Associations of Exercise Tolerance and Clinical Parameters in Japanese Patients With Chronic Obstructive Pulmonary Disease: Impact of Skeletal Muscle

Hiroki Tashiro (✉ si3222@cc.saga-u.ac.jp)

Saga University

Koichiro Takahashi

Saga University

Masahide Tanaka

Saga University

Hironori Sadamatsu

Saga University

Yuki Kurihara

Saga University

Ryo Tajiri

Saga University

Ayako Takamori

Saga University

Hiroyuki Naotsuka

Saga University

Hiroki Imaizumi

Saga University

Shinya Kimura

Saga University

Naoko Sueoka-Aragane

Saga University

Research Article

Keywords: exercise tolerance, cardiopulmonary exercise testing, skeletal muscle, COPD

Posted Date: February 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-199971/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Scientific Reports on August 5th, 2021. See the published version at <https://doi.org/10.1038/s41598-021-95413-9>.

Title

Associations of exercise tolerance and clinical parameters in Japanese patients with chronic obstructive pulmonary disease: Impact of skeletal muscle

Authors

Hiroki Tashiro¹, Koichiro Takahashi¹, Masahide Tanaka¹, Hironori Sadamatsu¹, Yuki Kurihara¹, Ryo Tajiri², Ayako Takamori², Hiroyuki Naotsuka³, Hiroki Imaizumi³, Shinya Kimura¹, Naoko Sueoka-Aragane¹

Affiliations

¹ Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan

² Clinical Research Center, Saga University Hospital, Saga, Japan

³ Advanced Comprehensive Functional Recovery Center, Saga University Hospital, Saga, Japan

Corresponding author: Hiroki Tashiro MD, PhD

Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University

5-1-1 Nabeshima, Saga, Saga Prefecture, 849-8501, Japan

Phone: +81-952-34-2369; Fax: +81-952-34-2017

E-mail: si3222@cc.saga-u.ac.jp

Abstract

Background

Decreasing exercise tolerance is one of the key features related to a poor prognosis in patients with chronic obstructive pulmonary disease (COPD). Cardiopulmonary exercise testing (CPET) is useful for evaluating exercise tolerance. The present study was performed to clarify the correlation between exercise tolerance and clinical parameters, focusing especially on the cross-sectional area (CSA) of skeletal muscle.

Methods

The present study retrospectively investigated 69 patients with COPD who underwent CPET. The correlations between oxygen uptake ($\dot{V}O_2$) at peak exercise and clinical parameters of COPD, including skeletal muscle area measured using single-section axial computed tomography (CT), were evaluated.

Results

The COPD assessment test score ($\rho = -0.35$, $p = 0.02$) and the CSA of the pectoralis muscles ($\rho = 0.32$, $p = 0.02$) were weakly correlated with $\dot{V}O_2$ at peak exercise. In addition, forced expiratory volume in one second (FEV₁) ($\rho = 0.39$, $p = 0.0009$), FEV₁/forced vital capacity ($\rho = 0.33$, $p = 0.006$), and the CSA of the erector spinae muscles ($\rho = 0.34$, $p = 0.009$) were correlated with $\dot{V}O_2$ at peak exercise.

Conclusions

Decreased FEV₁ and loss of skeletal muscles, especially anti-gravity muscles, are correlated with a low level of exercise tolerance in COPD patients.

46 **Keywords**

47 exercise tolerance, cardiopulmonary exercise testing, skeletal muscle, COPD

48

Introduction

Chronic pulmonary obstructive disease (COPD) is a common respiratory disease, with a reported global prevalence of 251 million cases ¹, and it is considered a life-threatening disease with decreasing pulmonary function and airflow limitation ².

Recently, factors related to a poor prognosis of COPD patients, including mortality and exacerbations, are becoming understood as evidence increases. For example, low-level physical activity, percent predicted forced expiratory volume in one second (%FEV₁), 6-minute walk distance, body mass index (BMI), and a high frequency of exacerbations are significantly associated with mortality in COPD patients ^{3,4}. We and others have also reported that low-level pulmonary function, exercise tolerance (including 6-minute walk distance and exercise-induced desaturation), and BMI are correlated with a high frequency of exacerbations ⁵⁻⁸, indicating that evaluations of exercise tolerance and body composition, in addition to pulmonary function, are important for predicting the clinical course of COPD.

Decreasing exercise tolerance, normally measured by the 6-minute walk test or cardiopulmonary exercise testing (CPET), is one of the important clinical features related to a poor prognosis in COPD patients ^{3,9,10}, and with CPET one can evaluate exercise tolerance with exertional ventilatory parameters precisely and safely ^{11,12}. For example, oxygen uptake ($\dot{V}_{O_2}$) at peak exercise, which represents exercise tolerance, is significantly correlated with FEV₁ and %FEV₁ reflecting the severity of COPD ^{13,14}. Notably, with CPET, one can detect physical problems including cardiac dysfunction and functional skeletal muscle disorders during the test, which contributes to rapid initiation of treatment ¹⁵.

Weight loss is a common systemic characteristic of patients with COPD ¹⁶, and skeletal muscle loss has greater impact on the severity of COPD than decreased BMI ¹⁷. Radiological analysis of skeletal muscles on computed tomography (CT) is a useful procedure for quantitation without onerous physical intervention ^{18,19}, and the cross-sectional area (CSA) of skeletal muscle on single-slice axial CT is significantly correlated with a poor prognosis in COPD patients ^{20,21}. In

addition, the CSA of the erector spinae muscles (ECMs), which are anti-gravity muscles, but not of the pectoralis muscles (PMs), is significantly associated with mortality in Japanese patients with COPD ²¹. Obviously, skeletal muscles are important for exercise tolerance, but the impact of exertional ventilatory parameters on CPET compared to clinical parameters in patients with COPD is not fully understood.

In the present real-world study, correlations between exercise tolerance indicated by $\dot{V}O_2$ at peak exercise and clinical parameters including skeletal muscle area were examined in Japanese patients with COPD. Decreases of FEV₁ and FEV₁/FVC are significantly correlated with a low level of exercise tolerance, and, importantly, skeletal muscle area, especially of the ECMs as anti-gravity muscles, is more correlated with $\dot{V}O_2$ at peak exercise than PM area on CT imaging. These data suggest that decreased FEV₁ and FEV₁/FVC are correlated with decreased exercise tolerance and loss of skeletal muscles, especially the anti-gravity muscles, that contribute to a low level of exercise tolerance.

Results

Clinical baseline characteristics of COPD patients

In the present study, 69 COPD patients (66 males, 3 females) who underwent CPET were enrolled; their average age was 71.1 years, BMI was 21.4 kg/m², and smoking history was 67.6 pack-years. GOLD stages I - IV were 12 (17.4%), 27 (39.1%), 25 (36.2%), and 5 (7.2%), respectively; mMRC dyspnea scale scores (0 - 4) were 5 (7.2%), 18 (26.1%), 27 (39.1%), 16 (23.2%), and 3 (4.3%), respectively. The average COPD assessment test score available for 41 patients was 16.8, and the average 6-minute walk distance for 48 patients was 386.1 m. For medications, long-acting muscarinic antagonist (LAMA) or long acting β_2 adrenergic agonist (LABA) monotherapy was given to 5 (7.2%) patients. LABA-LAMA and inhaled corticosteroid (ICS)-LABA combination therapies were given to 19 (27.5%) and 9 (13.0%) patients, respectively. Triple combination therapy was given to 19 (27.5%) patients. Five patients (7.2%) were not given respiratory medications. On pulmonary function testing, %VC and %FVC were 100.4% and 95.2%, respectively. FEV₁, FEV₁/FVC, and %FEV₁ were 1.35 L, 60.2%, and 65.9%, respectively. The average DLco was 65.9%. On CT, PM_{CSA} and ECM_{CSA} were 24.7 cm² and 27.1 cm², respectively (Table 1).

Parameters of cardiopulmonary exercise testing

$\dot{V}_{O_2}$, which is a marker that reflects exercise tolerance²², was 295.6 ml/min at rest and 926.0 ml/min at peak exercise. Body weight-adjusted $\dot{V}_{O_2}$ was 5.3 ml/min/kg at rest and 16.2 ml/min/kg at peak exercise. V_T and V_E were 773.2 ml and 12.9 L/min at rest and 1245.7 ml and 36.6 L/min at peak exercise, respectively. $\dot{V}_E/\dot{V}_{CO_2}$, which reflects pulmonary clearance of CO₂²², was 49.3 at rest and 41.1 at peak exercise. V_D/V_T , which reflects the efficacy of pulmonary gas exchange, was 0.28 at rest and 0.26 at peak exercise. The respiratory rate was 17.7 breaths/min at rest and 30.5 breaths/min at peak exercise (Table 2).

Correlations between $\dot{V}_{O_2}$ (ml/min/kg) at peak exercise and other parameters on CPET and the 6-minute walk distance

Because $\dot{V}_{O_2}$ (ml/min) is affected by body weight differences, $\dot{V}_{O_2}$ adjusted by body weight (ml/min/kg) at peak exercise is considered a precise marker for exercise tolerance²². Therefore, the evaluation focused on that and its correlations with other CPET parameters and the 6-minute walk distance. $\dot{V}_{O_2}$ at peak exercise was significantly correlated with $\dot{V}_E/\dot{V}_{CO_2}$ at rest ($\rho = -0.46$, $p < 0.0001$) and at peak exercise ($\rho = -0.45$, $p < 0.0001$), V_D/V_T at rest ($\rho = -0.36$, $p = 0.002$) and at peak exercise ($\rho = -0.53$, $p < 0.0001$), respiratory rate at rest ($\rho = -0.35$, $p = 0.003$) and at peak exercise ($\rho = -0.33$, $p = 0.006$), and the 6-minute walk distance ($\rho = 0.74$, $p < 0.0001$) (Table 3, Supplementary Fig. S1a online). These data showed that $\dot{V}_{O_2}$ (ml/min/kg) at peak exercise reflected exercise tolerance in COPD patients.

Comparisons of correlations between $\dot{V}_{O_2}$ (ml/min/kg) at peak exercise and clinical parameters of COPD including skeletal muscle area

To clarify the factors correlated with exercise tolerance as reflected by $\dot{V}_{O_2}$ (ml/min/kg) at peak exercise, correlation analysis between $\dot{V}_{O_2}$ (ml/min/kg) at peak exercise and clinical parameters of COPD including skeletal muscle area was performed. Age, BMI, %VC, %FVC, %FEV₁, and DLco were not significantly correlated with $\dot{V}_{O_2}$ at peak exercise. The COPD assessment test score ($\rho = -0.35$, $p = 0.02$, Supplementary Fig. S1b online) and PM_{CSA} ($\rho = 0.32$, $p = 0.02$, Fig. 1c) were weakly correlated with $\dot{V}_{O_2}$ at peak exercise. FEV₁ ($\rho = 0.39$, $p = 0.0009$, Fig. 1a), FEV₁/FVC ($\rho = 0.33$, $p = 0.006$, Fig. 1b), and ECM_{CSA} ($\rho = 0.34$, $p = 0.009$, Fig. 1d) were correlated with $\dot{V}_{O_2}$ at peak exercise (Table 4). Examining the difference in $\dot{V}_{O_2}$ at peak exercise by COPD stage, COPD stage III and IV patients had significantly lower levels of $\dot{V}_{O_2}$ at peak exercise than stage II patients (Fig. 2a). Additionally, examining the difference in $\dot{V}_{O_2}$ at peak exercise by the mMRC dyspnea scale score, patients with an mMRC scale score of 3 had a significantly lower $\dot{V}_{O_2}$ at peak exercise than those with an mMRC scale score of 0 (Fig. 2b).

For other parameters on CPET, $\dot{V}_E/\dot{V}_{CO_2}$ at peak exercise was significantly correlated with BMI ($\rho = -0.33$, $p = 0.007$), the COPD assessment test score ($\rho = 0.58$, $p < 0.0001$), DLco ($\rho = -0.42$, $p = 0.001$), PM_{CSA} ($\rho = -0.31$, $p = 0.02$), and ECM_{CSA} ($\rho = -0.31$, $p = 0.02$). In addition, V_D/V_T at peak exercise was significantly correlated with age ($\rho = 0.34$, $p = 0.005$), BMI ($\rho = -0.28$, $p = 0.02$), the COPD assessment test score ($\rho = 0.41$, $p = 0.009$), %VC ($\rho = -0.28$, $p = 0.02$), FEV_1 ($\rho = -0.42$, $p = 0.004$), FEV_1/FVC ($\rho = -0.36$, $p = 0.003$), % FEV_1 ($\rho = -0.27$, $p = 0.03$), PM_{CSA} ($\rho = -0.31$, $p = 0.02$), and ECM_{CSA} ($\rho = -0.27$, $p = 0.03$) (Supplementary Table S1 online).

Discussion

In the present real-world study, the exercise tolerance of COPD patients was evaluated by CPET, and it was confirmed that $\dot{V}_{O_2}$ at peak exercise was significantly correlated with 6-minute walk distance and other CPET parameters, such as $\dot{V}_E/\dot{V}_{CO_2}$, V_D/V_T , and respiratory rate, which suggested that $\dot{V}_{O_2}$ at peak exercise is a useful marker of exercise tolerance for COPD patients. The analysis of correlation coefficients showed that the COPD assessment test, FEV₁, FEV₁/FVC, PM_{CSA}, and ECM_{CSA} were correlated with $\dot{V}_{O_2}$ at peak exercise. Additionally, ECM_{CSA}, reflecting anti-gravity muscles, was more correlated with $\dot{V}_{O_2}$ at peak exercise than PM_{CSA}, showing that the loss of skeletal muscles, especially anti-gravity muscles, contributed to a low level of exercise tolerance.

Loss of exercise tolerance is an important and widely recognized clinical manifestation of COPD^{15, 22}. With respect to the mechanisms, exercise-induced dyspnea with dynamic pulmonary hyperinflation and desaturation of oxygen, which is a representative manifestation of COPD, contributes to a low threshold of exhaustion with the early appearance of anaerobic metabolites in skeletal muscles during exercise²². Thus, $\dot{V}_{O_2}$ at peak exercise on CPET, which is determined by cellular O₂ demand and the maximal rate of O₂ transport, is considered a useful marker of exercise tolerance in COPD patients¹⁵. Diaz et al analyzed 52 patients with mild to severe COPD, and air-flow limitation, which reflects the presence of dynamic hyperinflation, was found to be significantly associated with $\dot{V}_{O_2}$ at peak exercise¹². Moreover, Kagawa et al analyzed 294 patients with COPD who underwent CPET, and they found that decreased FEV₁ was associated with a low $\dot{V}_{O_2}$ at peak exercise¹³. These reports showed that limitation of exercise tolerance predicted by decreased $\dot{V}_{O_2}$ at peak exercise is an important phenotype of COPD, as shown in the current study (Table 4, Fig. 1a, Fig. 1b). The severity of COPD predicted by %FEV₁ is also related to the decrease of exercise tolerance, and Yamamoto et al reported that $\dot{V}_{O_2}$ at peak exercise was significantly higher in COPD patients in GOLD stages I and II than in those in GOLD stages III and IV¹⁴. The current results also showed that the level

of $\dot{V}_{O_2}$ at peak exercise tended to be decreased depending on the GOLD stage, except for stage I (Fig. 2a), although the correlation between $\dot{V}_{O_2}$ at peak exercise and %FEV₁ was weak (Table 4).

Loss of skeletal muscles with bodyweight reduction, called sarcopenia, is also an important characteristic of COPD patients^{20, 23, 24}. Reduction of fat-free mass containing skeletal muscle is associated with mortality in patients with COPD²⁵. In addition, a previous report showed that COPD patients with decreased skeletal muscles, calculated by bioelectrical impedance analysis, walked a significantly shorter distance on the incremental shuttle walk test, which is another index of exercise tolerance, than those with preserved skeletal muscles²⁶. With respect to the mechanisms, loss of skeletal muscles causes increased O₂ demand as exercise intensity increases and earlier reaching of the anaerobic threshold with metabolic acidosis and increased lactate, which limits exercise tolerance in patients with COPD^{27, 28}. The present study showed that skeletal muscle area including PM_{CSA} and ECM_{CSA} was significantly correlated with $\dot{V}_{O_2}$ at peak exercise, which is consistent with these data (Table 4, Fig. 1c, Fig. 1d).

Importantly, the present results showed that ECM_{CSA}, representing anti-gravity muscles, was more correlated with $\dot{V}_{O_2}$ at peak exercise than PM_{CSA} (Table 4), which suggests that loss of skeletal muscle might be heterogeneous, depending on the anatomical role of the muscle groups. Indeed, a prospective, observational study of 130 COPD patients showed that ECM_{CSA} is correlated with clinical parameters of COPD and more correlated with all-cause mortality than PM_{CSA}²⁰. In addition, a longitudinal, 10-year observational study showed that loss of ECM_{CSA}, but not PM_{CSA}, significantly increased the hazard ratio of mortality²¹, because physical activity is the strongest predictor of the prognosis of COPD patients³, and sedentary behavior, which affects the anti-gravity muscles, is particularly important in COPD^{29, 30}; thus, anti-gravity muscles might contribute to exercise tolerance in patients with COPD, as seen in the present study.

Notably, other gas exchange parameters on CPET such as $\dot{V}_E/\dot{V}_{CO_2}$ and V_D/V_T at peak exercise were associated with the clinical data of COPD, including skeletal muscle area (Supplementary Table S1 online). These parameters were reported to be significantly higher in patients with COPD than in healthy individuals³¹, and $\dot{V}_E/\dot{V}_{CO_2}$, which reflects decreased pulmonary clearance of CO₂ during exercise, was correlated with BMI, %FEV₁, and DLco, in addition to skeletal muscle areas. Moreover, V_D/V_T , which reflects worse pulmonary gas exchange efficacy, was correlated with age, BMI, %VC, FEV₁, FEV₁/FVC, and %FEV₁, in addition to skeletal muscle areas. Interestingly, the COPD assessment test score was strongly correlated with these parameters, suggesting that $\dot{V}_E/\dot{V}_{CO_2}$ and V_D/V_T might reflect COPD-related symptoms (Supplementary Table S1 online).

There are several limitations of the present study. First, correlations with physical activity were not evaluated. Second, correlations were evaluated using clinical parameters of COPD and skeletal muscle area, which acted as confounding factors. Partial correlation coefficients were calculated using factors including the COPD assessment test score, FEV₁, FEV₁/FVC, %FEV₁, DLco, PM_{CSA}, and ECM_{CSA}, and the COPD assessment test score, PM_{CSA}, and ECM_{CSA} were more correlated with $\dot{V}O_2$ at peak exercise than FEV₁, FEV₁/FVC, %FEV₁, and DLco after adjustment (data not shown), suggesting that skeletal muscle area might be more important than pulmonary function for exercise tolerance. Finally, the present study involved patients at a single hospital with limited ethnic diversity and a small sample size. To confirm the validity of the present results, multicenter, prospective studies with a larger number of patients should be performed.

224 **Conclusions**

225 The present study showed that decreases in FEV₁ and FEV₁/FVC are significantly correlated
226 with a low level of exercise tolerance and skeletal muscle area, and the area of the ECMs, as
227 anti-gravity muscles, is more correlated with $\dot{V}_{O_2}$ at peak exercise than the area of the PMs.
228 These data suggest that decreased pulmonary function and loss of skeletal muscles, especially
229 anti-gravity muscles, contribute to the low level of exercise tolerance in patients with COPD.

230

Methods

Patients and setting

The medical records of 69 patients diagnosed with COPD who underwent CPET at the Saga University Hospital between 2009 and 2020 were retrospectively reviewed. All patients satisfied the definition criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Briefly, patients were confirmed to have $FEV_1/FEV < 0.7$ after using a bronchodilator, a smoking index > 10 pack years, and symptoms including chronic cough, sputum, and dyspnea. Patients with either a current or a previous diagnosis of asthma were excluded. For patient information, age at the time CPET was performed was used, and clinical parameters including BMI, modified Medical Research Council (mMRC) dyspnea scale, COPD assessment test, 6-minute walk test, medication record, and pulmonary function at the time closest to when CPET was performed (within ± 3 months) were evaluated. Thus, 41 patients who underwent the COPD assessment test and 48 patients who underwent the 6-minute walk test were analyzed. Medications were selected at each physician's discretion. This study was approved by the ethics committee of Saga University Hospital (approval number: 2020-11-R-03, approval date: Jan 27, 2021) and was performed in accordance with the 1964 Declaration of Helsinki. Informed consent was obtained for participants in the form of opt-out on the web-site. Those who rejected were excluded.

Cardiopulmonary Exercise Testing

A symptom-limited cycle ergometer (Strength Ergo 8, Mitsubishi Electric Engineering, Japan) was used for CPET. Each patient wore a mask, and breath was analyzed using a gas analyzer (Cpex-1, Inter Reha; Japan); $\dot{V}_{O_2}$, expiratory tidal volume (V_T), minute ventilation (V_E), ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$), dead space to tidal volume ratio (V_D/V_T), and breathing frequency at rest and at peak exercise were evaluated. Oxygen saturation, blood pressure, and the electrocardiogram were measured during the test. In the exercise protocol, pre-

exercise resting measurements were obtained within the steady state period for more than 3 minutes. Incremental testing was then started by increasing the load by 10 W per minute. The examination was continued until exhaustion or above the predicted maximum heart rate or blood pressure, and showing electrocardiographic changes such as ST segment depression of greater than 2 mm and a short run of premature ventricular contractions. Dyspnea intensity was evaluated by a 10-point modified Borg category-ratio scale at rest and every 1 minute after initiation of the incremental load test. The data generated were measured breath-by-breath and as 30-second averages at rest and during exercise.

CT scan acquisition and analysis

Chest CT for analysis of the pectoralis and erector spinae muscles that was performed most closely to the time of CPET (within ± 3 years) was also selected; the average time between CPET and chest CT was 198 days. Consequently, 57 patients were examined. For quantitative analysis, the CSAs of the pectoralis muscles (PM_{CSA}) and the erector spinae muscles (ESM_{CSA}) were evaluated referring to the previously described method^{20, 24, 32}. Briefly, left and right areas of PM_{CSA} identified by the superior aspect of the aortic arch and ESM_{CSA} identified by the superior aspect of the 12th thoracic vertebrae on CT imaging reconstructed using the mediastinal setting were identified and shaded manually. Finally, the sum of the left and right muscle areas was examined. The measurements were performed by two pulmonary physicians independently.

Statistical analysis

For correlation analysis, Spearman's rank correlation coefficients between exercise tolerance parameters such as $\dot{V}O_2$, $\dot{V}_E/\dot{V}_{CO_2}$, V_D/V_T , breathing frequency, and 6-minute walk distance, and clinical parameters including age, BMI, COPD assessment test score, %VC, %FVC, FEV₁, FEV₁/FVC, %FEV₁, diffusing capacity of the lung for carbon monoxide (DLco), PM_{CSA} , and ECM_{CSA} were calculated to determine whether they were zero. Differences of $\dot{V}O_2$ at peak

283 exercise depending on GOLD stages and the mMRC dyspnea scale were analyzed by the Steel-
284 Dwass method. Quantitative data are presented as means $\pm$ standard deviation (SD);
285 significance was considered a p value less than 0.05. Statistical analysis was performed with
286 JMP Pro version 14.2.0 software (SAS Institute Inc., Cary, NC, USA).
287

288 **Data availability**

289 The datasets used and analyzed during the current study are available from the corresponding
290 author on reasonable request.

291

292

293 **References**

- 294 1. Halpin DMG, et al. The GOLD Summit on chronic obstructive pulmonary disease in
295 low- and middle-income countries. *Int J Tuberc Lung Dis.* **23**, 1131-41. (2019).
- 296 2. Hasegawa W, et al. Factors affecting mortality following emergency admission for
297 chronic obstructive pulmonary disease. *BMC Pulm Med.* **14**, 151. (2014).
- 298 3. Waschki B, et al. Physical activity is the strongest predictor of all-cause mortality in
299 patients with COPD: a prospective cohort study. *Chest.* **140**, 331-42. (2011).
- 300 4. Prudente R, et al. Predictors of mortality in patients with COPD after 9 years. *Int J Chron*
301 *Obstruct Pulmon Dis.* **13**, 3389-98. (2018).
- 302 5. Tashiro H, et al. Clinical features of Japanese patients with exacerbations of chronic
303 obstructive pulmonary disease. *BMC Pulm Med.* **20**, 318. (2020).
- 304 6. Kim EK, et al. Impact of Body Mass Index Change on the Prognosis of Chronic
305 Obstructive Pulmonary Disease. *Respiration.* 1-11. (2020).
- 306 7. Chang CH, et al. Factors Associated with Exercise-Induced Desaturation in Patients
307 with Chronic Obstructive Pulmonary Disease. *Int J Chron Obstruct Pulmon Dis.* **15**, 2643-52.
308 (2020).
- 309 8. Herer B, Chinnet T. Acute exacerbation of COPD during pulmonary rehabilitation:
310 outcomes and risk prediction. *Int J Chron Obstruct Pulmon Dis.* **13**, 1767-74. (2018).
- 311 9. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test.
312 *Am J Respir Crit Care Med.* **166**, 111-7. (2002).
- 313 10. Horie J, et al. Validation of Clinical Characteristics and Effectiveness of Pulmonary
314 Rehabilitation in a COPD Population with Discrepancy between Exercise Tolerance and FEV1.
315 *Healthcare (Basel).* **9**. (2021).
- 316 11. Puente-Maestu L, et al. Use of exercise testing in the evaluation of interventional
317 efficacy: an official ERS statement. *Eur Respir J.* **47**, 429-60. (2016).
- 318 12. Diaz O, et al. Role of inspiratory capacity on exercise tolerance in COPD patients with
319 and without tidal expiratory flow limitation at rest. *Eur Respir J.* **16**, 269-75. (2000).
- 320 13. Kagawa H, et al. Dyspnea and the Varying Pathophysiologic Manifestations of Chronic
321 Obstructive Pulmonary Disease Evaluated by Cardiopulmonary Exercise Testing With Arterial
322 Blood Analysis. *Front Physiol.* **9**, 1293. (2018).
- 323 14. Yamamoto Y, et al. Evaluation of Exertional Ventilatory Parameters Using Oscillometry
324 in COPD. *Int J Chron Obstruct Pulmon Dis.* **15**, 1697-711. (2020).
- 325 15. American Thoracic S, American College of Chest P. ATS/ACCP Statement on
326 cardiopulmonary exercise testing. *Am J Respir Crit Care Med.* **167**, 211-77. (2003).
- 327 16. Landbo C, et al. Prognostic value of nutritional status in chronic obstructive pulmonary
328 disease. *Am J Respir Crit Care Med.* **160**, 1856-61. (1999).
- 329 17. Ischaki E, et al. Body mass and fat-free mass indices in COPD: relation with variables
330 expressing disease severity. *Chest.* **132**, 164-9. (2007).
- 331 18. Giuliani HK, Gerstner GR, Mota JA, Ryan ED. Influence of Demographic
332 Characteristics and Muscle Strength on the Occupational Fatigue Exhaustion Recovery Scale in
333 Career Firefighters. *J Occup Environ Med.* **62**, 223-6. (2020).
- 334 19. Bak SH, Kwon SO, Han SS, Kim WJ. Computed tomography-derived area and density
335 of pectoralis muscle associated disease severity and longitudinal changes in chronic obstructive
336 pulmonary disease: a case control study. *Respir Res.* **20**, 226. (2019).
- 337 20. Tanimura K, et al. Quantitative Assessment of Erector Spinae Muscles in Patients with
338 Chronic Obstructive Pulmonary Disease. Novel Chest Computed Tomography-derived Index for
339 Prognosis. *Ann Am Thorac Soc.* **13**, 334-41. (2016).
- 340 21. Tanabe N, et al. Associations of CT evaluations of antigravity muscles, emphysema and
341 airway disease with longitudinal outcomes in patients with COPD. *Thorax.* (2020).
- 342 22. Arena R, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of

- patients with heart and lung disease. *Circulation*. **123**, 668-80. (2011).
23. Maltais F, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. **189**, e15-62. (2014).
24. McDonald ML, et al. Quantitative computed tomography measures of pectoralis muscle area and disease severity in chronic obstructive pulmonary disease. A cross-sectional study. *Ann Am Thorac Soc*. **11**, 326-34. (2014).
25. Vestbo J, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med*. **173**, 79-83. (2006).
26. Jones SE, et al. Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. *Thorax*. **70**, 213-8. (2015).
27. Patessio A, et al. Comparison of gas exchange, lactate, and lactic acidosis thresholds in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. **148**, 622-6. (1993).
28. Hughson RL, Weisiger KH, Swanson GD. Blood lactate concentration increases as a continuous function in progressive exercise. *J Appl Physiol* (1985). **62**, 1975-81. (1987).
29. Tremblay MS, et al. Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project process and outcome. *Int J Behav Nutr Phys Act*. **14**, 75. (2017).
30. Takahashi K, et al. First-Line Treatment with Tiotropium/Olodaterol Improves Physical Activity in Patients with Treatment-Naive Chronic Obstructive Pulmonary Disease. *Int J Chron Obstruct Pulmon Dis*. **15**, 2115-26. (2020).
31. Elbehairy AF, et al. Pulmonary Gas Exchange Abnormalities in Mild Chronic Obstructive Pulmonary Disease. Implications for Dyspnea and Exercise Intolerance. *Am J Respir Crit Care Med*. **191**, 1384-94. (2015).
32. Lee CS, et al. Dorsal muscle group area and surgical outcomes in liver transplantation. *Clin Transplant*. **28**, 1092-8. (2014).

371 **Acknowledgements**

372 Not applicable

373

374 **Author Contributions**

375 H.T., K.T. and M.T. conceived and designed the project. H.T., Y.K., H.N. and H.I. analyzed and
376 interpreted the data. R.T. and A.T. advised the statistical analysis. H.T., K.T. and H.S. prepared
377 the manuscript with input from all other authors. S.K. and N.A. checked the prepared
378 manuscript. All authors reviewed the manuscript.

379

380 **Competing interests**

381 The authors declare no competing interests.

382

Figure 1. Correlations between $\dot{V}_{O_2}$ at peak exercise and clinical parameters of COPD.

Correlations between $\dot{V}_{O_2}$ at peak exercise and (a) FEV₁, (b) FEV₁/FEV, (c) PM_{CSA}, and (d) ECM_{CSA}

Abbreviations: $\dot{V}_{O_2}$: oxygen uptake, COPD: chronic obstructive pulmonary disease, FEV₁: forced expiratory volume in 1 second, FVC: forced vital capacity, PM_{CSA}: cross-sectional area of the pectoralis muscles, ECM_{CSA}: cross-sectional area of the erector spinae muscles.

Figure 2. Results of $\dot{V}_{O_2}$ by (a) GOLD stage and (b) mMRC dyspnea scale score. * $p < 0.05$

Abbreviations: $\dot{V}_{O_2}$: oxygen uptake, GOLD: Global Initiative for Chronic Obstructive Lung Disease, mMRC: modified Medical Research Council

399 Table 1. Demographics of the study participants (n = 69)

Clinical parameters	
age (years)	71.1 ± 9.0
gender (male/female)	66/3
BMI (kg/m ²)	21.4 ± 3.8
smoking history (pack-year)	67.6 ± 33.0
GOLD stage (I/II/III/IV, n)	12/27/25/5
mMRC dyspnea scale (0/1/2/3/4, n)	5/18/27/16/3
COPD assessment test (n = 41)	16.8 ± 7.6
6-minute walk distance (n = 48) (m)	386.1 ± 115.8
Medications	
No respiratory medication, n (%)	5 (7.2%)
LAMA or LABA alone, n (%)	17 (24.6%)
LABA-LAMA combo, n (%)	19 (27.5%)
ICS-LABA combo, n (%)	9 (13.0%)
Triple combo, n (%)	19 (27.5%)
Pulmonary function	
%VC (%)	100.4 ± 18.4
%FVC (%)	95.2 ± 17.5
FEV ₁ (L)	1.35 ± 0.59
FEV ₁ /FVC (%)	43.8 ± 13.4
%FEV ₁ (%)	60.2 ± 24.2
DLco (%)	65.9 ± 24.3
Evaluation of skeletal muscle on CT (n = 57)	
PM _{CSA} (cm ²)	24.7 ± 8.1
ECM _{CSA} (cm ²)	27.1 ± 6.7

400
401 BMI; body mass index, GOLD; global initiative for chronic obstructive lung disease, mMRC;
402 modified medical research council, COPD; chronic obstructive pulmonary disease, LAMA;
403 long-acting muscarinic antagonist, LABA; long acting β_2 adrenergic agonist, ICS; inhaled
404 corticosteroid, VC; vital capacity, FVC; forced vital capacity, FEV₁; forced expiratory volume
405 in 1 second, DLco; diffusing capacity of lung for carbon monoxide, PM_{CSA}; cross-sectional area
406 of pectoralis muscles, ECM_{CSA}; cross-sectional area of erector spinae muscles. Data are
407 presented as mean ± standard deviation.

408 Table 2. Results of cardiopulmonary exercise testing at rest and at peak exercise (n = 69)

	at rest	at peak exercise
Incremental load testing		
$\dot{V}_{O_2}$ (ml/min)	295.6 ± 68.2	926.0 ± 338.4
$\dot{V}_{O_2}$ (ml/min/kg)	5.3 ± 1.2	16.2 ± 4.7
V_T (ml)	773.2 ± 204.5	1245.7 ± 362.6
V_E (L/min)	12.9 ± 2.6	36.6 ± 10.9
$\dot{V}_E / \dot{V}_{CO_2}$	49.3 ± 8.9	41.1 ± 8.4
V_D / V_T	0.28 ± 0.07	0.26 ± 0.07
Breathing frequency (times/min)	17.7 ± 4.2	30.5 ± 8.1

409

410 $\dot{V}_{O_2}$; oxygen uptake, V_T ; tidal volume, V_E ; minute ventilation, $\dot{V}_E / \dot{V}_{CO_2}$; ventilatory equivalent

411 for carbon dioxide, V_D / V_T ; dead space to tidal volume ratio. Data are presented as mean $\pm$

412 standard deviation.

413

414 Table 3. Correlation coefficients between $\dot{V}_{O_2}$ at peak exercise and other CPET parameters and
 415 the 6-minute walk distance

	$\dot{V}_{O_2}$ (ml/min/kg) at peak exercise	
	ρ	p value
$\dot{V}_E/\dot{V}_{CO_2}$ at rest	-0.46	<0.0001
$\dot{V}_E/\dot{V}_{CO_2}$ at peak exercise	-0.45	<0.0001
V_D/V_T at rest	-0.36	0.002
V_D/V_T at peak exercise	-0.53	<0.0001
Breathing frequency at rest	-0.35	0.003
Breathing frequency at peak exercise	-0.33	0.006
6-minute walk distance (n = 48)	0.74	<0.0001

416
 417 $\dot{V}_{O_2}$; oxygen uptake, V_T ; tidal volume, V_E ; minute ventilation, $\dot{V}_E/\dot{V}_{CO_2}$; ventilatory equivalent
 418 for carbon dioxide, V_D/V_T ; dead space to tidal volume ratio.
 419

Table 4. Correlation coefficients between $\dot{V}_{O_2}$ at peak exercise and other CPET parameters and the 6-minute walk distance

	$\dot{V}_{O_2}$ (ml/min/kg) at peak exercise	
	ρ	p value
age (years)	-0.22	0.08
BMI (kg/m ²)	0.08	0.54
COPD assessment test	-0.35	0.02
%VC (%)	0.19	0.11
%FVC (%)	0.16	0.2
FEV ₁ (L)	0.39	0.0009
FEV ₁ /FVC (%)	0.33	0.006
%FEV ₁ (%)	0.24	0.05
DLco (%)	0.26	0.05
PM _{CSA} (cm ²)	0.32	0.02
ECM _{CSA} (cm ²)	0.34	0.009

CPET; Cardiopulmonary exercise testing, $\dot{V}_{O_2}$; oxygen uptake, BMI; body mass index, COPD; chronic obstructive pulmonary disease, VC; vital capacity, FVC; forced vital capacity, FEV₁; forced expiratory volume in 1 second, DLco; diffusing capacity of lung for carbon monoxide, PM_{CSA}; cross-sectional area of pectoralis muscles, ECM_{CSA}; cross-sectional area of erector spinae muscles.

Figures

Figure 1

Tashiro H et al,

Figure 1

Correlations between $\dot{V}'_{O_2}$ at peak exercise and clinical parameters of COPD. Correlations between $\dot{V}'_{O_2}$ at peak exercise and (a) FEV₁, (b) FEV₁/FVC, (c) PM_{CSA}, and (d) ECM_{CSA}. Abbreviations: $\dot{V}'_{O_2}$: oxygen uptake, COPD: chronic obstructive pulmonary disease, FEV₁: forced expiratory volume in 1 second, FVC: forced vital capacity, PM_{CSA}: cross-sectional area of the pectoralis muscles, ECM_{CSA}: cross-sectional area of the erector spinae muscles.

Figure 2

Results of $\dot{V}'_{O_2}$ by (a) GOLD stage and (b) mMRC dyspnea scale score. * $p < 0.05$ Abbreviations: $\dot{V}'_{O_2}$: oxygen uptake, GOLD: Global Initiative for Chronic Obstructive Lung Disease, mMRC: modified Medical Research Council

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementaryinformation1.pptx](#)
- [supplementaryinformation2.docx](#)