Original Article

Intercept of minute ventilation versus carbon dioxide output relationship as an index of ventilatory inefficiency in chronic obstructive pulmonary disease

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Background: Ventilatory inefficiency contributes 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 ventilatory inefficiency parameter. However, its relationships with lung hyperinflation (LH) and airflow limitation are not known. This study aimed to evaluate correlations between the $\dot{V}_E/\dot{V}CO_2$ intercept and LH and airflow limitation to determine its physiological interpretation as an index of functional impairment in COPD.

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

Results: Compared to control, the slope (30.58±3.62, P<0.001) and intercept (4.85±1.11 L/min, P<0.05) were higher in $COPD_{stages1-2}$, leading to a higher nadir (31.47±4.47, P<0.01). Despite an even higher intercept in $COPD_{stages3-4}$ (7.16±1.41, P<0.001), the slope diminished with disease progression (from 30.58±3.62 in $COPD_{stages1-2}$ to 26.84±4.96 in $COPD_{stages3-4}$, P<0.01). There was no difference in nadir among COPD groups and higher intercepts across all stages. The intercept was 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 positively correlated with residual volume (RV) % predicted (r=0.571, P<0.001), RV/total lung capacity (TLC) (r=0.588, P<0.001), peak tidal volume (V_T)/FEV_1 (r=0.482, P<0.001) and negatively correlated with rest inspiratory capacity (IC)/TLC (r=−0.574, P<0.001), peak V_T/TLC (r=−0.585, P<0.001), airflow limitation forced expiratory volume in 1 s (FEV_1) % predicted (r=−0.606, P<0.001), and FEV_1/forced vital capacity (FVC) (r=−0.629, P<0.001).

Conclusions: $\dot{V}_E/\dot{V}CO_2$ intercept was consistently correlated with worsening static and dynamic LH, pulmonary gas exchange, and airflow limitation in COPD. The $\dot{V}_E/\dot{V}CO_2$ intercept emerged as a useful index of ventilatory inefficiency in COPD patients.

Keywords: Chronic obstructive pulmonary disease (COPD); ventilatory inefficiency; exercise; lung hyperinflation (LH); airflow limitation

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Introduction

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 pathophysiologies of dyspnea and exercise intolerance (2). LH has a static and dynamic component. Static lung hyperinflation (sLH) is defined as functional residual capacity (FRC) equal to increased relaxation respiratory volume (V*r*) resulting from loss of lung elastic recoil, while dynamic lung hyperinflation (dLH) when FRC exceeds V*r* (3). dLH that 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 (5). The diminished ventilatory capacity coupled with the increased ventilatory demand during exercise results in 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 due to a lower in dead space ventilation (V_D)/tidal volume (V_T) ratio. When the lactic acidosis first develops, both $\dot{V}_E$ and $\dot{V}CO_2$ increase curvilinearly, resulting in no further change in $\dot{V}_E/\dot{V}CO_2$ and $P_{ET}CO_2$. (isocapnic buffering). The $\dot{V}_E/\dot{V}CO_2$ nadir is typically reached at isocapnic buffering period and then ventilation starts to increase to compensate for lactic acidosis at the respiratory compensation point (RCP) (6). The $\dot{V}_E/\dot{V}CO_2$ nadir was found to be highly reproducible in healthy subjects (7) and COPD patients (8). However, the $\dot{V}_E/\dot{V}CO_2$ nadir might underestimate ventilatory inefficiency if the descending curve is prematurely interrupted by lactic acidosis or a very short test duration (9). On the other hand, the $\dot{V}_E/\dot{V}CO_2$ ratio might be higher than the nadir due to the hyperventilation response to late-exercise acidosis in patients who can exercise beyond the RCP (10).

The $\dot{V}_E/\dot{V}CO_2$ slope has been used to assess disease progression and identify the presence of comorbidities (11-16). However, in many patients with moderate-to-severe COPD, 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 progresses if CO_2 retention worsens during exercise. 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 (10).

The $\dot{V}_E/\dot{V}CO_2$ intercept is a novel parameter derived from $\dot{V}_E$ *vs.* $\dot{V}CO_2$ relationship by extrapolating a regression line during exercise, which theoretically equates to the V_D (17) and cannot be constrained by dynamic mechanics (unlike the slope) or the test duration (unlike the nadir) (10,18). Indeed, $\dot{V}_E/\dot{V}CO_2 = 863/[PaCO_2 \times (1 - V_D/V_T)]$. If two periods—$PaCO_2$ and the V_D/V_T ratio are constant during exercise, no intercept can appear. Otherwise, we can show an intercept during exercise because $PaCO_2$ increases with greater exercise intensity, even in the absence of V_D.

The $\dot{V}_E/\dot{V}CO_2$ intercept depends on the patterns of change in multiple parameters during exercise. The increased intercept in COPD patients might result from an altered breathing strategy such as 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 COPD severity continuum (10). 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 except few study reported the relationship between intercept and dLH (19).

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 a particularly useful index for ventilatory inefficiency in COPD.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-2725).

Methods

Study participants

This study was a retrospective analysis of incremental cardiopulmonary exercises data collected from Jan. 1, 2016 to Dec. 31, 2019 at the Respiratory Investigation Unit, Beijing Friendship Hospital, Capital Medical University (Beijing, China). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Participants were males and females aged ≥40 years with body mass index (BMI) of 18–35 kg/m^2 and given informed consent before taking part in. The study was approved by the Institutional ethics committee of Beijing Friendship Hospital of Capital Medical University (No. 2018-P2-048-01) and the written informed consent was obtained from every participant. The 53 patients were current or ex-smokers (smoking history ≥10 pack-years) and had a well-established diagnosis of COPD (20) without asthma or other pulmonary diseases. Patients were required to have had no exacerbation in the preceding 6 weeks. Fourteen 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), 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 (21).

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 control subjects, 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. Participants 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 consecutive 30 s data. Arterial oxygen saturation was measured noninvasively by pulse oximetry (SpO_2 %). The $\dot{V}_E/\dot{V}CO_2$ nadir and peak $\dot{V}_E/\dot{V}CO_2$ were averaging the consecutive 30 s data points at lowest and peak time, respectively (7). 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 exercise data points, excluding data above the respiratory compensation point (7,22). 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 ×40. Peak V_T/FEV_1 was considered as emphysema factor (19) and peak V_T/TLC as dLH parameter during exercise (23) while IC/TLC, RV % predicted and RV/TLC were used as sLH (24).

Statistical analysis

The sample size required was based on compare k means: one-way analysis of variance (ANOVA) pairwise, two-sided equality for α of 0.05, a power (1-β) of 0.8 to detect this difference by using Medcalc Statistical Software version 19.1.3 (Medcalc Software BV, Ostend, Belgium; https: // www.medcalc.org; 2019). Values were 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 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 peak $\dot{V}_E$/MVV,

Table 1 Demographics and selected resting pulmonary function variables in control and COPD patients

Variables	Control (n=14)	$COPD_{stages1-2}$ (n=35)	$COPD_{stages3-4}$ (n=18)	ANOVA P value
Male, n (%)	12 (85.71)	31 (88.57)	16 (88.89)	–
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 % 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 % 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
DL_{CO} % predicted (%)	87.2±8.83	72.32±13.84**	43.47±14.42***###	0.000

Data are presented as mean ± standard deviation. 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<0.001 $COPD_{stages3-4}$ *vs.* $COPD_{stages1-2}$. 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; DL_{CO}, diffusing capacity of the lung for carbon monoxide.

peak $\dot{V}O_2$/Watt, static and dynamic hyperinflation measures (RV % predicted, RV/TLC, IC/TLC and peak V_T/TLC, peak V_T/FEV_1), and airflow limitation (FEV_1 % predicted and FEV_1/FVC). All analyses were performed with SPSS Statistics 20.0 (IBM, 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. 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 % predicted, RV/TLC, from $COPD_{stages1-2}$ to $COPD_{stages3-4}$ (P<0.001). *Table 1* shows demographics and selected resting pulmonary function variables in control and COPD patients.

Exercise characteristics

Table 2 shows the exercise variables at peak exercise in control and COPD patients. All subjects completed the exercise testing without complications. No one repeated the CPET and no one peak workload more than 200 W. Among them ranges of exercise duration were found from 6 to 10 min. 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 except peak $\dot{V}_E$/MVV in comparison to control (P<0.001). $COPD_{stages3-4}$ patients had significantly reduced $\dot{V}O_2$ % predicted, $\dot{V}_E$, and WR while peak $\dot{V}_E$/MVV increased in comparison to $COPD_{stages1-2}$ (P<0.001). 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), and significantly lower than control (1.79±0.22) (P<0.001). Considering emphysema factor, peak V_T/FEV_1 (%) in $COPD_{stages3-4}$ (114±23.28) was higher than in $COPD_{stages1-2}$ (84.72±17.18), and significantly higher than control (65.49±12.95) (P<0.001). There was also significant difference between $COPD_{stages1-2}$ and $COPD_{stages3-4}$ (P<0.001). Regarding the measures of dLH peak V_T/TLC (%), compared to control (33.15±5.5), $COPD_{stages1-2}$ (27.45±5.02, P<0.01) and $COPD_{stages3-4}$ (19.88±4.78, P<0.001) patients all exhibited significant difference; there was also significant

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

Variables	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/beat)	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***###	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
$\dot{V}_E/\dot{V}CO_2$ slope	24.75±3.07	30.58±3.62***	26.84±4.96##	0.000
$\dot{V}_E/\dot{V}CO_2$ nadir	26.9±2.92	31.47±4.47**	32.82±5.29***	0.001
$\dot{V}_E/\dot{V}CO_2$ intercept (L/min)	3.91±1.03	4.85±1.11*	7.16±1.41***###	0.000
$\dot{V}_E$/MVV (%)	53.29±12.04	69.17±12.67**	89.52±17.7***###	0.000
WR (W)	140.79±25.16	107.26±24.92***	80.44±16.86***###	0.000
$\dot{V}O_2$/Watt (mL/min/W)	12.65±1.6	12.97±1.33	14.14±1.51**##	0.007
peakV_T (L)	1.79±0.22	1.64±0.35	1.3±0.2***##	0.000
peakV_T/TLC (%)	33.15±5.5	27.45±5.02**	19.88±4.78***###	0.000
peakV_T/FEV_1 (%)	65.49±12.95	84.72±17.18***	113.93±23.28***###	0.000

Data are presented as mean ± standard deviation. 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<0.01 $COPD_{stages3-4}$ *vs.* $COPD_{stages1-2}$; ###, P<0.001 $COPD_{stages3-4}$ *vs.* $COPD_{stages1-2}$. $\dot{V}O_2$, 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; FEV_1, forced expiratory volume in 1 s.

difference between $COPD_{stages1-2}$ and $COPD_{stages3-4}$ (P<0.001).

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). The nadir was increased in $COPD_{stages1-2}$ (31.47±4.47, P<0.01) and almost stable in $COPD_{stages3-4}$ (32.82±5.29, P<0.001) in comparison to control (26.9±2.92). There was no difference between $COPD_{stages1-2}$ and $COPD_{stages3-4}$. As for the intercept, the $COPD_{stages1-2}$ and $COPD_{stages3-4}$ had higher intercepts (4.85±1.11, P<0.05), and (7.16±1.41, P<0.001) respectively in comparison to control (3.91±1.03). There was significant difference between $COPD_{stages3-4}$ and $COPD_{stages1–2}$ (P<0.001). $\dot{V}_E/\dot{V}CO_2$ intercept increased across the severity spectrum of COPD. Among ventilatory inefficiency parameters (slope, nadir and intercept), only $\dot{V}_E/\dot{V}CO_2$ intercept exhibited 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 $\dot{V}_E/\dot{V}CO_2$ 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 LH and airflow limitation

Table 3 shows the correlation coefficients of the ventilatory inefficiency parameters and measures of LH, airflow limitation. The relationships between the measures of ventilatory inefficiency and LH and airflow limitation were assessed in COPD patients. The $\dot{V}_E/\dot{V}CO_2$ intercept was correlated with the measures of sLH and dLH (*Table 3*), rest IC/TLC (r=–0.574, P<0.001), RV % predicted (r=0.571, P<0.001), RV/TLC (r=0.588, P<0.001), peak V_T/FEV_1 (r=0.482, P<0.001) and peak V_T/TLC (r=–0.585, P<0.001)

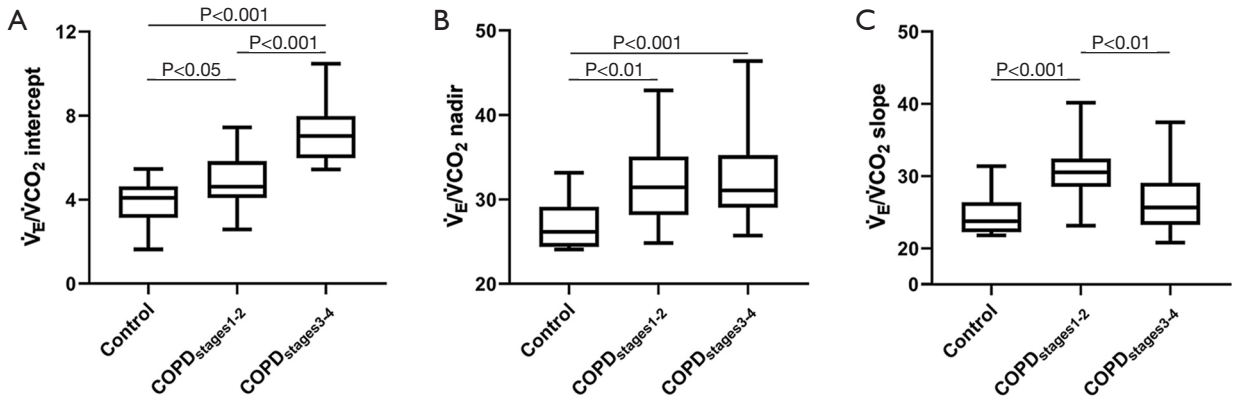

Figure 1 Measures of ventilatory inefficiency in control and COPD patients. (A) $\dot{V}_E/\dot{V}CO_2$ intercept, (B) $\dot{V}_E/\dot{V}CO_2$ nadir, and (C) $\dot{V}_E/\dot{V}CO_2$ slope in control and COPD patients. (A) The $COPD_{stages1-2}$ and $COPD_{stages3-4}$ had higher intercepts in comparison to control. $\dot{V}_E/\dot{V}CO_2$ intercept increased across the severity spectrum of COPD (P<0.001). (B) The nadir was increased in COPD patients in comparison to control. There was no difference between $COPD_{stages1-2}$ and $COPD_{stages3-4}$. (C) Compared to control, the slope was increased in $COPD_{stages1-2}$ (P<0.001) and then decreased in $COPD_{stages3-4}$. There was no difference between $COPD_{stages3-4}$ and control. COPD, chronic obstructive pulmonary disease; $\dot{V}_E$, minute ventilation; $\dot{V}CO_2$, carbon dioxide output.

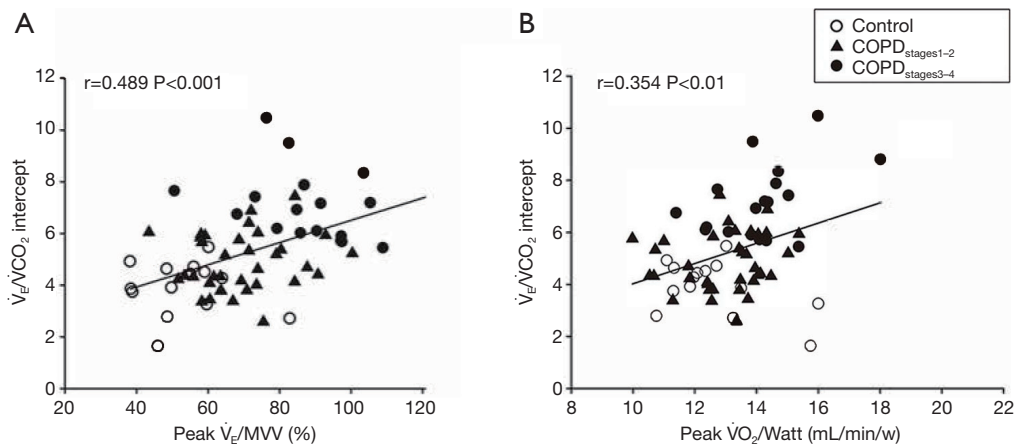

Figure 2 Correlations between $\dot{V}_E/\dot{V}CO_2$ intercept and peak $\dot{V}_E$/MVV and peak $\dot{V}O_2$/Watt in the entire study group. (A) $\dot{V}_E/\dot{V}CO_2$ intercept *vs.* peak $\dot{V}_E$/MVV (r=0.489, P<0.001); (B) $\dot{V}_E/\dot{V}CO_2$ intercept *vs.* peak $\dot{V}O_2$/Watt (r=0.354, P<0.01). MVV, maximal voluntary ventilation; $\dot{V}_E$, minute ventilation; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}O_2$, oxygen uptake.

respectively while the $\dot{V}_E/\dot{V}CO_2$ slope not. The $\dot{V}_E/\dot{V}CO_2$ nadir was also correlated with rest IC/TLC (r=−0.35, P=0.004), RV % predicted (r=0.383, P=0.001) RV/TLC (r=0.431, P<0.001), and peak V_T/TLC (r=−0.503, P<0.001). A similar pattern of results was found in correlation to airflow limitation. The $\dot{V}_E/\dot{V}CO_2$ intercept showed correlation with FEV_1 % predicted (r=−0.606, P<0.001) and FEV_1/FVC (r=−0.629, P<0.001) while $\dot{V}_E/\dot{V}CO_2$ slope not. $\dot{V}_E/\dot{V}CO_2$ nadir was also correlated with FEV_1 % predicted (r=−0.368, P=0.002) and FEV_1/FVC (r=0.424, P<0.001).

Discussion

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

Abnormalities in the $\dot{V}_E/\dot{V}CO_2$ relationship were present across the spectrum of COPD severity. Increases in both the $\dot{V}_E/\dot{V}CO_2$ nadir and slope were associated with lower

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

Variables	$\dot{V}_E/\dot{V}CO_2$ 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
Peak V_T/FEV_1	−0.253	0.036	0.195	0.113	0.482	0.000
IC/TLC (%)	−0.006	0.962	−0.35	0.004	−0.574	0.000
RV % predicted (%)	0.146	0.242	0.383	0.001	0.571	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
$\dot{V}_E$/MVV (%)	0.181	0.142	0.424	0.000	0.489	0.000
$\dot{V}O_2$/Watt (mL/min/W)	−0.058	0.639	0.213	0.083	0.354	0.003

V_T, tidal volume; IC, inspiratory capacity; TLC, total lung capacity; RV, residual volume, FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; $\dot{V}_E$, minute ventilation; MVV, maximal voluntary ventilation; $\dot{V}O_2$, oxygen uptake.

maximal exercise capacity in COPD patients (10,25-27). In our study, compared to control, $COPD_{stages1-2}$ had a higher slope and nadir. For healthy subjects who can tolerate high levels of exercise, the $\dot{V}_E/\dot{V}CO_2$ nadir and ratio at the anaerobic threshold were usually very similar (7). As the lactate threshold may not always be identified, particularly in clinical populations with low exercise capacity (28), the $\dot{V}_E/\dot{V}CO_2$ nadir seems a more accurate indication of ventilatory efficiency than the $\dot{V}_E/\dot{V}CO_2$ at the lactate threshold. However, the $\dot{V}_E/\dot{V}CO_2$ nadir, might underestimate ventilatory efficiency for early lactic acidosis or an excessively short test duration (9). The results showed patients with $COPD_{stages1-2}$ had a higher slope and nadir, while $COPD_{stages3-4}$ had a lower slope, and a stable nadir. The $\dot{V}_E/\dot{V}CO_2$ intercept, by definition, cannot be constrained by worsening mechanics (as the slope) or test duration (as the nadir). It should be recognized that including the data points after the RCP will necessarily increase the computed slope and decrease the computed intercept. Furthermore, including the data points after the RCP does not accurately reflect $\dot{V}_E$ *vs.* $\dot{V}CO_2$ plot profile. In present study, we excluded the data above the RCP for linear regression to calculate the slope and intercept. The $\dot{V}_E/\dot{V}CO_2$ intercept was higher across all stages in current study. This is in line with a retrospective study reported by Neder of 316 patients with a large range of resting pulmonary function (FEV_1 =12–148% predicted) (10). A lower slope, stable nadir, and a higher intercept in more advanced COPD stage likely reflected the opposite changes in $\dot{V}_E/\dot{V}CO_2$ slope and intercept.

There is mounting evidence that ventilatory inefficiency parameters are powerful prognostic predictors in COPD patients with comorbidity. A retrospective study of 145 COPD patients undergoing surgery for non-small cell cancer (NSCLC) showed that a $\dot{V}_E/\dot{V}CO_2$ slope >34 predicted mortality after lung resection surgery (29). A high-intensity pulmonary rehabilitation programs could improve ventilatory efficiency in patients with COPD undergoing lung resection for NSCLC ($\dot{V}_E$ /$\dot{V}CO_2$ slope from 32.0±2.8 to 30.1±4.0, P<0.01) (30). As for the $\dot{V}_E/\dot{V}CO_2$ nadir, Neder *et al.* reported that a value >34 in combination with resting hyperinflation predicted mortality in COPD (31). Importantly, a series of studies demonstrated that the $\dot{V}_E/\dot{V}CO_2$ intercept (cutoff values ranging from 2.64–4.07 L/min) might discriminate COPD from heart failure (32,33).

Ventilatory inefficiency increases ventilatory demand and exercise capacity limitation in COPD patients. The increase of peak $\dot{V}_E$/MVV across all stages reflected the worsening breathing reserve in COPD. Interestingly, the $\dot{V}_E/\dot{V}CO_2$ nadir and intercept were highly positively related to the peak $\dot{V}_E$/MVV in the current study. $\dot{V}O_2$-work rate relationship describes how much O_2 is utilized by exercise subject in relation to the quantity of external work performed. Among the $\dot{V}_E/\dot{V}CO_2$ slope, nadir and intercept, only $\dot{V}_E/\dot{V}CO_2$ intercept was positively related to the peak $\dot{V}O_2$/Watt (*Table 3*). This was consistent with Neder's reports that $\dot{V}_E/\dot{V}CO_2$ intercept was correlated with the peak metabolic stress ($\dot{V}O_2$peak) (10).

Two other independent studies found 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 (34,35). Teopompi reported that patients with the ratio of peak V_T/FEV_1 ≥1 had a predominant pulmonary emphysema profile, thereby showing a higher degree of airflow obstruction (19). We found the $\dot{V}_E/\dot{V}CO_2$ intercept was positively related to peak V_T/FEV_1 and particularly the ratio of peak V_T/FEV_1 in $COPD_{stages3-4}$ was more than 1 (1.13±0.23). The consequence of pulmonary parenchyma destruction and loss of elastic recoil is static hyperinflation. Emphysema and development of expiratory flow limitation promote progressive air trapping with an increase in the EELV and a decrease in IC. RV was also increased in emphysema/COPD due to both loss of elastic recoil and premature closure of the small airways (3,36,37). In expiratory flow-limited patients, EELV was a continuous dynamic variable dependent on expiratory duration and breathing pattern. DH refers to this temporary and variable increase in EELV. As ventilation increases and expiratory duration decreases, there is not enough time to allow EELV to decline to its baseline resting value (38).

Studies reported that both sLH and the degree of dLH were associated with the development of dyspnea and exercise intolerance in COPD patients (39,40). Assuming TLC stability, the resting IC and inspiratory reserve (IRV) showed the operating position of V_T relative to the TLC. The smaller the resting IC, the shorter the exercise time before V_T plateaus and dyspnea abruptly escalates (41). A 4-year longitudinal study reported that significant reductions in peak $\dot{V}O_2$ and $\dot{V}_E$ were related to a decreased resting IC (42). Both rest IC/TLC and RV/TLC in patients with COPD reflected the degree of sLH and also the functional reserve. Rest 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 (43). The present study showed that the $\dot{V}_E/\dot{V}CO_2$ intercept was more strongly correlated with a series of highly relevant parameters, rest IC/TLC (r=−0.574, P<0.001), RV % predicted (r=0.571, P<0.001) and RV/TLC (r=0.588, P<0.001) , and $\dot{V}_E/\dot{V}CO_2$ nadir with rest IC/TLC (r=−0.35, P=0.004), RV % predicted (r=0.383, P=0.001), RV/TLC (r=0.431, P<0.001). The $\dot{V}_E/\dot{V}CO_2$ slope had no correlation with sLH parameters.

A progressive increase in EELV, while IC decreases was associated with dyspnea and exercise intolerance in COPD during exercise (44). Serial measurements of IC to detect its changes were reported as a classic way to identify dynamic hyperinflation (39,40,45). However, the study participants had to be familiar with the maneuvers, and IC measurements also had to be standardized by researchers (46). Dynamic IC measurement is not recommended for ramp-pattern protocols where V_T cannot steadily proceed to perform the IC maneuver. However, the ramp-pattern protocol is a widely used for incremental testing (46). Elevated EELV can substantially constrain V_T expansion at higher exercise intensities. It is logical that COPD patients reach a V_T plateau and have similar minimal inspiratory reserve volume. Chuang *et al.* investigated peak V_T/TLC as a convenient new marker of DH and reported a cutoff of 0.27 (23). In this study, we used peak V_T/TLC instead of Δ (peak-rest) IC as the index of dLH. Among ventilatory inefficiency parameters (slope, nadir, and intercept), we found that only the $\dot{V}_E/\dot{V}CO_2$ intercept exhibited a better correlation to peak V_T/TLC (r=−0.585, P<0.001). To our knowledge, this is the first study to describe the relationship between ventilatory inefficiency parameters and rest IC/TLC, RV/TLC and peak V_T/TLC as static and dynamic LH index. Interestingly, the $\dot{V}_E/\dot{V}CO_2$ intercept was also correlated with worsening pulmonary airflow limitation as indicated by FEV_1/FVC (r=−0.629, P<0.001) and FEV_1 % predicted (r=−0.606, P<0.001). This was consistent with Teopompi's reports, expressed as FEV_1 % predicted (r=−0.482, P<0.001) (19) and FEV_1/VC in subjects with COPD (r=−0.38, P=0.009) (47).

A limitation of our study is the small number of subjects although well matched proportions of female patients in three groups (2/14 in control, 4/35 in $COPD_{stages1-2}$, and 2/18 in $COPD_{stages3-4}$, respectively). We did not correlated the $\dot{V}_E/\dot{V}CO_2$ slope, nadir and intercept with dyspnea in current study. Notably, our findings of a significantly lower $\dot{V}_E/\dot{V}CO_2$ slope in $COPD_{stages3-4}$ compared with $COPD_{stages1-2}$ might be due to changes in V_D/V_T, which we did not calculation in present study. 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 set of variables that are indirect markers of pulmonary gas-exchange disturbances. We also recognize that variables related to disease phenotypes and test factors (e.g., duration) affect different strategies to reflect ventilatory inefficiency. Therefore, we can only infer, not establish the mechanism underlying the ventilatory inefficiency in COPD patients during exercise. Further an additional study with V_D/V_T and

$PaCO_2$ measurements is needed.

Conclusions

$\dot{V}_E/\dot{V}CO_2$ intercept increased across the severity spectrum of COPD patients and consistently correlated with exercise capacity. Increases in $\dot{V}_E/\dot{V}CO_2$ intercept were consistently correlated with worsening static and dynamic LH and airflow limitation. A hitherto underappreciated variable, the $\dot{V}_E/\dot{V}CO_2$ intercept, was found to be a particularly useful index of ventilatory inefficiency during incremental exercise in COPD patients. Further comprehensive studies are promised to corroborate these preliminary results.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional ethics committee of Beijing Friendship Hospital of Capital Medical University (No. 2018-P2-048-01) and the written informed consent was obtained from every participant.

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