspects of breathlessness under the same exercise load in patients with COPD. Breathing discomfort with constant exercise predicted exacerbations within 1 year.

To the Editor:

Dyspnoea is a risk factor for mortality in patients with chronic obstructive pulmonary disease (COPD).[1] Awareness of the magnitude of respiratory drive to the respiratory muscles contributes to dyspnoea.[2] In line with this mechanism, elevated respiratory neural drive during hospitalisation and at hospital discharge predicts readmission and mortality in patients with acute exacerbation of COPD.[3, 4] Furthermore, patients with COPD who experienced frequent exacerbations had heightened dyspnoea due to hypercapnia, compared with those with infrequent exacerbations.[5] Therefore, changes in the afferent and efferent loops involved in dyspnoea contribute to COPD exacerbations.

Dyspnoea comprises multiple sensations and emotional aspects, and different respiratory sensations are attributed to different mechanisms. Exercise testing in stable outpatients with COPD, who are often asymptomatic at rest, can provide an early insight into the sensory and emotional aspects of dyspnoea.[6] In particular, the sensory types of dyspnoea upon exercise in patients with COPD are multifactorial.[7] An elevated neural respiratory drive imposes larger respiratory and mental breathing efforts (i.e., own breathing requires concentration), whereas an insufficient expansion of tidal volume in response to respiratory drive causes air-hunger and unpleasantness.[8] Consistent with these sensory-perceptual aspects, anxiety or fear can often be co-exhibited.[9] This study investigated how sensory and emotional aspects of dyspnoea during the same exercise load were related to future exacerbations in stable outpatients with COPD.

This was a prospective observational study conducted at a respiratory clinic (Himeji, Hyogo, Japan). Outpatients with COPD who were clinically stable during the 4 weeks before testing were included. The exclusion criteria were the inability to perform a 3-minute step test (3-MST), presence of active cardiovascular comorbidity, long-term use of oxygen therapy, or any other condition that could affect dyspnoea or exercise

capacity. Out of the initial 79 patients, 53 were enrolled after the exclusion criteria was applied. All patients provided informed consent before enrolling in the study, and the study was approved by the institutional ethics review board (approval number: Himedokusei-19-10). Demographic, anthropometric, and medication data were collected from electronic records. Exacerbation was defined as the worsening of symptoms and requiring treatment with oral corticosteroids or antibiotics, or both; exacerbations were recorded for 1 year after testing.

Spirometry and maximal inspiratory pressure ($P_{I_{max}}$) measurements as well as quadriceps strength (QS), hand grip strength (HGS), and skeletal mass index (SMI) were measured.[7]

Constant-exercise testing was performed using the 3-MST, which consisted of 3-minute bouts of exercise at an externally paced stepping rates of 16 steps per minute. Ventilatory responses upon exertion were measured throughout the test.[10, 11] Inspiratory capacity (IC) manoeuvres were performed at rest and at the end of the 3-MST.[12] Immediately after each 3-MST, sensory and affective dimensions of dyspnoea were evaluated using the Multidimensional Dyspnoea Profile (MDP).[9]

Patient characteristics were compared using the Mann–Whitney U test and Chi-squared test. A univariate analysis and multivariate logistic regression were used to identify the factors associated with the exacerbation. Receiver-operator characteristic (ROC) analysis were used to assess the performance of the predictors of an exacerbation during a 1 year observation period. The data of exacerbation-free survival was analysed using the Kaplan–Meier method. Spearman rank correlation and a multi linear regression analysis were used to test the effects of dyspnoea on exacerbation.

Twenty exacerbators were identified over a 1 year observation period, and the patients were divided into two groups: exacerbators and non-exacerbators. The patients were matched between the two groups for baseline characteristics of age (76.21 ± 7.63 versus 76.76 ± 6.24 years, sex (male/female: 15/5 versus 26/7 $p = 0.75$), %FEV₁ (58.78 ± 13.94 versus 58.93 ± 18.45 %, $p = 0.95$), %FVC (84.26 ± 14.08 versus 83.47 ± 16.35 %, $p = 0.61$), and $P_{I_{max}}$ (69.68 ± 26.23 versus 62.67 ± 29.63 cm H₂O, $p = 0.37$). In addition, no significant differences between the groups were found in body mass index (BMI) (21.68 ± 3.52 versus 22.35 ± 7.63 kg · m⁻², $p = 0.43$), HGS (29.07 ± 7.64 versus 29.29 ± 8.64 kg, $p = 0.99$), QS (26.27 ± 9.78 versus 24.62 ± 8.34 kg, $p = 0.70$), and SMI (6.52 ± 0.99 versus 6.60 ± 1.03 , $p = 0.68$). There was no significant difference between the use of the inhaled corticosteroid and long-acting muscarinic antagonist inhalers between the two groups. However, 14 out of 20 exacerbators and 30 out of 33 non-exacerbators used β_2 -agonist inhalers ($p = 0.049$). According to patient history, exacerbators had significantly higher frequency of exacerbations than non-exacerbators (1.00 ± 0.56 versus 0.09 ± 0.29 , $p < 0.001$)

IC decreased progressively during 3-MST in both groups. The changes in IC (-0.16 ± 0.25 versus -0.15 ± 0.23 L $p = 0.75$), inspiratory reserve volume at the end of exercise (0.72 ± 0.48 versus 0.65 ± 0.37 L, $p = 0.56$), the frequency of breathing (f_R) at the end of exercise (32.92 ± 7.42 versus 32.52 ± 9.32 , breaths · min⁻¹, $p = 0.44$) and peak V'_E during 3-MSTs (25.76 ± 7.06 versus 27.03 ± 7.45 L · min⁻¹, $p = 0.53$) at the end of exercise did not differ between the exacerbators and non-exacerbators. The SpO₂ levels at the end of the exercise tended to be lower for exacerbators compared with non-exacerbators (88.00 ± 15.83 versus 92.58 ± 4.50 %, $p = 0.15$).

No patient had resting complaints of breathlessness. However, breathing discomfort at the end of the 3-MST was significantly higher in exacerbators than in non-exacerbators. The emotional aspects of dyspnoea during the 3-MST (frustration, anger, and fear) were significantly higher in exacerbators than in non-exacerbators

(Figure 1a). Regarding the sensory dimension of dyspnoea, mental breathing effort at the end of the 3-MST was significantly higher in exacerbators than in non-exacerbators (Figure 1a).

Although the univariate logistic regression analysis demonstrated that breathing discomfort, mental breathing effort, and fear at the end of the 3-MST predicted exacerbation within 1 year, only breathing discomfort was a reliable predictor after adjusting for %FEV₁, long-acting β_2 -agonist use, and BMI. In the ROC analysis for predicting exacerbation within 1 year, areas under the curve for breathing discomfort, mental breathing effort, fear, and %FEV₁ were 0.69 (p=0.28), 0.70 (p=0.02), 0.67 (p=0.44), and 0.50 (p=0.95), respectively (Figure 1b). Breathing discomfort of ≥ 5 after 3-MST had 66.7% sensitivity and 40.1% specificity, respectively. Patients with COPD with a breathing discomfort of ≥ 5 had a statistically significantly shorter time from tests to exacerbations than those with a breathing discomfort of < 5 (HR=0.383; 95% CI=0.146–0.990; p=0.048; Figure 1c). A multivariable stepwise logistic regression analysis revealed that breathing discomfort on the 3-MST predicted exacerbations within 1 year (C statistic=0.69). Among exacerbators, mental breathing effort was negatively correlated with FEV₁/FVC (r=-0.43, p=0.03) and Δ IC (r = -0.41, p = 0.04), whereas fear after 3-MST showed significant positive correlations with peak V_E (r = 0.49, p = 0.01) and breathing frequency (r = 0.59, p = 0.003).

Exacerbation frequency was significantly correlated with the lowest SpO₂ after 3-MST (r = -0.47, p < 0.001), breathing discomfort (r = 0.36, p < 0.01), mental breathing effort (r = 0.31, p = 0.02), fear (r = 0.34, p = 0.01), anger (r = 0.30, p = 0.03), and frustration (r = 0.30, p = 0.03). Increase in breathing discomfort and desaturation for the 3-MST were independently associated with exacerbation frequency in a multiple linear regression analysis (breathing discomfort, standardised coefficient β = 0.25, p = 0.04; desaturation β = -0.45, p = 0.01).

Although dynamic lung hyperinflation, muscle strength, and mass were similar between the exacerbators and non-exacerbators, breathing discomfort, mental

breathing effort, and fear on exertion were significantly higher in exacerbators than in non-exacerbators. In addition, our key results are that patients with COPD with a breathing discomfort of ≥ 5 had a statistically significantly shorter time from tests to exacerbations than those with a breathing discomfort of < 5 , and this revealed breathing discomfort at end-3-MST predicted exacerbations within 1 year.

In the increased emotional aspect of breathlessness observed after exercise in exacerbators, fear was positively correlated with V_E and f_R during exercise, suggesting that driving limbic system involvement in ventilatory response plays an important part in the worsening of breathing discomfort upon exertion. Identifying sensory and emotional aspects of dyspnoea upon exertion was shown to be predictive of exacerbations, even in the absence of breathlessness at static state in stable outpatients with COPD.

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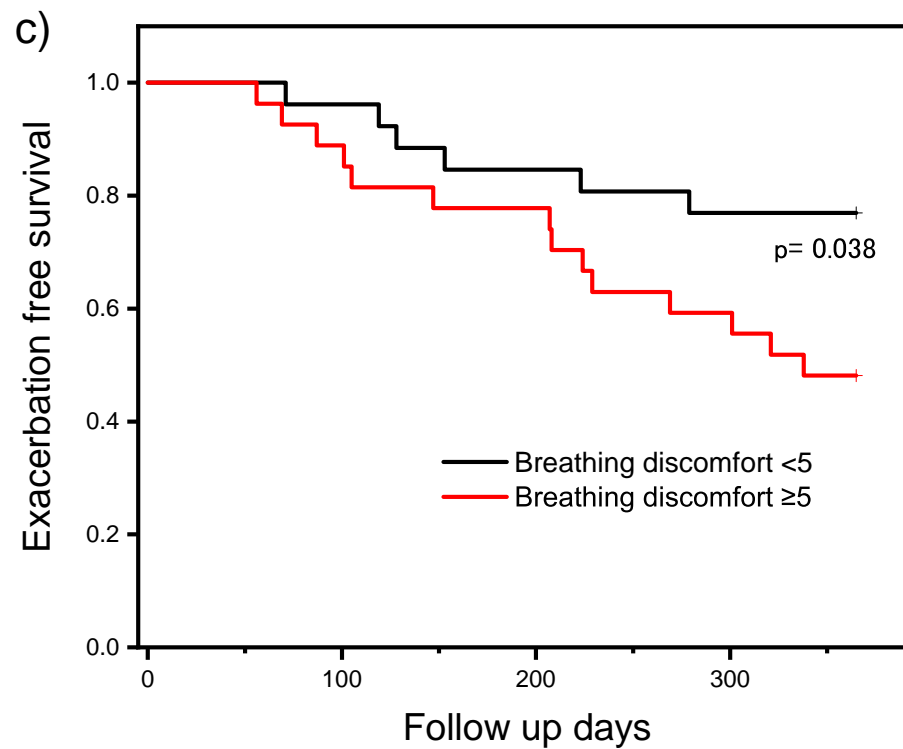
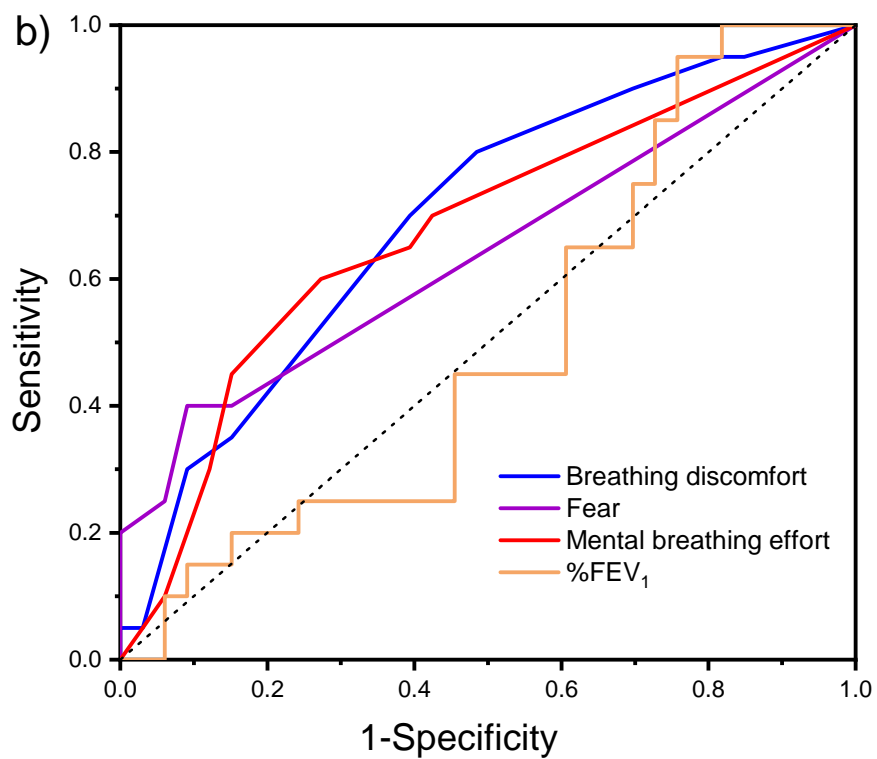
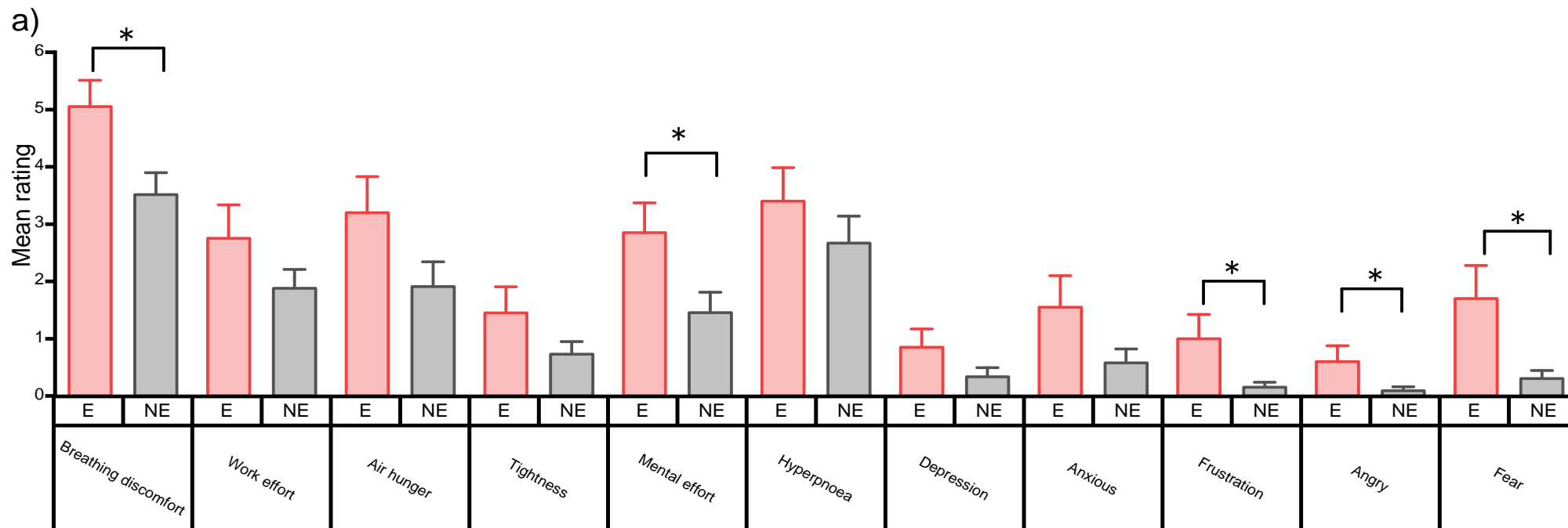


Figure 1

a) Multidimensional Dyspnoea Profile (MDP) at the end of exercise. E indicates patients with COPD who had exacerbations within 1 year. NE indicates patients with COPD who had no exacerbations within 1 year. b) Receiver-operator characteristic plots for predicting exacerbation within 1 year. Area under the curve for breathing discomfort, mental breathing effort, fear, and %FEV₁ are 0.69 (p = 0.28), 0.70 (p = 0.02), 0.67 (p = 0.44), and 0.50 (p = 0.95), respectively. FEV₁: forced expiratory volume in 1 second. c) Kaplan–Meier plots from testing to exacerbation time (days) for patients with respiratory discomfort of five or more after a 3-minute stepping exercise (red line) and those with breathing discomfort of less than 5 (black line).