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Gas exchange efficiency slopes to assess exercise tolerance in chronic obstructive pulmonary disease

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Abstract

Background In patients with chronic obstructive pulmonary disease (COPD), the clinical use of the minute ventilation-carbon dioxide production ($\dot{V}_E$-$\dot{V}_{CO2}$) slope has been reported as a measure of exercise efficiency, but the oxygen uptake efficiency slope (OUES), i.e., the slope of oxygen uptake ($\dot{V}_{O2}$) versus the logarithmically transformed $\dot{V}_E$, has rarely been reported.

Methods We hypothesized that the $\dot{V}_E$-$\dot{V}_{CO2}$ slope is more useful than OUES in clinical use for the pathophysiological evaluation of COPD. Then, we investigated the cardiopulmonary exercise testing parameters affecting each of these slopes in 122 patients with all Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD grades selected from our database.

Results Compared with the GOLD I-II group ($n=51$), peak $\dot{V}_{O2}$ ($p<0.0001$), OUES ($p=0.0161$), $\dot{V}_E$ at peak exercise ($p<0.0001$), and percutaneous oxygen saturation (SpO_2) at peak exercise ($p=0.0004$) were significantly lower in the GOLD III-IV group ($n=71$). The GOLD III-IV group was divided into two groups by the exertional decrease in SpO_2 from rest to peak exercise: 3% or less (the non-desaturation group: $n=23$), or greater than 3% (the desaturation group: $n=48$). OUES correlated only weakly with peak $\dot{V}_{O2}$, $\dot{V}_E$ at peak exercise, and the difference between inspired and expired mean O_2 concentrations (ΔF_{O2}) at peak exercise, i.e., an indicator of oxygen consumption ability throughout the body, in the GOLD III-IV group with exertional hypoxemia. In contrast, the $\dot{V}_E$-$\dot{V}_{CO2}$ slope was significantly correlated with ΔF_{O2} at peak exercise, regardless of the COPD grade and exertional desaturation. Across all COPD stages, there was no correlation between the $\dot{V}_E$-$\dot{V}_{CO2}$ slope and $\dot{V}_E$ at peak exercise, and stepwise analysis identified peak $\dot{V}_{O2}$ ($p=0.0345$) and ΔF_{O2} ($p<0.0001$) as variables with a greater effect on the $\dot{V}_E$-$\dot{V}_{CO2}$ slope.

Conclusions The OUES may be less useful in advanced COPD with exertional hypoxemia. The $\dot{V}_E$-$\dot{V}_{CO2}$ slope, which is independent of $\dot{V}_E$, focuses on oxygen consumption ability and exercise tolerance in COPD, regardless of the exertional hypoxemia level and COPD grade. Therefore, the $\dot{V}_E$-$\dot{V}_{CO2}$ slope might be useful in establishing or evaluating tailor-made therapies for individual patient's pathologies in COPD as an indicator focusing on oxygen consumption ability.

Keywords Oxygen, Carbon dioxide, Exercise tolerance, Gas exchange, Pulmonary rehabilitation, Ventilatory efficiency

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Background

With the aging of the population, there is an urgent need to improve and maintain exercise tolerance irrespective of disease severity in chronic obstructive pulmonary disease (COPD) patients [1–3]. In cardiopulmonary exercise testing (CPET) using expiratory gas analysis, all parameters are calculated from directly measured ventilation flow and carbon dioxide (CO_2) and oxygen (O_2) concentrations [4]. As shown in the online supplementary Methods, oxygen uptake ($\dot{V}_{O2}$), is calculated using the following equation:

$$\dot{V}_{O2} = \frac{\Delta F_{O2} \times \dot{V}_E - F_{IO2} \times \dot{V}_{CO2}}{1 - F_{IO2}} (\mathrm{mL} \cdot \mathrm{min}^{-1})$$

where F_{IO2} and F_{EO2} are inspired and expired mean O_2 concentrations, respectively, $\dot{V}_E$ is minute ventilation, and $\dot{V}_{CO2}$ is carbon dioxide output. Based on the above equation and defining $\Delta F_{O2} = F_{IO2} - F_{EO2}$, $\dot{V}_{O2}$ is considered dependent on $\dot{V}_E$ and ΔF_{O2}. ΔF_{O2} is considered to reflect the ability of oxygen consumption processed by the entire body, including the muscles [4, 5], as shown in online supplementary Figure S1. Given that the primary indicator of exercise tolerance in CPET is peak $\dot{V}_{O2}$ [4, 6], information on the individual contributions of $\dot{V}_E$ or ΔF_{O2} to exercise tolerance, might be important when formulating treatment plans by considering which of the two factors has greater potential for improving exercise intolerance. However, this assumption has not been adequately evaluated in COPD.

We previously reported that ΔF_{O2}, which is directly measured in incremental exercise at peak exercise, has a strong negative correlation with ventilatory efficiency, indicated (1) by the $\dot{V}_E$-$\dot{V}_{CO2}$ slope, which indicates the degree of CO_2 clearance during exercise [7, 8], and (2) by the $\dot{V}_E/\dot{V}_{CO2}$ nadir, which is defined as the lowest value of the ratio between $\dot{V}_E$ and $\dot{V}_{CO2}$ during exercise, but is not well correlated with $\dot{V}_E/\dot{V}_{CO2\ intercept}$, that is, the Y intercept from the $\dot{V}_E$ versus $\dot{V}_{CO2}$ regression line [9]. Furthermore, the only indicators that were independent of $\dot{V}_E$ at peak exercise were ΔF_{O2} and the $\dot{V}_E$-$\dot{V}_{CO2}$ slope [9]. Therefore, of the three ventilatory efficiency indicators, this study focused on the $\dot{V}_E$-$\dot{V}_{CO2}$ slope. We also previously reported that, after pulmonary rehabilitation in patients with advanced COPD, the increased ΔF_{O2} at peak exercise in incremental exercise was correlated with the improvement in not only ventilatory efficiency, but also peak $\dot{V}_{O2}$. However, the increase in $\dot{V}_E$ does not affect the improvement in the $\dot{V}_E$-$\dot{V}_{CO2}$ slope [10]. Furthermore, no significant correlation was confirmed between the change in $\dot{V}_E$ and that in ΔF_{O2} at peak exercise following pulmonary rehabilitation. Interestingly, the calculated ratio of oxygen uptake to ventilation (i.e., $\dot{V}_{O2}/\dot{V}_E$), which is almost equivalent, but not equal, to actually measured ΔF_{O2}, is known as Oxygen Uptake Efficiency, and its highest plateau (OUEP) during incremental exercise has been reported as a useful factor for assessing the severity of dysfunction and as a prognostic factor for mortality and morbidity in patients with chronic heart failure, though it has not been evaluated in COPD [11]. More in depth knowledge of specialized indicators that reflect the ability of oxygen consumption to increase ΔF_{O2} during exercise separately from ventilatory ability to increase $\dot{V}_E$ would be useful for establishing therapeutic strategies and assessing exercise therapy targeting peripheral muscles not only in COPD patients, but in all patients for whom exercise therapy is indicated.

On the other hand, the Oxygen Uptake Efficiency Slope (OUES) in the regression equation $\dot{V}_{O2} = \mathrm{OUES} \times \log_{10}\dot{V}_E + \mathrm{intercept}$ is considered an objective estimate of cardiopulmonary functional reserve even at submaximal exercise. OUES has been proposed as a surrogate for maximal oxygen uptake ($\dot{V}_{O2}$ max.) based on the concept of OUES [12], because OUES has the ability to interrogate responses at submaximal exercise, which can be beneficial in patients whose peak $\dot{V}_{O2}$ is low (i.e., due to premature exercise termination because of symptoms or failure of $\dot{V}_{O2}$ to increase due to oxygen extraction difficulties). Although the physiological meaning of OUES has been highlighted in healthy subjects [13], children [12], and adult patients with cardiac disease [14], it has not been evaluated in COPD. Traditionally, OUES and OUEP have been used for outcome prediction in cardiovascular patients in whom respiratory limitation is not an issue. Given the advantage of the logarithm step, OUES emphasizes the physical condition in $\dot{V}_E$ in the early exercise phase. Therefore it might be a different exercise indicator from the later exercise phase evaluation of COPD such as the $\dot{V}_E$-$\dot{V}_{CO2}$ slope [7, 8] and peak $\dot{V}_{O2}$, because the severity of ventilatory disorders due to airflow limitation is greater at the end of exercise. In other words, the cardiopulmonary functional reserve suggested by OUES in advanced COPD with severe airflow limitation might be an overestimation that cannot actually be reached.

We hypothesized that, in COPD patients with exertional dyspnea, the $\dot{V}_E$-$\dot{V}_{CO2}$ slope is more useful than OUES in understanding their exercise pathophysiology and formulating a specific treatment plan for each patient based on that pathophysiology. In this study, we evaluated patients with all Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD grades, to examine the clinical implications of the $\dot{V}_E$-$\dot{V}_{CO2}$ slope and OUES, and to determine which of the pathophysiological indicators, especially ventilatory variables and ΔF_{O2} during exercise are affected by them.

Methods

Subjects

This was a retrospective study using existing clinical records. Of a cumulative total of 1212 patients who required evaluation of their exertional dyspnea during routine medical care and underwent CPET to understand their exercise pathophysiology or before treatment such as pulmonary rehabilitation at the NHO Osaka Toneyama Medical Centre from January 2015 to August 2022, 122 patients diagnosed with COPD ranging from mild to very severe according to the GOLD criteria, were selected and their data were retrospectively analyzed. Patients were excluded if: (1) they were diagnosed with bronchial asthma, active infection, or severe heart disease; (2) had a history of lung resection; (3) there were changes in their drug regimen within 4 weeks before CPET; or (4) they were unstable due to other reasons. This study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of the NHO Osaka Toneyama Medical Center (approval number: TNH-A-2022018). Each patient provided, written, informed consent before CPET evaluation during routine medical care, with the understanding that CPET was performed because it was considered necessary in daily clinical practice, and that the data obtained may be used in clinical research or other settings.

Pulmonary function tests (PFTs)

Post-bronchodilator spirometry was performed (CHESTAC 8800; CHEST M.I. Inc., Tokyo, Japan) according to the recommendations of the American Thoracic Society [15]. PFTs were performed within 2 weeks before or after CPET.

Cardiopulmonary exercise testing (CPET)

A CPET system (Aero monitor AE310S; Minato Medical Science Co., Ltd, Osaka, Japan) was used for symptom-limited incremental exercise tests performed in 1-minute or 2-minute stages with a 10-watt step protocol using an electrically braked cycle ergometer (CV-1000SS; Lode, Groningen, The Netherlands) [10, 16]. Calibrations for ventilatory measurement and gas measurements (CO_2 and O_2) were performed before each CPET. Pre-exercise resting measurements were obtained during the steady-state period after at least 3 min of rest after preparation for CPET. Ventilatory variables were measured on a breath-by-breath basis using a face mask, and they are presented as 30-s averages at rest, at 2-min intervals during exercise, and at the end of exercise. Dyspnea levels were assessed at rest, during the last 15 s of each exercise stage, and at the end of exercise using a 10-point modified Borg category-ratio scale. ΔF_{O2} was calculated from the difference between F_{IO2} and F_{EO2} measured during exercise. As measurements, the maximum value of ΔF_{O2} during exercise (ΔF_{O2} max) and ΔF_{O2} at peak exercise were examined. In addition, from January 2015 to August 2022, CPET was performed using the same expiratory gas analyzer based on the above protocol without any changes. The $\dot{V}_E$-$\dot{V}_{CO2}$ slope and $\dot{V}_E/\dot{V}_{CO2}$ nadir were calculated and defined as previously described [9]. Based on the assumption that log-transforming $\dot{V}_E$ will make the relationship between $\dot{V}_E$ and $\dot{V}_{O2}$ more linear than using $\dot{V}_E$, as shown in Fig. 1 and online supplemental Figure S2, OUES was calculated as the slope of the regression line relating $\dot{V}_{O2}$ (mL · min^{-1}) to the common logarithm of $\dot{V}_E$ (L · min^{-1}) by the equation: $\dot{V}_{O2}$ (mL · min^{-1}) = slope × log $_{10}$ $\dot{V}_E$ (L · min^{-1}) + intercept, where the constant 'slope' is OUES, using breath-by-breath gas-exchange measurements [12]. Basically, to avoid possible irregular breathing patterns, data from the 3-min resting period, from the first minute of exercise, and from a plateau in $\dot{V}_{O2}$ were excluded from the calculation of OUES. The anaerobic threshold (AT) was determined using the V-slope method [4]. Predicted maximal voluntary ventilation (MVV) was calculated as $FEV_1 \times 35$ [4]. Predicted maximum heart rate was calculated as 220–age in years [4].

Statistical analysis

Variables are presented as means (standard deviation) or medians (interquartile range) depending on the normality of the distribution (Shapiro–Wilk test) unless otherwise stated. Depending on the normality of the distribution, for continuous variables, (1) an unpaired *t*-test or the Wilcoxon rank-sum test was used for comparison between patients with GOLD grades I-II and III-IV, and (2) univariate analysis using Pearson's correlation or Spearman's rank correlation coefficient was used to evaluate correlations between clinical variables. R squared was used to confirm how close the data were to the fitted regression line. The chi-squared test was used for categorical variables. Bidirectional stepwise variable selection was performed to determine variables more correlated with the $\dot{V}_E$-$\dot{V}_{CO2}$ slope of the exertional variables related to oxygen uptake including COPD grade, which was divided into GOLD grades I-II and III-IV, and the desaturation level at peak exercise, with variance inflation factors (VIFs) less than 3. In the stepwise regression models, the *p* values were set at 0.20 for variables to both enter and stay. A *p* value of less than 0.05 was considered significant. Statistical analyses were performed using JMP software, version 11 (SAS Institute Inc., Cary, NC, USA).

Results

The study sample consisted of 122 patients distributed across all GOLD stages (Table 1). There were no significant differences in age, sex, smoking history, and the

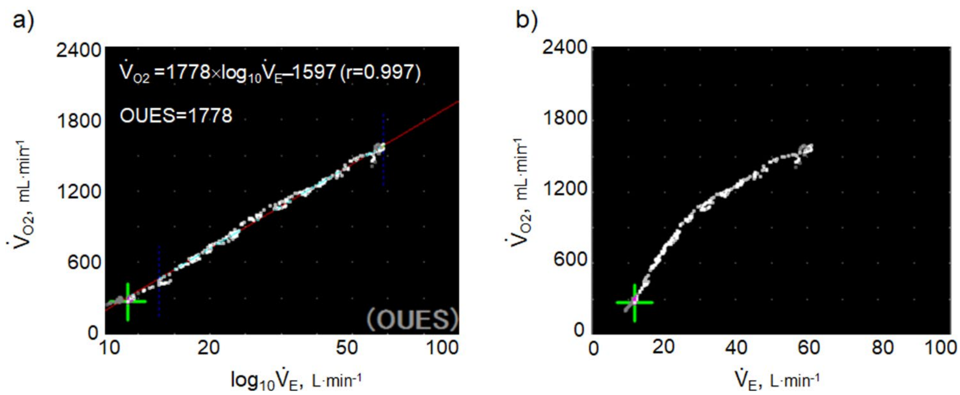

Fig. 1 Calculation of OUES. **a**) The relationship between oxygen uptake ($\dot{V}_{O2}$: mL · min^{-1}) and the common logarithm of minute ventilation ($\dot{V}_E$: L · min^{-1}) (**b**) the relationship between $\dot{V}_{O2}$ (mL · min^{-1}) and $\dot{V}_E$ (L · min^{-1}). $\dot{V}_{O2}$ and $\dot{V}_E$ obtained from breath-by-breath gas-exchange measurements in one COPD patient with GOLD I (75 years old, 64.2 kg) were used. OUES was calculated as the slope of the regression line relating $\dot{V}_{O2}$ (mL · min^{-1}) to the common logarithm of $\dot{V}_E$ (L · min^{-1}) by the equation: $\dot{V}_{O2}$ = slope × log $_{10}\dot{V}_E$ + intercept. where the constant 'slope' is the OUES. Basically, to avoid possible irregular breathing patterns, data from the 3-min resting period, from the first minute of exercise, and from a plateau in $\dot{V}_{O2}$ were excluded from the calculation of the OUES. Green cross: exercise starting point; blue crosses: period during which OUES was calculated

Table 1 Baseline characteristics of COPD patients classified according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria

	All COPD patients (n = 122)	GOLD spirometric severity		
		I + II (n = 51)	III + IV (n = 71)	*p*-value
Age, y	74 (6) [75 (70; 78)]	75 (5)	73 (6) [74 (70; 78)]	0.2253
Sex, male/female (n)	112/10	47/4	65/6	0.9040
BMI, kg · m^{-2}	21.5 (3.3)	22.2 (3.1)	21.0 (3.4)	0.0322
Pulmonary function test				
FEV_1, L	1.27 (0.58) [1.09 (0.86; 1.58)]	1.81 (0.52) [1.71 (1.49; 2.14)]	0.88 (0.19)	< 0.0001
%FEV_1, % predicted	50.8 (22.4) [45.6 (35.2; 63.7)]	72.0 (18.0) [67.9 (57.6; 82.6)]	35.6 (8.4)	< 0.0001
FEV_1/FVC, %	42.2 (12.2) [40.6 (31.9;49.3)]	51.8 (10.0) [50.0 (43.8; 60.3)]	35.3 (8.2) [32.9 (29.9; 40.0)]	< 0.0001
VC, L	3.05 (0.77)	3.50 (0.68)	2.72 (0.65)	< 0.0001
%VC, %	99.0 (23.1)	113.8 (122.1)	88.5 (20.6)	< 0.0001
IC, L	1.96 (0.52)	2.27 (0.48)	1.73 (0.43)	< 0.0001
Medications (n)				
LAMA	102	37	65	0.0052
LABA	92	31	61	0.0015
ICS	64	21	43	0.0344
Triple inhalation therapy	45	10	35	0.0008

Data are presented as means (standard deviation) or [medians (interquartile range: 25th percentile to 75th percentile)], unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IC: inspiratory capacity; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; VC: vital capacity. Medications are presented separately. Pulmonary function tests were performed after bronchodilator administration

choice of inhalation therapy between the GOLD I-II and III-IV groups, although BMI (p=0.0322) was lower, and especially, the frequency of triple inhalation therapy (p=0.0008) was higher in the GOLD III- IV group than in the GOLD I-II group (Table 1).

Peak exercise variables

Incremental exercise parameters at peak exercise in COPD patients in the GOLD I-II and III-IV groups are shown in Table 2. Compared with the GOLD I-II group, peak$\dot{V}_{O2}$ (p<0.0001), OUES (p=0.0161), O_2 pulse (p<0.0001), percutaneous oxygen saturation (SpO_2) (p=0.0004) at peak exercise, and $\dot{V}_E$ (p<0.0001) at peak exercise were significantly lower in the GOLD III-IV group with reduced breathing reserve, as expected by 1-$\dot{V}_E$/maximal voluntary ventilation (MVV). Reduced $\dot{V}_E$ in the GOLD III-IV group was caused by expiratory airflow limitation, indicated by lower values of tidal volume (V_T) (p<0.0001), respiratory frequency (f_R) (p=0.0079), and inspiratory duty cycle (T_I/Ttot, where Ti is the inspiratory time of a single breath in seconds and Ttot is the total time of a single respiratory cycle in seconds) (p<0.0001). There were no significant differences in ΔF_{O2} max during exercise, ΔF_{O2} at peak exercise, and the $\dot{V}$

Table 2 Incremental exercise variables in COPD patients classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria

	GOLD spirometric severity		
	I+II (n=51)	**III+IV (n=71)**	***p*-value**
At peak exercise			
Dyspnea, Borg scale	5.6 (1.8) [5.0 (4.0; 7.0)]	6.0 (1.9) [6.0 (5.0; 8.0)]	0.2126
$\dot{V}_{O2}$, mL·min^{-1} · kg^{-1}	14.9 (3.8) [15.2 (11.7; 17.3)]	10.6 (2.3)	< 0.0001
R	1.10 (0.10)	1.01 (0.08) [1.01 (0.96; 1.05)]	< 0.0001
$\dot{V}_E$, L · min^{-1}	43.7 (12.6)	28.0 (6.6)	< 0.0001
V_T, mL	1397 (320)	987 (239)	< 0.0001
f_R, breaths · min^{-1}	31.7 (6.1)	28.9 (5.3)	0.0079
T_I/Ttot	0.41 (0.05) [0.41 (0.38; 0.43)]	0.34 (0.05)	< 0.0001
$\dot{V}_E/\dot{V}_{O2}$	49.7 (10.1)	48.0 (7.4) [47.0 (44.0; 51.2)]	0.2892
$\dot{V}_E/\dot{V}_{CO2}$	45.1 (8.7)	47.8 (8.4) [46.8 (42.7; 51.0)]	0.1623
$1-\dot{V}_E$/MVV, %	29.2 (15.4)	8.4 (19.0) [11.9 (2.9; 19.4)]	< 0.0001
HR, beats · min^{-1}	124 (17.6)	112 (16.8)	0.0005
HR/predicted maximum HR, %	80.8 (12.4)	80.0 (10.7)	0.7007
SpO_2, %	93 (4) [95 (91; 97)]	91 (5) [92 (87; 94)]	0.0004
O_2 pulse, mL · beats^{-1}	7.3 (1.9)	5.4 (1.6) [5.1 (4.2; 6.4)]	< 0.0001
OUES	1319 (420)	1135 (440) [1115 (880; 1328)]	0.0161
ΔF_{O2}, %	2.58 (0.50) [2.52 (2.28; 2.74)]	2.59 (0.38)	0.5014
During exercise			
ΔF_{O2} max., %	2.88 (0.57) [2.78 (2.47; 3.11)]	2.72 (0.41)	0.2062
$\dot{V}_E$-$\dot{V}_{CO2}$ slope	39.1 (8.9)	40.3 (10.9) [39.2 (34.2; 43.2)]	0.8073
$\dot{V}_E/\dot{V}_{CO2}$ nadir	43.1 (7.9)	46.8 (7.6) [46.0 (41.0; 50.0)]	0.0294
Number of patients reaching AT, n (%)	49 (96)	51 (72)	0.0006
$\dot{V}_{O2}$ at AT, mL · min^{-1}	601 (178) [575 (490; 670)]	481(104)	0.0001
Number of patients reaching RCP, n (%)	19 (37)	7 (10)	0.0003

Data are presented as means (standard deviation) or [medians (interquartile range: 25th percentile to 75th percentile)], unless otherwise stated. AT: anaerobic threshold; ΔF_{O2}: difference between inspired mean oxygen concentration and expired mean oxygen concentration; ΔFO_2 max.: the highest value during exercise; f_R: breathing frequency; HR: heart rate; O_2 pulse: $\dot{V}_{O2}$/HR; predicted maximum HR: 220−age (y); OUES: oxygen uptake efficiency slope (see the Methods for details); R: gas exchange ratio; RCP: respiratory compensation point; T_I/*T*tot: inspiratory duty cycle; $\dot{V}_{CO2}$: carbon dioxide output; $\dot{V}_E$: minute ventilation; and $\dot{V}_E/\dot{V}_{CO2}$-slope: the slope was determined by linear regression analysis of $\dot{V}_E$ to $\dot{V}_{CO2}$ obtained during exercise (see the Methods for details); $\dot{V}_E/\dot{V}_{CO2}$-nadir: the lowest value during exercise (see the Methods for details); $\dot{V}_{O2}$: oxygen uptake; V_T: tidal volume. Estimated maximal voluntary ventilation (MVV) (L·min^{-1}) was equal to forced expiratory volume in one second (FEV_1)×35

$_E$-$\dot{V}_{CO2}$ slope between the GOLD I-II and III-IV groups. However, the dependence of ΔF_{O2} at peak exercise on peak $\dot{V}_{O2}$, expressed as the square of the correlation coefficient, was highest in the GOLD IV group (GOLD I (n=18): r^2=0.21; GOLD II (n=33): r^2=0.29; GOLD III (n=51): r^2=0.12; GOLD IV (n=20): r^2=0.68). In contrast, OUES (p=0.0161) was lower in the GOLD III-IV group than in the GOLD I-II group.

Correlations of OUES with exercise variables

In all GOLD grades, and in the GOLD I-II and GOLD III-IV groups, OUES was not strongly correlated with peak $\dot{V}_{O2}$, $\dot{V}_E$, ventilatory efficiency, ΔF_{O2} at peak exercise, and resting pulmonary function; the square of the correlation coefficient was not greater than 0.5 in all groups. (Table 3; Fig. 2a-d). The GOLD III-IV group was divided into two groups depending on the exertional decrease from rest to peak exercise in SpO_2 into the non-desaturation group (3% or less, n=23) and the desaturation group (greater than 3%, n=48), as shown in Table 4. The correlation coefficients of OUES with exertional variables, such as peak $\dot{V}_{O2}$, $\dot{V}_E$, oxygen pulse, and ΔF_{O2} at peak exercise, were higher in the non-desaturation group than in the desaturation group (Fig. 3a-d). In the desaturation group of the GOLD III-IV group, $\dot{V}_E$ at peak exercise (p=0.0124) was significantly lower, and O_2-pulse at peak exercise (p=0.0818) tended to be lower than in the non-desaturation group, but peak $\dot{V}_{O2}$ (p=0.4505) and ΔF_{O2} at peak exercise (p=0.2839) were not (Table 4; Fig. 4).

Correlation of the $\dot{V}_E$-$\dot{V}_{CO2}$ slope with exercise variables

In all GOLD grades, and in the GOLD I-II and GOLD III-IV groups, there was no correlation between $\dot{V}_E$-$\dot{V}_{CO2}$ slope and $\dot{V}_E$ at peak exercise (Table 5). There were, however, correlations between the $\dot{V}_E$-$\dot{V}_{CO2}$ slope and oxygen uptake-related variables (peak $\dot{V}_{O2}$, $\dot{V}_{O2}$ at the AT, OUES, ΔF_{O2} at peak exercise, and maximum ΔF_{O2} during exercise) (Table 3 5; Fig. 2e-g). In the GOLD III-IV group, the

Table 3 Square of the correlation coefficient of parameters related to OUES in COPD patients ($n=122$)

	All COPD patients	GOLD I-II ($n=51$)	GOLD III-IV ($n=71$)
Peak incremental exercise parameters			
Dyspnoea, Borg scale	0.02	0.00	0.03
$\dot{V}_{O2}$, mL · min^{-1} · kg	0.35	0.60	0.19
$\dot{V}_E$, L · min^{-1}	0.27	0.25	0.26
V_T, mL	0.27	0.30	0.19
f_R, breaths · min^{-1}	0.01	0.01	0.00
T_I/Ttot	0.03	0.01	0.00
$\dot{V}_E/\dot{V}_{CO2}$	0.26	0.31	0.14
HR, beats · min^{-1}	0.05	0.09	0.01
O_2 pulse, mL · beats^{-1}	0.47	0.66	0.35
ΔF_{O2}, %	0.21	0.33	0.17
During exercise			
ΔF_{O2} max., %	0.18	0.34	0.07
$\dot{V}_E - \dot{V}_{CO2}$ slope	0.25	0.29	0.20
$\dot{V}_E/\dot{V}_{CO2}$ nadir	0.22	0.28	0.08
AT ($\dot{V}_{O2}$), mL · min^{-1}	0.39	0.46	0.33
Pulmonary function and others			
FEV_1, L	0.16	0.19	0.12
VC, L	0.19	0.08	0.07
FVC, L	0.18	0.07	0.14
IC, L	0.17	0.16	0.10
Age, y	0.00	0.00	0.02
BMI, kg · m^{-2}	0.14	0.13	0.15

AT: anaerobic threshold; BMI: body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; ΔF_{O2}: difference between inspired mean oxygen concentration and expired mean oxygen concentration; ΔFO_2 max.: the highest ΔF_{O2} value during exercise; f_R: breathing frequency; HR: heart rate; IC: inspiratory capacity; O_2 pulse: $\dot{V}_{O2}$/HR; OUES: oxygen uptake efficiency slope (see the Methods for details); T_I/Ttot: inspiratory duty cycle; VC: vital capacity; $\dot{V}_{CO2}$: carbon dioxide output; $\dot{V}_E$: minute ventilation; $\dot{V}_E/\dot{V}_{CO2}$-nadir: the lowest value during exercise (see the Methods for details); and $\dot{V}_E-\dot{V}_{CO2}$-slope: the slope was determined by linear regression analysis of $\dot{V}_E$ to $\dot{V}_{CO2}$ obtained during exercise (see the Methods for details); $\dot{V}_{O2}$: oxygen uptake; V_T: tidal volume

correlation coefficients of the $\dot{V}_E$-$\dot{V}_{CO2}$ slope with exertional variables, such as peak $\dot{V}_{O2}$, ΔF_{O2} at peak exercise, and maximal ΔF_{O2} during exercise were almost the same between the groups with and without exertional desaturation (Fig. 3e-g). Of the four exercise variables related to oxygen uptake (peak $\dot{V}_{O2}$, $\dot{V}_{O2}$ at the AT, OUES, ΔF_{O2} at peak exercise), and including COPD grade and SpO_2 at peak exercise, investigations of more influential variables that correlated with the $\dot{V}_E$-$\dot{V}_{CO2}$ slope across all GOLD grades were performed using stepwise variable selection. The analysis identified peak $\dot{V}_{O2}$ (F value=4.6, p=0.0345) and ΔF_{O2} at peak exercise (F value=148.4, $p<0.0001$) as more influential variables correlated with the $\dot{V}_E$-$\dot{V}_{CO2}$ slope.

Discussion

We investigated the clinical implications of OUES and the $\dot{V}_E$-$\dot{V}_{CO2}$ slope as indicators of pathophysiological conditions during incremental exercise in patients with all COPD grades. The main findings of this study were as follows. First, OUES was not strongly correlated across all GOLD grades with exercise tolerance, ventilatory variables, ventilatory efficiency, and oxygen consumption ability. In particular, these correlations were weaker in the GOLD III-IV group with exertional oxygen desaturation. In contrast, the $\dot{V}_E$-$\dot{V}_{CO2}$ slope was specifically correlated with oxygen consumption ability and exercise tolerance regardless of COPD grade and exertional oxygen desaturation, having only a minimal correlation with $\dot{V}_E$.

Admittedly, though OUES and the $\dot{V}_E$-$\dot{V}_{CO2}$ slope are commonly used indicators of gas exchange efficiency evaluated by CPET, there have been no reports of their clinical use in COPD patients based on the differences between the two indicators. In particular, little is known about what OUES really means. Based on the formula, $\dot{V}_{O2}$=OUES × $\log_{10}\dot{V}_E$+intercept, given that the value of $\log_{10}\dot{V}_E$ is smaller than that of the actually measured value of $\dot{V}_E$, and that OUES represents the absolute rate of increase in $\dot{V}_{O2}$ per $\log_{10}\dot{V}_E$, even if minor ventilatory abnormalities occur up to submaximal exercise before reaching peak exercise, OUES allows detection of the resultant ventilatory variations more sensitively than does the $\dot{V}_E$-$\dot{V}_{CO2}$ slope, which is evaluated using the actual measured value of $\dot{V}_E$. Indeed, Barron et al. [17] reported that OUES, rather than the $\dot{V}_E$-$\dot{V}_{CO2}$ slope, was useful for differentiating between heart failure requiring excessive ventilatory compensation and COPD resulting in reduced ventilatory ability with the same exercise tolerance, which might indicate that OUES is more sensitive to the exertional ventilatory response during exercise. In the present study, regardless of COPD severity, compared with the $\dot{V}_E$-$\dot{V}_{CO2}$ slope, OUES correlated with $\dot{V}_E$ at peak exercise, although the correlation was not strong (Tables 3 and 5). Certainly, in the population investigated in the present study, OUES may have been extensively, but never strongly, correlated with not only $\dot{V}_E$ and ΔF_O, but also with peak $\dot{V}_{O2}$, and O_2-pulse as an indicator of cardiac function. However, if COPD progressed to GOLD III and IV with exertional hypoxia, OUES correlated only weakly with the above exercise variables (Fig. 3). In the GOLD III-IV group with exertional hypoxia, $\dot{V}_E$ at peak exercise was lower, and O_2-pulse tended to be lower, but there were no significant differences in HR at peak exercise and HR at peak exercise/predicted maximal HR between the groups with and without exertional hypoxia (Table 4). These findings may not suggest that cardiac function is decreasing in the group with exertional hypoxia, but they may suggest that

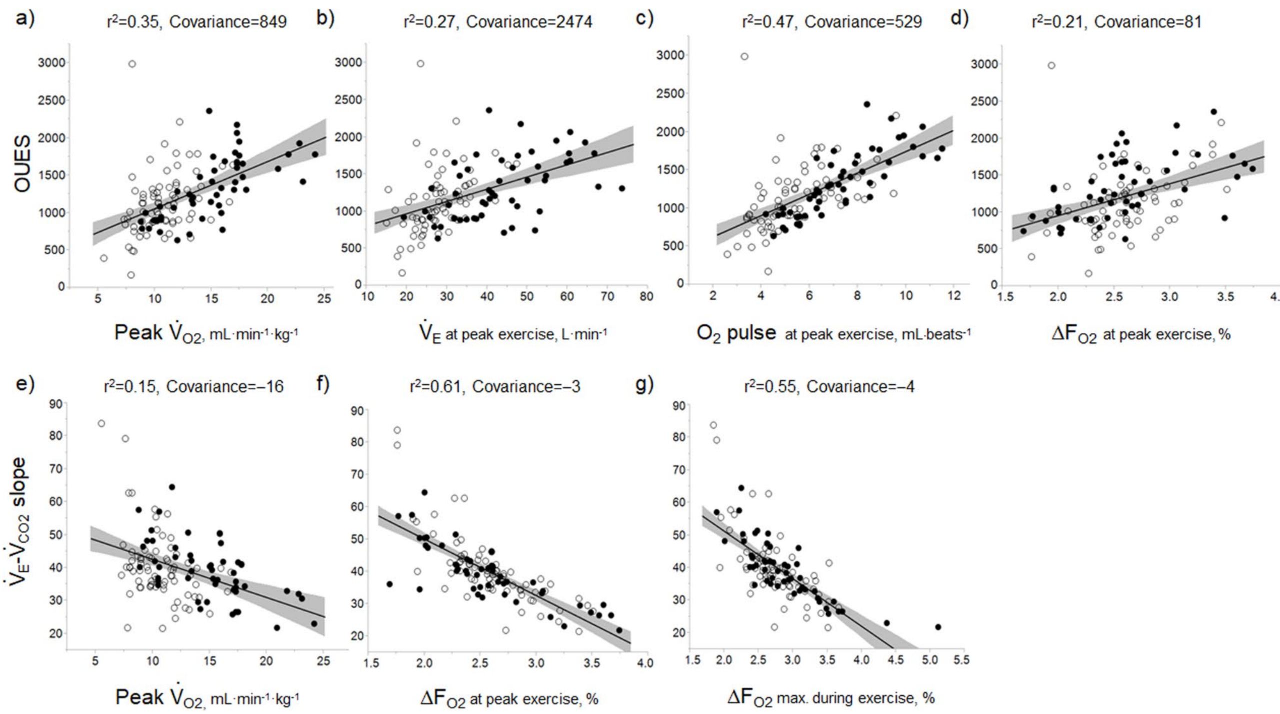

Fig. 2 In all COPD stages, correlations of the oxygen uptake efficiency slope (OUES) (upper panel) and the $\dot{V}_E/\dot{V}_{CO2}$ slope (bottom panel) with exertional variables during cardiopulmonary exercise testing. Correlations of OUES with peak $\dot{V}_{O2}$ (**a**), $\dot{V}_E$ at peak exercise (**b**), O_2 pulse at peak exercise (**c**), and ΔF_{O2} at peak exercise (**d**) are shown. Correlations of the $\dot{V}_E/\dot{V}_{CO2}$ slope with peak $\dot{V}_{O2}$ (**e**), ΔF_{O2} at peak exercise (**f**), and ΔF_{O2} max. during exercise (**g**) are shown. ΔF_{O2}: difference between inspired and expired mean oxygen concentrations; ΔF_{O2} max.: highest ΔF_{O2} value during exercise; O_2 pulse: $\dot{V}_{O2}$/heart rate; $\dot{V}_E$: minute ventilation; $\dot{V}_{O2}$: oxygen uptake. Closed circle: Global Initiative for Chronic Obstructive Lung Disease (GOLD) I-II group (*n* = 51). Open circle: GOLD III-IV group (*n* = 71). The shaded area indicates the CI. The correlation coefficient (r) was obtained in the analysis of all COPD stages

exertional hypoxia is involved as one of the reasons for the reduced O_2-pulse during exercise [4]. Furthermore, though Fig. 1 and online supplement Figure S2 demonstrate that the relationship between $\dot{V}_{O2}$ and $\dot{V}_E$ during exercise is such that using the log transformation of $\dot{V}_E$ was valid in the present study, a lack of increase in $\dot{V}_E$ during exercise in advanced COPD might decrease the utility of the logarithmic conversion of $\dot{V}_{E,}$ because the relationship between $\dot{V}_E$ and $\dot{V}_{O2}$ was more linear in the desaturation group of the GOLD III-IV group (Fig. 4). Given that most advanced COPD is associated with reduced $\dot{V}_E$ and exertional hypoxia, the clinical utility of OUES, especially in advanced COPD may be less.

In advanced COPD, due to the existing ventilatory disorders, even with maximal ventilatory effort only reduced $\dot{V}_E$ can be achieved, which is a factor that limits exercise performance and reduces exercise tolerance [18, 19]. In such cases, to enable higher $\dot{V}_{O2}$, the subjects often rely on the compensatory increase in ΔF_{O2} due to the reduction in F_{EO2}, that is, higher oxygen consumption ability throughout the body [9, 10]. In the present study, the dependence of ΔF_{O2} on peak $\dot{V}_{O2}$, expressed as the square of the correlation coefficient, was higher in the GOLD IV group than in the other stages. The following two conflicting findings in our previous studies might be very useful to suggest that specific CPET parameters related to exertional oxygen consumption ability would enable planning of treatment strategies and their evaluation. First, increasing ΔF_{O2} at peak exercise in pulmonary rehabilitation with exercise therapy in severe and very severe COPD patients led to improvement in both ventilatory efficiency and peak $\dot{V}_{O2}$ [10]. Second, in contrast, a treatment specifically aimed at improving ventilation using expiratory pressure load training, resulted in improved ventilation without improving ΔF_{O2} at peak exercise in patients with COPD, improving peak $\dot{V}_{O2}$, but with no significant change in ventilatory efficiency [20]. When assessing exertional variables using CPET in many diseases, many reports have shown that the $\dot{V}_E$-$\dot{V}_{CO2}$ slope is related to exercise intolerance [8, 21]. So far, the $\dot{V}_E$-$\dot{V}_{CO2}$ slope has been considered to mainly reflect lung efficiency as a physiological mechanism. However, the $\dot{V}_E$-$\dot{V}_{CO2}$ slope was also found to be affected by the oxygen consumption ability resulting from circulatory disturbance, in addition to excessive ventilation in the lung [22], and Nayor et al. [23] reported that $\dot{V}_E/\dot{V}_{CO2}$ nadir is related to the arteriovenous O_2 difference at peak exercise, suggesting that ventilatory efficiency correlates with the oxygen extraction ability of peripheral muscles. In the present study, ΔF_{O2} at peak exercise correlated with

Table 4 Incremental exercise variables in GOLD III-IV COPD patients divided into two groups by the desaturation level at peak exercise

	Non-desaturation group: 3% or less ($n=23$)	Desaturation group: greater than 3% ($n=48$)	*p*-value
At peak exercise			
Dyspnea, Borg scale	5.7 (1.7)	6.2 (1.9) [6.5 (5.0; 8.0)]	0.2520
$\dot{V}_{O2}$, mL·min^{-1} · kg^{-1}	11.0 (3.0)	10.5 (1.9)	0.4505
R	1.02 (0.10) [1.02 (0.95; 1.07)]	1.00 (0.07)	0.7119
$\dot{V}_E$, L · min^{-1}	30.7 (7.2)	26.6 (5.9)	**0.0124**
V_T, mL	1029 (240)	967 (238) [917 (794; 1082)]	0.2796
f_R, breaths · min^{-1}	30.3 (5.2)	28.2 (5.2)	0.1058
T_I/Ttot	0.35 (0.06)	0.34 (0.04)	0.2806
$\dot{V}_E/\dot{V}_{O2}$	49.5 (8.1)	47.3 (7.0)	0.2310
$\dot{V}_E/\dot{V}_{CO2}$	48.9 (9.8) [48.0 (43.0; 52.0)]	47.3 (7.6) [46.0 (41.4; 51.0)]	0.6055
$1-\dot{V}_E$/MVV, %	2.2 (15.9) [10.2 (−8.1; 17.8)]	11.3 (13.9) [12.7 (3.3; 20.3)]	0.2169
HR, beats · min^{-1}	111 (17)	113 (17)	0.5799
HR/predicted maximum HR, %	78.8 (10.4)	80.6 (11.0)	0.5280
SpO_2, %	95 (2)	88 (5)	ND
O_2 pulse, mL · beats^{-1}	6.0 (2.1)	5.1 (1.3)	0.0818
OUES	1086 (437)	1158 (444) [1129 (880; 1345)]	0.4317
ΔF_{O2}, %	2.52 (0.39)	2.63 (0.37)	0.2839
During exercise			
ΔF_{O2} max., %	2.68 (0.43)	2.73 (0.41)	0.6083
$\dot{V}_E$-$\dot{V}_{CO2}$ slope	41.7 (11.4) [39.1 (34.6; 44.8)]	39.6 (10.7) [39.3 (34.1; 42.8)]	0.5972
$\dot{V}_E/\dot{V}_{CO2}$ nadir	47.4 (8.1)	46.5 (7.3) [45.5 (41.0; 49.0)]	0.6387
Number of patients reaching AT, n (%)	16 (70)	35 (73)	0.7689
$\dot{V}_{O2}$ at AT, mL · min^{-1}	515 (144)	464(78)	0.1109

Data are presented as means (standard deviation) or [medians (interquartile range: 25th percentile to 75th percentile)], unless otherwise stated. AT: anaerobic threshold; ΔF_{O2}: difference between inspired mean oxygen concentration and expired mean oxygen concentration; ΔF_{O2} max.: the highest value during exercise; f_R: breathing frequency; HR: heart rate; O_2 pulse: $\dot{V}_{O2}$/HR; predicted maximum HR: 220−age (y); ND: not done; OUES: oxygen uptake efficiency slope (see the Methods for details); R: gas exchange ratio; RCP: respiratory compensation point; T_I/*T*tot: inspiratory duty cycle; $\dot{V}_{CO2}$: carbon dioxide output; $\dot{V}_E$: minute ventilation; and $\dot{V}_E/\dot{V}_{CO2}$-slope: the slope was determined by linear regression analysis of $\dot{V}_E$ to $\dot{V}_{O2}$ obtained during exercise (see the Methods for details); $\dot{V}_E/\dot{V}_{CO2}$-nadir: the lowest value during exercise (see the Methods for details); $\dot{V}_{O2}$: oxygen uptake; V_T: tidal volume. Estimated maximal voluntary ventilation (MVV) (L·min^{-1}) was equal to forced expiratory volume in one second (FEV_1)×35

ventilatory efficiency not only across all COPD grades (Table 5), but also in advanced COPD, regardless of exertional hypoxemia (Fig. 3). In addition, stepwise variable analysis, including the COPD grade and the SpO_2 level at peak exercise, identified ΔF_{O2} at peak exercise rather than peak $\dot{V}_{O2}$ as a more influential variable correlated with the $\dot{V}_E$-$\dot{V}_{CO2}$ slope across all GOLD grades. Although this needs to be studied in other diseases that result in excess ventilation during exercise, the above findings suggest that, at least in ventilation-limited diseases such as COPD, the $\dot{V}_E$-$\dot{V}_{CO2}$ slope is a specific indicator of oxygen consumption ability that is independent of ventilatory ability to increase $\dot{V}_E$. Given that (1) for advanced COPD with exertional hypoxia, assessment of exercise variables by OUES appears to have limitations, as shown in the present study, and that (2) in advanced COPD, pulmonary rehabilitation is often required to focus on improving oxygen consumption ability rather than ventilation due to the presence of a severe ventilatory disorder, the $\dot{V}_E$-$\dot{V}_{CO2}$ slope might be useful for planning and assessing personalized pulmonary rehabilitation.

This study has some limitations. First, since the present study involved COPD patients at a single center, a multicenter evaluation including not only COPD patients, but also those with many other diseases, is needed to confirm the physiological mechanisms reflected by the $\dot{V}_E$-$\dot{V}_{CO2}$ slope and OUES. Second, assessment of blood circulation, such as by echocardiography or right heart catheterization, would have been useful [24, 25]. Given that there was no strong relationship between the arterial desaturation level and ΔF_{O2} at peak exercise in the non-desaturation group and the desaturation group in the GOLD III-IV group in the present study, and that among the variables related to ΔF_{O2}, F_{IO2} is almost constant at 21%, and, therefore, ΔF_{O2} depends primarily on F_{EO2}, it was assumed that F_{EO2} is probably closely related to mixed venous oxygen pressure, which is obtained by right heart catheterization. This assumption has not been fully investigated and requires further study. Third, treatment strategies targeted at improving oxygen consumption ability are underdeveloped [3, 26, 27]. If such treatments become available, the importance of the $\dot{V}_E$-$\dot{V}_{CO2}$ slope in relation to oxygen consumption ability might become

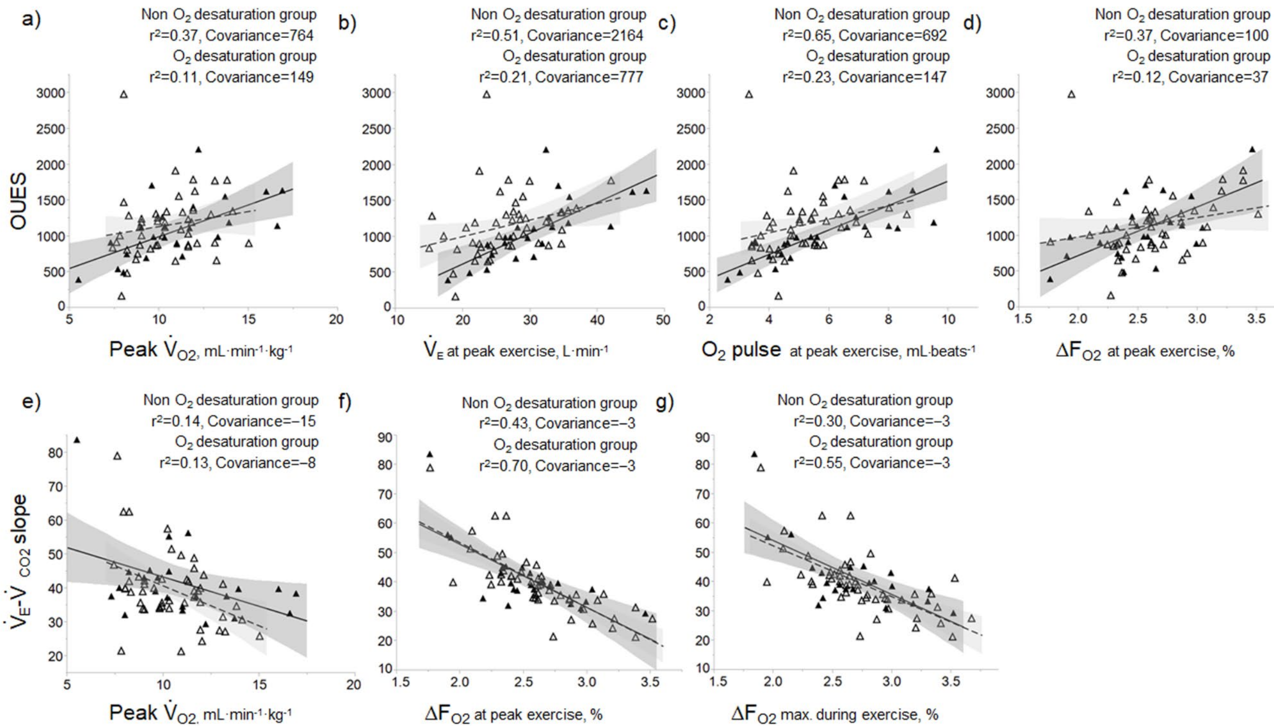

Fig. 3 In COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) III and IV stages, the correlations of oxygen uptake efficiency slope (OUES) (upper panel) and the $\dot{V}_E/\dot{V}_{CO2}$ slope (bottom panel) with exertional variables during cardiopulmonary exercise testing classified by oxygen (O_2) desaturation level. Correlations of OUES with peak $\dot{V}_{O2}$ (**a**), $\dot{V}_E$ at peak exercise (**b**), O_2 pulse at peak exercise (**c**), and ΔF_{O2} at peak exercise (**d**) are shown. Correlations of the $\dot{V}_E/\dot{V}_{CO2}$ slope with peak $\dot{V}_{O2}$ (**e**), ΔF_{O2} at peak exercise (**f**), and ΔF_{O2} max. during exercise (**g**) are shown. ΔF_{O2}: difference between inspired and expired mean oxygen concentrations; ΔF_{O2} max.: highest ΔF_{O2} value during exercise; O_2 pulse: $\dot{V}_{O2}$/heart rate; $\dot{V}_E$: minute ventilation; $\dot{V}_{O2}$: oxygen uptake. Closed triangle and solid line: group with O_2 desaturation of 3% or less during exercise ($n=23$). Open triangle and dotted line: group with O_2 desaturation greater than 3% during exercise ($n=48$). The shaded area indicates the CI. The correlation coefficient (r) was obtained in the analysis for each group

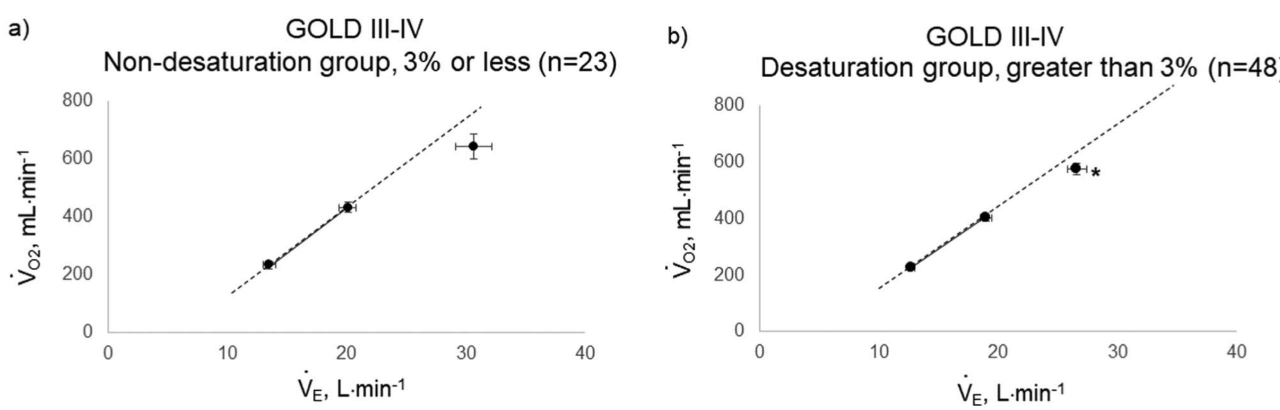

Fig. 4 Relationship between oxygen uptake ($\dot{V}_{O2}$: mL · min^{-1}) and minute ventilation ($\dot{V}_E$: L · min^{-1}) in (**a**) GOLD III-IV without exertional desaturation, 3% or less decrease ($n=23$) and (**b**) GOLD III-IV with exertional desaturation, greater than 3% decrease ($n=48$). Plots from left to right at rest, at 2 min, and at peak exercise. To see whether it is inappropriate to represent the relationship of $\dot{V}_{O2}$ to $\dot{V}_E$ as a line, the dotted line is a straight line connecting the resting and 2-minute plots. GOLD: Global Initiative for Chronic Obstructive Lung Disease. Mean ± standard error. *: $p<0.05$ between the non-desaturation and desaturation groups in $\dot{V}_E$ (x-component)

Table 5 Square of the correlation coefficient of parameters related to $\dot{V}_E$-$\dot{V}co_2$ slope in COPD patients ($n=122$)

	All COPD patients	GOLD I-II ($n=51$)	GOLD III-IV ($n=71$)
Peak incremental exercise parameters			
Dyspnoea, Borg scale	0.00	0.03	0.00
$\dot{V}_{O2}$, mL · min^{-1} · kg	0.15	0.34	0.14
$\dot{V}_E$, L · min^{-1}	0.00	0.00	0.00
V_T, mL	0.04	0.07	0.06
f_R, breaths · min^{-1}	0.05	0.04	0.06
T_I/Ttot	0.00	0.02	0.00
$\dot{V}_E/\dot{V}_{O2}$	0.57	0.55	0.60
HR, beats · min^{-1}	0.13	0.23	0.11
O_2 pulse, mL · beats^{-1}	0.08	0.13	0.06
ΔF_{O2}, %	0.61	0.57	0.63
During exercise			
ΔF_{O2} max., %	0.55	0.69	0.45
$\dot{V}_E/\dot{V}_{CO2}$ nadir	0.61	0.81	0.54
AT ($\dot{V}_{O2}$), mL · min^{-1}	0.07	0.14	0.09
Pulmonary function and others			
FEV_1, L	0.00	0.04	0.00
IC, L	0.00	0.01	0.00
Age, y	0.00	0.00	0.01
BMI, kg · m^{-2}	0.02	0.00	0.04

AT: anaerobic threshold; BMI: body mass index; FEV_1: forced expiratory volume in one second; ΔFO_2: difference between inspired mean oxygen concentration and expired mean oxygen concentration; ΔF_{O2} max.: the highest ΔF_{O2} value during exercise; f_R: breathing frequency; HR: heart rate; IC: inspiratory capacity; O_2 pulse: $\dot{V}_{O2}$/HR; T_I/Ttot: inspiratory duty cycle; $\dot{V}_{CO2}$: carbon dioxide output; $\dot{V}_E$: minute ventilation; $\dot{V}_E/\dot{V}_{CO2}$-nadir: the lowest value during exercise (see the Methods for details); $\dot{V}_E$-$\dot{V}_{CO2}$-slope: the slope was determined by linear regression analysis of $\dot{V}_E$ to $\dot{V}_{CO2}$ obtained during exercise (see the Methods for details); $\dot{V}_{O2}$: oxygen uptake; V_T: tidal volume

more apparent. Increasing muscle mass while improving oxygen extraction ability, rather than simply increasing muscle mass as the endpoint, is necessary to improve exercise intolerance, which, as of now, still remains an unresolved issue.

Conclusions

We demonstrated the characteristics of OUES and the $\dot{V}_E$-$\dot{V}_{CO2}$ slope as indicators of pathophysiological exertional conditions in patients with all COPD grades. OUES is a comprehensive exercise index extensively involving pulmonary, cardiovascular, and muscle crosstalk in the body in COPD, but its association with them was never strong, and it may not be useful in cases of advanced COPD with exertional hypoxemia. In contrast, the $\dot{V}_E$-$\dot{V}_{CO2}$ slope is an index that is independent of ventilatory ability, and it assesses oxygen consumption ability and exercise tolerance in COPD cases, regardless of the exertional hypoxemia level and COPD grade. Therefore, the $\dot{V}_E$-$\dot{V}_{CO2}$ slope might be useful in establishing tailor-made pulmonary rehabilitation strategies for individual pathologies in COPD, serving as an indicator that focuses more on oxygen consumption ability independent of ventilatory ability.

Abbreviations

CPET	Cardiopulmonary exercise testing
ΔF_{O2}	Difference between inspired and expired mean oxygen concentrations
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	Inhaled corticosteroid
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonist
OUES	Oxygen-uptake efficiency slope
$\dot{V}_E$-$\dot{V}_{CO2}$ slope	Minute ventilation-carbon dioxide production slope

Supplementary Information

The online version contains supplementary material available athttps://doi.org/10.1186/s12890-024-03312-2.

Supplementary Material 1

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Author contributions

All authors contributed substantially to this article. M.K. was responsible for the study conception and design. Y. H., M.K., K.K., M.S., M.Y., N.Y., H.K., H.H., F.M., M.T., Y.R., S.S., N.T., M.T., T.K., and K.H. were responsible for data acquisition, analysis and interpretation. Y.H. was responsible for drafting the article. Y. H., M.K., K.K., M.S., M.Y., N.Y., H.K., H.H., F.M., M.T., Y. R., S.S., N.T., M.T., T.K., and K.H. were responsible for revising the article. Each author approved the submission of this manuscript for publication.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The institutional review board of the National Hospital Organization Osaka Toneyama Medical Center approved the study protocol (approval number: TNH-R-2022018) and the protocol was in accordance with the Declaration of Helsinki for experiments involving human subjects. The patients/participants provided their written informed consent for study participation before cardiopulmonary exercise testing.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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