Intercept of minute ventilation vs. carbon dioxide output relationship in chronic obstructive pulmonary disease: utility as an index of ventilatory inefficiency

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Abstract

Background: Ventilatory inefficiency is known to be a contributor to exercise intolerance in chronic obstructive pulmonary disease (COPD). The intercept of the minute ventilation ($\dot{V}_E$) vs. carbon dioxide output ($\dot{V}CO_2$) plot is a key ventilator inefficiency parameter. However, its relationships with lung hyperinflation (LH) and airflow limitation are not known. This study aimed to evaluate the correlations between the $\dot{V}_E/\dot{V}CO_2$ intercept and LH in COPD to determine its utility as an index of functional impairment.

Methods: We conducted a retrospective analysis of data from 53 COPD patients and 14 healthy controls performed incremental cardiopulmonary exercise tests and resting pulmonary function. Ventilatory inefficiency was represented by parameters reflecting the $\dot{V}_E/\dot{V}CO_2$ nadir and slope (linear region), and intercept of the $\dot{V}_E/\dot{V}CO_2$ plot. Their correlations with measures of LH and airflow limitation were evaluated.

Results: Compared to the control, the slope (30.58±3.62) and intercept (4.85±1.11) higher in $COPD_{stages1-2}$, leading to a higher nadir (31.47±4.47) (p<0.05). Despite an even higher intercept in $COPD_{stages3-4}$ (7.16±1.41), the slope diminished with disease progression (from 30.58±3.62 in $COPD_{stages1-2}$ to 28.36±4.58 in $COPD_{stages3-4}$). Compared to the $\dot{V}_E/\dot{V}CO_2$ nadir and $\dot{V}_E/\dot{V}CO_2$ slope, the intercept was better correlated with peak $\dot{V}_E$/maximal voluntary ventilation (MVV) (r=0.489, p<0.001) and peak $\dot{V}O_2$/watt (r=0.354, p=0.003). The intercept was also significantly correlated with RV/TLC (r=0.588, p<0.001), IC/TLC (r=-0.574, p<0.001), peak V_T/TLC (r=-0.585, p<0.001); and airflow limitation forced expiratory volume in 1s (FEV_1) % predicted (r=-0.606, p<0.001) and FEV_1/forced vital capacity (FVC) (r=-0.629, p<0.001).

Conclusion: $\dot{V}_E/\dot{V}CO_2$intercept was consistently better correlated with worsening static and dynamic lung hyperinflation and airflow limitation in COPD. $\dot{V}_E/\dot{V}CO_2$ intercept emerged as a useful index of ventilatory inefficiency across the severity spectrum of COPD patients.

Background

Activity-related dyspnea is the defining complaint in patients with chronic obstructive pulmonary disease (COPD) [1]. The limitations in activity and dyspnea are multifactorial. The development of lung hyperinflation (LH) plays an important role in the pathophysiology of dyspnea and exercise intolerance [2]. Static hyperinflation which is caused by destructions of pulmonary parenchyma and loss of lung elastic recoil is characterized by increased functional residual capacity (FRC) and reduced inspiratory capacity (IC) [3]. Dynamic hyperinflation which occurs when the expiratory time becomes insufficient to allow the lung to achieve full exhalation yields an increased end-expiratory lung volume (EELV) during exercise [4]. LH increases ventilatory workload and decreases inspiratory muscle pressure generating

capacity, despite some compensatory mechanisms [3]. The diminished ventilatory capacity coupled with the increased ventilatory demand during exercise yields exercise intolerance.

The minute ventilation ($\dot{V}_E$) vs. carbon dioxide production ($\dot{V}CO_2$) relationship is a measure of the ventilatory efficiency at removing CO_2 produced by the body. Early in exercise, $\dot{V}_E/\dot{V}CO_2$ decreases with a decrease in dead space ventilation (V_D)/tidal volume (V_T) ratio. The $\dot{V}_E/\dot{V}CO_2$ nadir is typically reached just before ventilation starts to increase to compensate for lactic acidosis at the respiratory compensation point [5]. The $\dot{V}_E/\dot{V}CO_2$ nadir was found to be highly reproducible in healthy subjects [6] and COPD patients [7]. However, the $\dot{V}_E/\dot{V}CO_2$ nadir might underestimate ventilatory efficiency if the descending curve is prematurely interrupted by lactic acidosis or an excessively short test duration [8]. On the other hand, $\dot{V}_E/\dot{V}CO_2$ ratio might higher than the nadir as the hyperventilation response to late-exercise acidosis in patients who are able to can exercise beyond the respiratory compensation point [9].

The $\dot{V}_E/\dot{V}CO_2$ slope has been used to assess disease progression and to identify the presence of comorbidities [10–15]. However, in many patients with moderate-to-severe COPD, concomitant increases in the partial pressure of carbon dioxide ($PaCO_2$) and mechanical constraints will predictably flatten the $\dot{V}_E/\dot{V}CO_2$ curve. In these patients, the $\dot{V}_E/\dot{V}CO_2$ slope might, paradoxically, decrease as the disease evolves if CO_2 retention during exercise worsens. It is plausible that the $\dot{V}_E/\dot{V}CO_2$ nadir might be stable while the slope and intercept change in opposite directions despite COPD progression [9].

Theoretically, the y-intercept of the $\dot{V}_E/\dot{V}CO_2$ plot (intercept = $\dot{V}_E$ when $\dot{V}CO_2 = 0$, that is, in the absence of pulmonary gas exchange) corresponds to the basal $\dot{V}_E$ that contributes to the wasted V_D [16]. By definition, the intercept cannot be constrained by dynamic mechanics (unlike the slope) or the test duration (unlike the nadir). The increased intercept in COPD patients theoretically results from dead space (when metabolic demand is null) and might result from an altered breathing strategy (increased breathing frequency to compensate for reduced V_T secondary to greater mechanical constraints) and/or a progressive ventilation-perfusion mismatch in COPD patients [1]. Thus, the $\dot{V}_E/\dot{V}CO_2$ intercept increases with greater disease severity in COPD patients, and it seems to be a particularly useful index for ventilatory inefficiency across the continuum of COPD severity [9]. However, the clinical implications of the $\dot{V}_E/\dot{V}CO_2$ intercept and its association with LH in COPD have not been formally examined.

This study aimed to evaluate the relationship between the $\dot{V}_E/\dot{V}CO_2$ intercept and LH and airflow limitation in patients with COPD. We hypothesized that the $\dot{V}_E/\dot{V}CO_2$ intercept correlated well with measures of both LH and airflow limitation and could be used as a particularly useful index for ventilatory inefficiency in COPD.

Methods:

Study participants

This study was a retrospective analysis of data collected during incremental cardiopulmonary exercises from ethically-approved research studies on COPD at the Respiratory Investigation Unit, Beijing Friendship Hospital, Capital Medical University (Beijing, China). Participants were males and females aged ≥ 40 years with body mass index (BMI) of 18–35 kg/m^2. The patients were current or ex-smokers (smoking history ≥ 10 pack-years) and had a well-established diagnosis of COPD [17] without asthma or other pulmonary diseases. Patients were required to have had no exacerbation in the preceding 6 weeks. Control subjects with no smoking history were in the same age range and they had no major orthopedic, neuromuscular, cardiac or metabolic diseases, to allow them to safely undertake the incremental exercise tests.

Pulmonary Function Tests

Each subject underwent resting spirometry (MasterScreen Body, CareFusion, Hoechberg, Germany), including inspiratory capacity (IC) assessment. Body plethysmography was performed to measure residual volume (RV), total lung capacity (TLC) and diffusing capacity of the lungs for carbon monoxide (DL_{CO}). Patients took 400 μg albuterol by inhalation 20 min before testing. All pulmonary function tests fulfilled the American Thoracic Society /European Respiratory Society guidelines [18].

Cardiopulmonary Exercise Test (CPET)

Symptom-limited incremental exercise testing was performed on an electronically braked cycle ergometer (ViaSprint, CareFusion, Hoechberg, Germany) with a pedaling rate of 60/min. After 3 min of rest and 3 min of unloaded pedaling, the work rate (WR) was increased by 5–15 W/min in a ramp fashion (5 W/min if FEV_1 < 1.0 L and 10 W/min if FEV_1 ≥ 1.0 L for the COPD patients; 15 W/min for the controls, with repetition at 20 W/min if the peak WR was ≥ 200 W). Participants were asked to continue to exercise to the limit of tolerance, marked by the inability (despite encouragement) to maintain pedaling frequency or intolerable shortness of breath. Any participant with chest pain suggestive of ischemia, ventricular tachycardia and blood pressure (BP) ≥ 240/130 mmHg was prevented further exercise. Patients were continuously monitored with a 12-lead electrocardiogram and blood pressure by sphygmomanometer every 2 min.

Data Collection

Respiratory gas exchange ($\dot{V}_E$, $\dot{V}O_2$, and $\dot{V}CO_2$) and V_T were measured breath-by-breath throughout the exercise testing. Serial measurements of these parameters were averaged at 30-s intervals. Arterial oxygen saturation was measured noninvasively by pulse oximetry (SpO_2; %). The $\dot{V}_E/\dot{V}CO_2$ nadir and peak were the lowest and the mean of the last 30-s of data, respectively [19]. The slope of the $\dot{V}_E/\dot{V}CO_2$ relationship was determined based on the $\dot{V}_E$ vs.$\dot{V}CO_2$ plot ($\dot{V}_E$ on the y-axis and $\dot{V}CO_2$ on the x-axis). A

linear regression line was determined based on these data points [19, 20] from the start of loading exercise to the nadir. The $\dot{V}_E/\dot{V}CO_2$ intercept was calculated by extrapolating the regression line to $\dot{V}CO_2 = 0$. Maximal voluntary ventilation (MVV) was calculated as $FEV_{1\times4}0$. Peak V_T/TLC, was used as measures dynamic LH during exercise while IC/TLC and RV/TLC were used as static LH [21].

Statistical analysis

Values are reported as mean ± SD unless otherwise stated. P-value < 0.05 was considered significant in all analyses. Intraclass correlation coefficients were used to determine the level of between-investigator agreement in the calculation of the slope and intercept. Between-group comparisons were performed using one-way analysis of variance (ANOVA) with LSD post-hoc testing of significant variables. Pearson's correlation coefficient (r) was used to assess the correlations between the ventilatory inefficiency parameters ($\dot{V}_E/\dot{V}CO_2$ intercept, slope and nadir) and ventilatory capacity (peak $\dot{V}_E$/MVV, peak $\dot{V}O_2$/watt), static or dynamic hyperinflation measures (RV/TLC, IC/TLC and peak V_T/TLC), and airflow limitation ($FEV_{1\%}$ predicted and FEV_1/FVC). All analyses were performed with IBM SPSS Statistics 20.0 (Chicago, USA).

Results

Participant characteristics and resting spirometric measurements

As shown in Table 1, the $COPD_{stages1-2}$ (n = 35), $COPD_{stages3-4}$ (n = 18) and control (n = 14) were well matched in terms of age, weight, and BMI. The resting spirometric measures of the participants presented in Table 1. There are the expected decreases in FEV_1 % predicted, FEV_1/FVC, IC % predicted, IC/TLC, DL_{CO} % predicted and the expected increases in RV%, RV/TLC, FRC/TLC from $COPD_{stages1-2}$ to $COPD_{stages3-4}$ (p < 0.01). Table 1 shows demographics and selected resting pulmonary function variables in control and COPD patients.

Table 1

Demographics and selected resting pulmonary function variables in control and COPD patients.

	Control (n = 14)	$COPD_{stages1-2}$ (n = 35)	$COPD_{stages3-4}$ (n = 18)	ANOVA P-value
Age (yr)	61 ± 7.65	64.66 ± 7.65	65.61 ± 6.79	0.193
Height (cm)	167.29 ± 4.84	168.09 ± 7.6	170.33 ± 5.67	0.377
Weight (kg)	70.5 ± 9.88	68.43 ± 10.49	66.88 ± 8.1	0.595
BMI (kg/m^2)	25.07 ± 3.81	24.52 ± 2.76	23.03 ± 2.3	0.108
FEV_1 (L)	2.80 ± 0.46	1.99 ± 0.47***	1.16 ± 0.22***###	0.000
FEV_1 % predicted (%)	102.65 ± 15.46	71.84 ± 13.57***	39.87 ± 7.4***###	0.000
FEV_1/FVC (%)	81.74 ± 6.67	61.05 ± 6.89***	43.22 ± 6.9***###	0.000
TLC % predicted (%)	92.3 ± 11.07	98.33 ± 12.21	103.12 ± 16.76*	0.084
IC (L)	2.46 ± 0.44	2.35 ± 0.45	1.98 ± 0.49***###	0.008
IC % predicted (%)	96.73 ± 16.04	90.47 ± 15.41	69.66 ± 16.45***###	0.000
IC/TLC (%)	44.86 ± 4.68	39.32 ± 7.1*	30.14 ± 7.39***###	0.000
RV % predicted (%)	97.66 ± 17.91	134.58 ± 30.73**	174.68 ± 52.44***###	0.000
RV/TLC (%)	39.6 ± 6.12	52.53 ± 5.1***	62.71 ± 8.61***###	0.000
FRC/TLC (%)	55.14 ± 4.68	60.68 ± 7.10*	69.86 ± 7.39***###	0.000
DL_{CO} % predicted (%)	87.2 ± 8.83	72.32 ± 13.84**	43.47 ± 14.42***###	0.000

Data are presented as mean ± standard deviation. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; IC: inspiratory capacity; TLC: total lung capacity; RV: residual volume; FRC, functional residual capacity; RV: residual volume; DL_{CO}: diffusing capacity of the lung for carbon monoxide.

The * and # labeled for results of the post-hoc test. *p < 0.05 vs. control; **p < 0.01 vs. control; ***p < 0.001 vs. control; #p < 0.05 COPDstages3-4 vs. COPDstages1-2; ## p < 0.01 COPDstages3-4 vs. COPDstages1-2; ### p < 0.001 COPDstages3-4 vs. COPDstages1-2.

Exercise Characteristics

All subjects completed the exercise testing without complications. Peak exercise capacity was progressively reduced from the control to $COPD_{stages1-2}$ and $COPD_{stages3-4}$ patients. Measures at peak

exercise showed that the $COPD_{stages3-4}$ patients had significantly reduced $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}O_{2\%}$predicted, $\dot{V}O_2$/HR, $\dot{V}CO_2$ and WR in comparison to the control ($p < 0.001$) (Table 2). During exercise, the peak V_T in $COPD_{stages3-4}$ (1.3 ± 0.2) was lower than in $COPD_{stages1-2}$ (1.64 ± 0.35). COPD groups were significantly lower than the control (1.79 ± 0.22), ($p < 0.05$). Regarding the measures of DH (peak V_T/TLC), $COPD_{stages1-2}$ (27.45 ± 5.02) and $COPD_{stages3-4}$ (19.88 ± 4.78) patients all exhibited significant difference compared to the control (33.15 ± 5.5) ($p < 0.01$); Table 2 shows the exercise variables at peak exercise in the control and COPD patients categorized by GOLD.

Table 2
Selected variables at peak exercise in control and COPD patients.

	Control (n = 14)	$COPD_{stages1-2}$ (n = 35)	$COPD_{stages3-4}$ (n = 18)	ANOVA P-value
$\dot{V}O_2$ (L/min)	1.77 ± 0.34	1.37 ± 0.27***	1.14 ± 0.26***##	0.000
$\dot{V}O_2$% predicted (%)	99 ± 17.2	77.29 ± 12.47***	60.94 ± 12.25***###	0.000
$\dot{V}O_2$/HR (ml)	11.92 ± 2.03	10.37 ± 1.77**	9.39 ± 1.49***	0.001
$\dot{V}_E$ (L/min)	59.21 ± 13.93	53.71 ± 11.02	40.94 ± 8.61***##3	0.000
$\dot{V}CO_2$ (L/min)	2.1 ± 0.44	1.63 ± 0.34***	1.25 ± 0.31***##	0.000
$\dot{V}_E/\dot{V}O_2$	33.37 ± 4.43	39.49 ± 6.17*	36.84 ± 7.32	0.009
$\dot{V}_E/\dot{V}CO_2$	27.65 ± 3.12	32.51 ± 4.78**	32.48 ± 6.08**	0.007
$\dot{V}_E$/MVV (%)	53.29 ± 12.04	69.17 ± 12.67**	89.52 ± 17.7***###	0.000
WR (watt)	140.79 ± 25.16	107.26 ± 24.92***	80.44 ± 16.86***###	0.000
$\dot{V}O_2$/watt (ml/min/watt)	12.65 ± 1.6	12.97 ± 1.33	14.14 ± 1.51**##	0.007
V_T (L)	1.79 ± 0.22	1.64 ± 0.35	1.3 ± 0.2***##	0.000
V_T/TLC (%)	33.15 ± 5.5	27.45 ± 5.02**	19.88 ± 4.78***###	0.000

Data are presented as mean ± standard deviation. $\dot{V}O_2$: oxygen uptake; $\dot{V}_E$: minute ventilation; $\dot{V}CO_2$: carbon dioxide output; HR: heart rate; MVV: maximal voluntary ventilation; WR: work rate; V_T: tidal volume; TLC: total lung capacity. The * and # labeled for results of the post-hoc test. *$p < 0.05$ vs. control; **$p < 0.01$ vs. control; ***$p < 0.001$ vs. control; #$p < 0.05$ $COPD_{stages3-4}$ vs. $COPD_{stages1-2}$; ## $p < 0.01$ $COPD_{stages3-4}$ vs. $COPD_{stages1-2}$; ### $p < 0.001$ $COPD_{stages3-4}$ vs. $COPD_{stages1-2}$

Ventilatory Inefficiency In COPD Patients

The $\dot{V}_E/\dot{V}CO_2$ relationships were expressed in terms of the slope, nadir, and intercept. Compared to control (24.75 ± 3.07), the slope was increased in $COPD_{stages1-2}$ (30.58 ± 3.62) and decreased in $COPD_{stages3-4}$ (26.84 ± 4.96). As for the intercept, the $COPD_{stages1-2}$ and $COPD_{stages3-4}$ had higher intercepts (4.85 ± 1.11 and 7.16 ± 1.41, respectively) in comparison to control (3.91 ± 1.03). There were significant differences between COPD patients and control ($p < 0.05$). Furthermore, $\dot{V}_E/\dot{V}CO_2$ intercept increased across the severity spectrum of COPD ($p < 0.001$). The nadir was increased in $COPD_{stages1-2}$ (31.47 ± 4.47) and almost stable in $COPD_{stages3-4}$ (32.82 ± 5.29) in comparison to control (26.9 ± 2.92). Among ventilatory inefficiency parameters (slope, nadir and intercept), only $\dot{V}_E/\dot{V}CO_2$ intercept exhibited a better correlation with peak $\dot{V}O_2$/watt ($r = 0.354$, $p = 0.003$) and peak $\dot{V}_E$/MVV ($r = 0.489$, $p < 0.001$). Figure 1 shows measures of ventilatory inefficiency in control and COPD patients. Figure 2 shows ṼE/ṼCO2 intercept in correlation with peak $\dot{V}_E$/MVV and peak $\dot{V}O_2$/watt in the entire study group.

Correlation of ventilatory inefficiency with lung hyperinflation and airflow limitation

The relationships between the measures of ventilatory inefficiency and lung hyperinflation and airflow limitation were assessed in COPD patients. The $\dot{V}_E/\dot{V}CO_2$ intercept was better correlated with rest IC/TLC ($r=-0.574$, $p < 0.001$), RV/TLC ($r = 0.588$, $p < 0.001$) compared to the $\dot{V}_E/\dot{V}CO_2$ slope with rest IC/TLC ($r=-0.006$, $p = 0.962$), RV/TLC ($r = 0.191$, $p = 0.121$) and the $\dot{V}_E/\dot{V}CO_2$ nadir with rest IC/TLC ($r=-0.35$, $p = 0.004$), RV/TLC ($r = 0.431$, $p < 0.001$). The intercept also exhibited better correlation with peak V_T/TLC ($r=-0.585$, $p < 0.001$) than the nadir with peak V_T/TLC ($r=-0.503$, $p < 0.001$) and the slope with peak V_T/TLC ($r=-0.148$, $p = 0.232$)

A similar pattern of results was found in relation to airflow limitation. $\dot{V}_E/\dot{V}CO_2$ slope was not correlated with $FEV_{1\%}$ predicted ($r=-0.064$, $p = 0.609$) or FEV_1/FVC ($r=-0.167$, $p = 0.178$). The intercept showed significantly correlation with $FEV_{1\%}$ predicted ($r=-0.606$, $p < 0.001$) and FEV_1/FVC ($r=-0.629$, $p < 0.001$) compared to the $\dot{V}_E/\dot{V}CO_2$ nadir with $FEV_{1\%}$ predicted ($r=-0.368$, $p = 0.002$) and FEV_1/FVC ($r = 0.434$, $p < 0.001$). Table 3 shows the correlations between the ventilatory inefficiency parameters and measures of lung hyperinflation and airflow limitation. Figure 3 shows $\dot{V}_E/\dot{V}CO_2$ intercept significant correlations with peak V_T/TLC, IC/TLC, RV/TLC, and $FEV_{1\%}$ predicted in the entire study group.

Table 3
Correlation coefficients of ventilatory inefficiency parameters with measures of LH and airflow limitation.

	$\dot{V}_E/\dot{V}CO_2$ slope		$\dot{V}_E/\dot{V}CO_2$ nadir		$\dot{V}_E/\dot{V}CO_2$ intercept	
	r	P-value	r	P-value	r	P-value
peak V_T/TLC	-0.148	0.232	-0.503	0.000	-0.585	0.000
IC/TLC, %	-0.006	0.962	-0.35	0.004	-0.574	0.000
RV/TLC, %	0.191	0.121	0.431	0.000	0.588	0.000
FEV_1/FVC, %	-0.167	0.178	-0.434	0.000	-0.629	0.000
FEV_1 % predicted, %	-0.064	0.609	-0.368	0.002	-0.606	0.000

V_T: tidal volume; IC: inspiratory capacity; TLC: total lung capacity; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Discussion

The main finding of this study was that $\dot{V}_E/\dot{V}CO_2$ intercept was consistently correlated with worsening LH and increasing airflow limitation in COPD. $\dot{V}_E/\dot{V}CO_2$ intercept could be a useful index for ventilatory inefficiency during incremental exercise in COPD.

$\dot{V}_E/\dot{V}CO_2$ relationship was analyzed according to the $\dot{V}_E/\dot{V}CO_2$ ratio vs. time plot [22]. For healthy subjects who can tolerate high levels of exercise, the $\dot{V}_E/\dot{V}CO_2$ nadir and $\dot{V}_E/\dot{V}CO_2$ ratio at the anaerobic threshold were usually very similar [6]. Abnormalities in the $\dot{V}_E/\dot{V}CO_2$ relationship were present across the spectrum of COPD severity. The $\dot{V}_E/\dot{V}CO_2$ nadir showed superior test-retest reliability compared to the $\dot{V}_E/\dot{V}CO_2$ slope in COPD patients [23]. Increases both in $\dot{V}_E/\dot{V}CO_2$ nadir and slope were associated with lower maximal exercise capacity in COPD patients [24, 25]. A retrospective study with a large range of resting pulmonary function (FEV_1 = 12–148% predicted) showed an increased $\dot{V}_E/\dot{V}CO_2$ slope in mild-moderate COPD but a decreased slope in advanced stage in comparison to control. As for $\dot{V}_E/\dot{V}CO_2$ nadir, there was no significant difference in different stages. However, the $\dot{V}_E/\dot{V}CO_2$ intercept was higher across all stages of COPD [9]. In our study, compared to control, $COPD_{stages1-2}$ had a higher slope and nadir, while patients with more advanced stages ($COPD_{stages3-4}$) had a lower slope and a stable nadir (i.e., with no significant change compared to $COPD_{stages1-2}$). The $\dot{V}_E/\dot{V}CO_2$ intercept increased from $COPD_{stages1-2}$ to $COPD_{stages3-4}$. In advanced-stage COPD, the stable $\dot{V}_E/\dot{V}CO_2$ nadir likely reflected the opposite changes in the $\dot{V}_E/\dot{V}CO_2$ slope and intercept.

There was mounting evidence that ventilatory inefficiency parameters were powerful prognostic predictors in COPD patients with comorbidity. A retrospective study in 145 COPD patients undergoing surgery for non-small cell cancer showed that $\dot{V}E/\dot{V}CO2$ slope > 34 predicted mortality after lung

resection surgery [26]. As for the $\dot{V}E/\dot{V}CO2$ nadir, Neder et al. reported that the nadir > 34 in combination with resting hyperinflation predicted mortality in COPD [27]. Importantly, a series of studies demonstrated that the $\dot{V}E/\dot{V}CO2$ intercept (cutoff values ranging from 2.64–4.07 L/min) might discriminate COPD from heart failure [28, 29].

Ventilatory inefficiency increases ventilatory demand and exercise capacity limitation due to expiratory flow limitation that enhances dynamic hyperinflation. Two other independent studies showed correlations between the $\dot{V}_E/\dot{V}CO_2$ nadir and emphysema severity on high-resolution computed tomography scans in COPD patients with largely preserved FEV_1 [30, 31]. Static LH caused by reduction of elastic recoil due to emphysema in COPD and development of expiratory flow limitation promoted progressive air trapping with an increase in the EELV and a decrease in IC. RV was also increased in emphysema/COPD because of both loss of elastic recoil and premature closure of the small airways [32–34]. In expiratory flow-limited patients, EELV was a continuous dynamic variable, which depended on expiratory duration and breathing pattern. DH referred to this temporary and variable increase in EELV. DH was a consequence as ventilation increases and expiratory duration decreases, there was not enough time to allow EELV to decline to its baseline resting value during exercise [35].

Studies reported both static hyperinflation and the degree of dynamic lung hyperinflation were associated with the development of dyspnea and exercise intolerance in COPD patients [36, 37]. Assuming stability of TLC, the resting IC and inspiratory reserve (IRV) showed the operating position of V_T relative to TLC. The smaller the resting IC, the shorter the exercise time before V_T reached plateau and dyspnea abruptly escalates [38]. A four-year longitudinal study reported that significant reductions in peak $\dot{V}O_2$ and $\dot{V}_E$ were related to a decrease in resting IC [39]. Both IC/TLC and RV/TLC in patients with COPD reflected not only the degree of lung static hyperinflation but also the functional reserve. IC/TLC was also found to be a valuable and independent predictor of all-cause and respiratory mortality in COPD compared with that of the BODE (body mass index, airflow obstruction, dyspnea, exercise performance) index [40]. The present study showed $\dot{V}_E/\dot{V}CO_2$ intercept exhibited better correlated with rest IC/TLC (r=-0.574, $p < 0.001$) and RV/TLC ($r = 0.588$, $p < 0.001$) than $\dot{V}_E/\dot{V}CO_2$ nadir .with peak IC/TLC (r=-0.350, $p = 0.004$) and RV/TLC ($r = 0.431$, $p < 0.001$) while $\dot{V}_E/\dot{V}CO_2$ slope had no correlation with static LH parameters.

The EELV progressively increases while IC decreases were associated with dyspnea and exercise intolerance in COPD during exercise [41]. Serial measurements of IC to detect its changes had been reported to be a classic way to identify dynamic hyperinflation [36, 37, 42]. However, the study participates had to be familiar with the maneuvers, and IC measurements also had to be standardized by researchers [43]. Nevertheless, dynamic IC measurement was not recommended for ramp-pattern protocols where V_T cannot steadily proceed to perform IC maneuver. However, the ramp-pattern protocol was a widely used for incremental test [43]. Elevated EELV can substantially constrain the expansion of V_T at higher exercise intensities. It followed that COPD patients reached a V_T plateau and a similar minimal inspiratory reserve volume. Chuang et al. investigated peak V_T/TLC as a convenient new marker of DH and the cutoff value was 0.27 [44]. The present results showed among ventilatory inefficiency

parameters (slope, nadir and intercept), only $\dot{V}_E/\dot{V}CO_2$ intercept exhibited better correlated with peak V_T/TLC (r=-0.585, p < 0.001) than $\dot{V}_E/\dot{V}CO_2$ nadir with peak V_T/TLC (r=-0.503, p < 0.001) and $\dot{V}_E/\dot{V}CO_2$ slope with peak V_T/TLC (r=-0.148, p = 0.232). To our knowledge, this is the first study to describe the relationship between ventilatory inefficiency and DH. Interestingly, the $\dot{V}_E/\dot{V}CO_2$ intercept was better correlated with worsening pulmonary airflow limitation, FEV_1/FVC (r=-0.629, p < 0.001) and $FEV_{1\%}$ predicted (r=-0.606, p < 0.001), than with the other ventilator inefficiency parameters.

A limitation of our study is the modest number of subjects. We believe that the increased ventilatory inefficiency associated with LH might be more pronounced in patients with more advanced COPD. However, in the absence of a true criterion test for ventilatory inefficiency during exercise, we relied on a cluster of variables that were indirect markers of pulmonary gas-exchange disturbances. We also recognize that variables related to disease phenotypes and test factors (e.g., duration) affect the different strategies to reflect ventilatory inefficiency.

Conclusion

$\dot{V}_E/\dot{V}CO_2$ intercept, by definition, equals basal $\dot{V}_E$ when $\dot{V}CO_2$ equals zero, that is, in the absence of pulmonary gas exchange. $\dot{V}_E/\dot{V}CO_2$ intercept cannot be constrained by dynamic mechanics (unlike the slope) or the test duration (unlike the nadir). Increases in $\dot{V}E/\dot{V}CO2$ intercept correlated well with worsening static and dynamic lung hyperinflation and resting airflow limitation. $\dot{V}E/\dot{V}CO2$ intercept increased across the severity spectrum of COPD. A hitherto underappreciated variable, the $\dot{V}E/\dot{V}CO2$ intercept, was found to be a particularly useful index for ventilatory inefficiency during incremental exercise in COPD patients.

Abbreviations

BMI
body mass index;
COPD
chronic obstructive pulmonary disease;
CPET
cardiopulmonary exercise test;
LH
lung hyperinflation;
DL_{CO}
diffusing capacity of the lungs for carbon monoxide;
EELV
end-expiratory lung volume;
FEV_1
forced expiratory volume in 1 s;

FRC
functional residual capacity;
FVC
forced vital capacity;
GOLD
Global Initiative for Chronic Obstructive Lung Disease;
IC
inspiratory capacity;
MVV
maximal voluntary ventilation;
RV
residual volume;
SpO_2
oxygen saturation via pulse oximetry;
TLC
total lung capacity;
$\dot{V}CO_2$
carbon dioxide output;
$\dot{V}_E$
minute ventilation;
$\dot{V}O_2$
oxygen uptake;
V_D
dead space ventilation;
V_T
tidal volume
WR
work rate;

Declarations

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Availability of data and materials

The datasets used and analyzed in the present study will be available from the corresponding author on reasonable request.

Authors' contributions

Haoyan Wang and Bo Xu participated in the conception, the design and coordination of the study. Fang Lin collected data, interpreted the patient data and drafted the manuscript. Min Cao participated in its coordination and helped to draft the manuscript. Shan Nie, Ranran Zhao, Wei Yuan Yunxiao Li, Chunting Tan participated in collecting data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the ethics committee of the Beijing Friendship Hospital and the written informed consent was obtained from every participant.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests**.**

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Figures

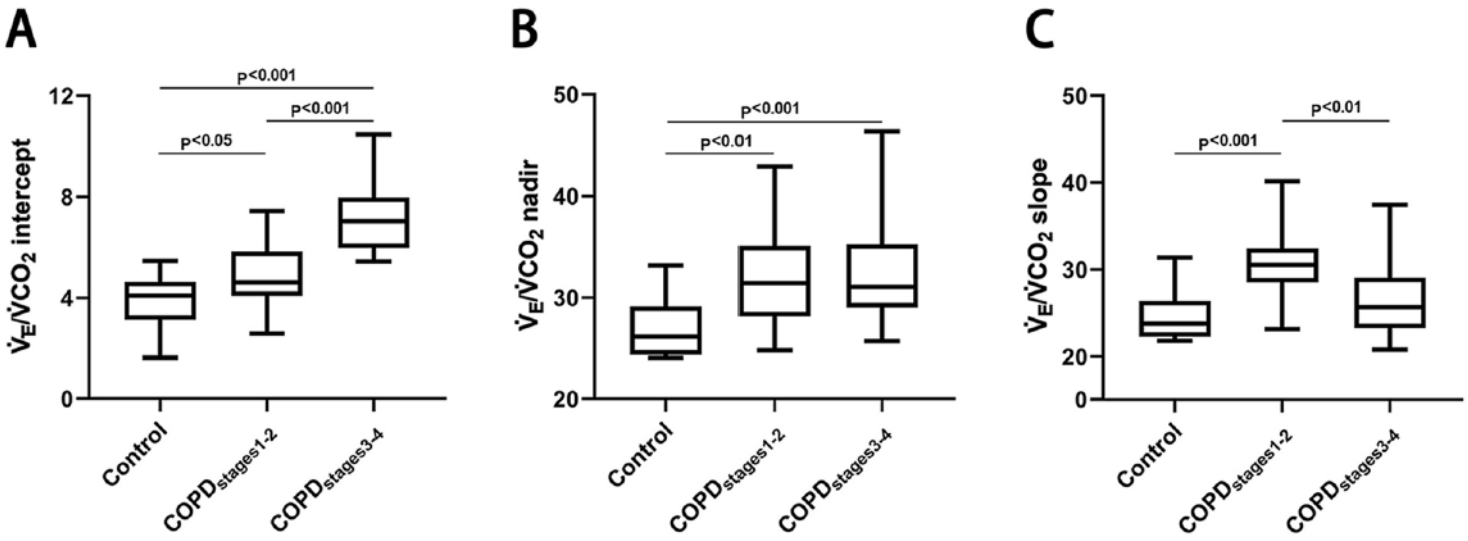

Figure 1

Measures of ventilatory inefficiency in control and COPD patients. (A) V̇E/V̇CO2 intercept, (B) V̇E/V̇CO2 nadir, and (C) V̇E/V̇CO2 intercept in control and COPD categorized by GOLD. A; the COPDstages1-2 and COPDstages3–4 had higher intercepts in comparison to control. V̇E/V̇CO2 intercept increased across the severity spectrum of COPD (p<0.001). B; the nadir was increased in COPDstages1-2 and almost stable in COPDstages3–4 in comparison to control. C; compared to control, the slope was increased in COPDstages1-2 and decreased in COPDstages3-4 (26.84±4.96). V̇E: minute ventilation; V̇CO2: carbon dioxide output.

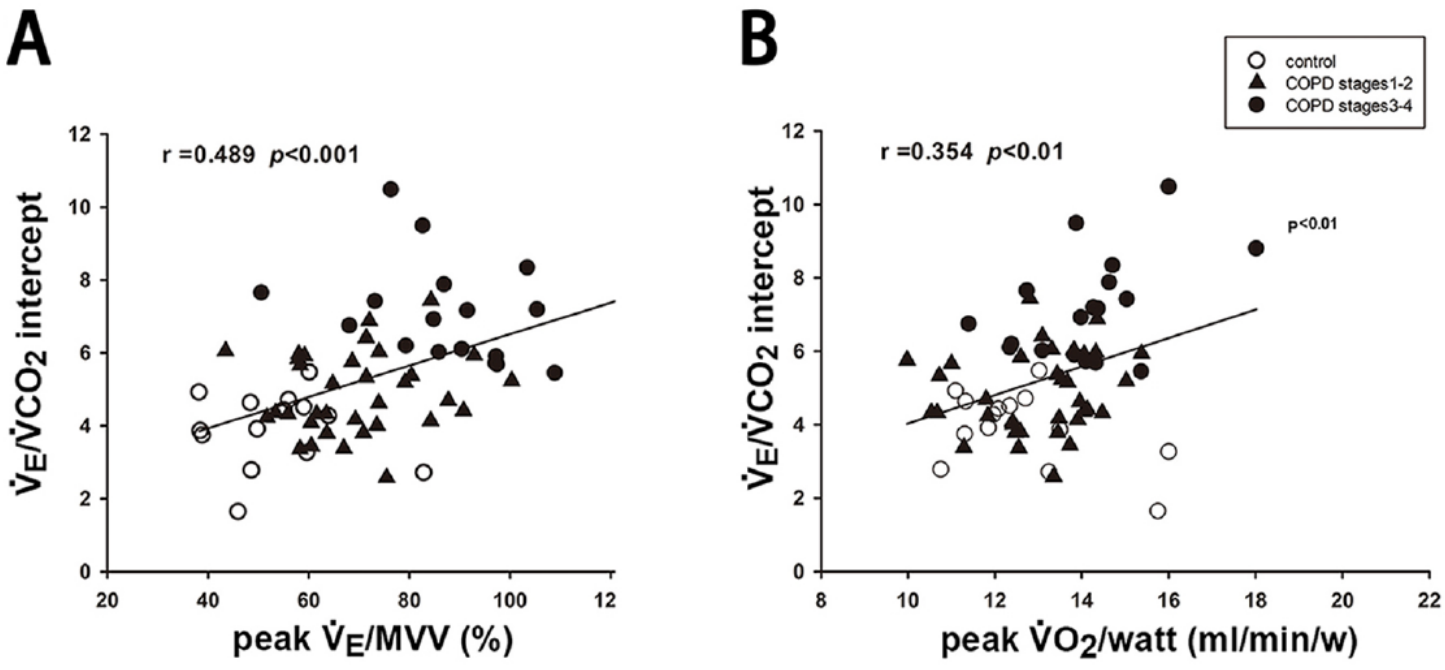

Figure 2

Correlations between V̇E/V̇CO2 intercept and peak V̇E/MVV and peak V̇O2/watt in the entire study group. (A) V̇E/V̇CO2 intercept vs. peak V̇E/MVV (r=0.489, p<0.001); (B) V̇E/V̇CO2 intercept vs. peak V̇O2/watt (r=0.354, p<0.01). MVV: maximal voluntary ventilation; V̇E: minute ventilation; V̇CO2: carbon dioxide output.

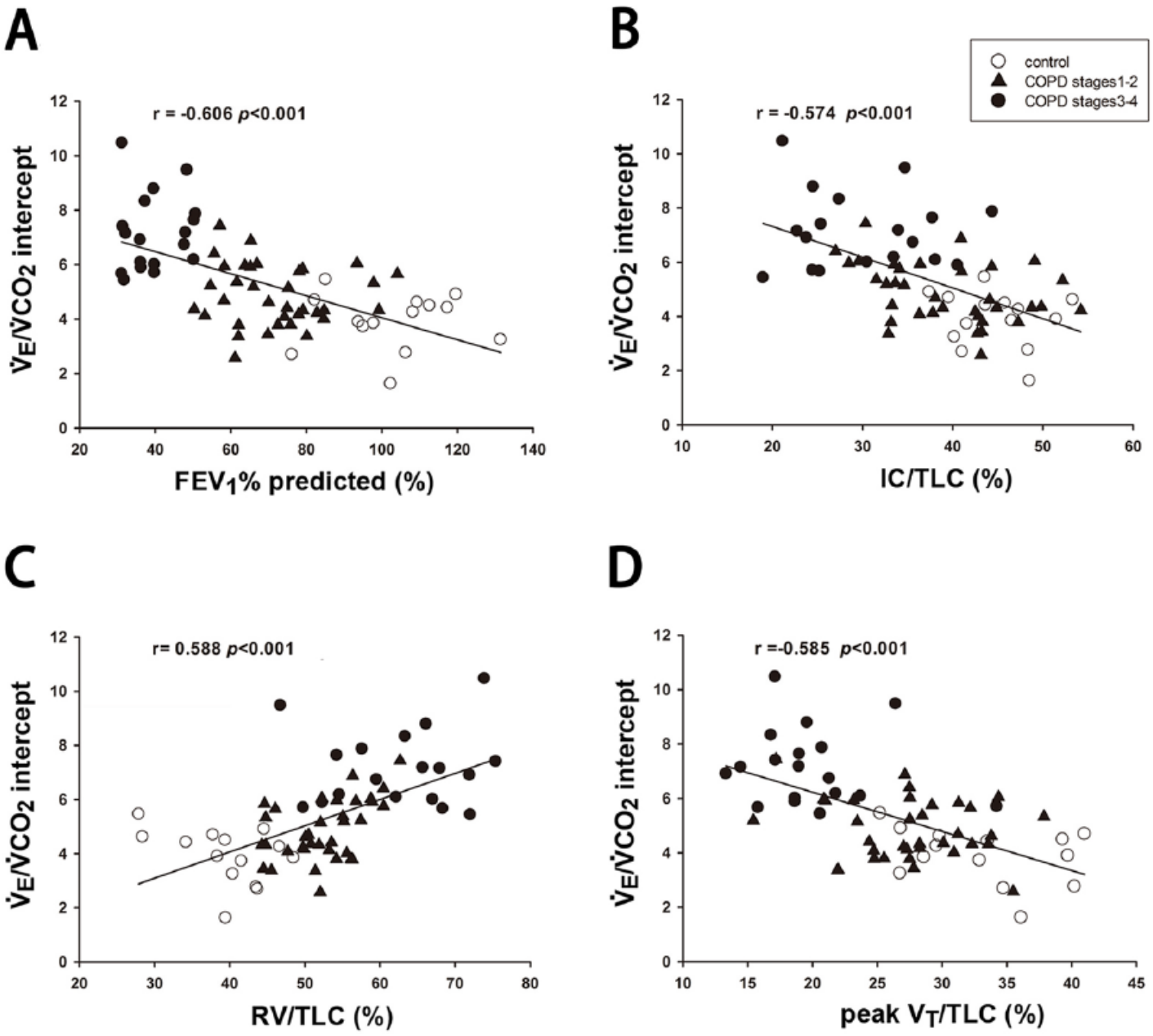

Figure 3

Correlations between the V̇E/V̇CO2 intercept and LH and airflow limitation (A) V̇E/V̇CO2 intercept vs. FEV1 % predicted (r=-0.606, p<0.001); (B) V̇E/V̇CO2 intercept vs. IC/TLC (%) (r=-0.574, p<0.01); (C) V̇E/V̇CO2 intercept vs. RV/TLC (%) (r=0.588, p<0.001); (D) V̇E/V̇CO2 intercept vs. peak VT/TLC (r=-0.585, p<0.001). FEV1: forced expiratory volume in 1s; IC: inspiratory; capacity; RV: residual volume; TLC: total lung capacity; V̇E: minute ventilation; V̇CO2: carbon dioxide output.