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Prediction and types of dead-space fraction during exercise in male chronic obstructive pulmonary disease patients

Ming-Lung Chuang, MD[a,b,*], Benjamin Yung-Thing Hsieh, BA[c], I-Feng Lin, DrPH[d]

Abstract

A high dead space (V_D) to tidal volume (V_T) ratio during peak exercise (V_D/V_{Tpeak}) is a sensitive and consistent marker of gas exchange abnormalities; therefore, it is important in patients with chronic obstructive pulmonary disease (COPD). However, it is necessary to use invasive methods to obtain V_D/V_{Tpeak}, as noninvasive methods, such as end-tidal PCO_2 ($P_{ET}CO_{2peak}$) and $P_{ET}CO_2$ adjusted with Jones' equation (P_JCO_{2peak}) at peak exercise, have been reported to be inconsistent with arterial PCO_2 at peak exercise (P_aCO_{2peak}). Hence, this study aimed to generate prediction equations for V_D/V_{Tpeak} using statistical techniques, and to use $P_{ET}CO_{2peak}$ and P_JCO_{2peak} to calculate the corresponding V_D/V_{Tpeak}s (i.e., $V_D/V_{TpeakET}V_D/V_{TpeakJ}$).

A total of 46 male subjects diagnosed with COPD who underwent incremental cardiopulmonary exercise tests with P_aCO_2 measured via arterial catheterization were enrolled. Demographic data, blood laboratory tests, functional daily activities, chest radiography, two-dimensional echocardiography, and lung function tests were assessed.

In multivariate analysis, diffusing capacity, vital capacity, mean inspiratory tidal flow, heart rate, and oxygen pulse at peak exercise were selected with a predictive power of 0.74. There were no significant differences in the PCO_{2peak} values and the corresponding V_D/V_{Tpeak} values across the three types (both p = NS).

In subjects with COPD, V_D/V_{Tpeak} can be estimated using statistical methods and the $P_{ET}CO_{2peak}$ and P_JCO_{2peak}. These methods may have similar predictive power and thus can be used in clinical practice.

Abbreviations: FEV_1 = forced expired volume in one second, P_aCO_2 = arterial PCO_2, P_B = barometric pressure, $P_{\bar{E}}CO_2$ = mixed expired PCO_2, $P_{ET}CO_2$ = end-tidal PCO_2, P_JCO_{2p} = $P_{ET}CO_{2p}$ adjusted with Jones' equation, V_D/V_{Tpeak} = V_D fraction at peak exercise measured, $V_D/V_{TpeakET}$ = V_D/V_{Tpeak} calculated using end-tidal PCO_2, V_D/V_{TpeakJ} = V_D/V_{Tpeak} measured using end-tidal PCO_2 adjusted using Jones equation, V_{Dm} = dead space dead space of the mouth piece and pneumotachograph, V_T = tidal volume.

Keywords: air trapping, arterial blood gas, diffusing capacity, end-tidal CO_2 pressure, Jones equation for arterial PCO_2

1. Introduction

In patients with chronic obstructive pulmonary disease, increased dead space (V_D) causes inefficient ventilation in the lung regions with a ventilation/perfusion ratio >100 and a high V_D fraction during peak exercise (V_D/V_{Tpeak}).[1,2] Notably, V_D/V_{Tpeak} is a unique variable that differs between lung function tests. Its robustness has been reported in patients with abnormal spirometry, even in those with only mildly impaired spirometry,[3] as well as in patients with chronic obstructive pulmonary disease and heart failure overlap, where V_D/V_{Tpeak} has been

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shown to allow for better differentiation of the pathophysiology of exertional dyspnea.[4] Furthermore, compared with resting dead space fraction, V_D/V_{Tpeak} may also be more sensitive in determining abnormal pulmonary gas exchange and may confirm the correctness of resting dead space fraction, although resting physiological or alveolar dead space fraction has been widely and successfully used to predict mortality in pediatric[5,6] and adult critical care medicine,[7,8] in adult patients with inhalation injury,[9] during the postoperative course in patients who underwent cardiac surgery for congenital heart disease,[10] and to assist in the diagnosis of pulmonary embolism.[11] In addition, V_D/V_{Tpeak} has been used to evaluate the pathophysiology and successfully predict mortality in patients with chronic thromboembolic pulmonary hypertension.[12]

Although measuring V_D/V_{Tpeak} is valuable, it requires invasive arterial catheterization to record P_aCO_2 at peak exercise, as well as sophisticated equipment to measure CO_2 output, minute ventilation, and mixed expired PCO_2 ($P_{\bar{E}}CO_2$). Statistical analysis can be used as a noninvasive method for measuring V_D/V_{Tpeak}, and it has been applied in normal subjects using age, height, weight, and sex.[13] However, lung diseases may affect the lungs to different degrees and severities; therefore, the use of statistical methods in normal subjects may be inappropriate.

Alternatively, end-tidal PCO_2 at peak exercise ($P_{ET}CO_{2peak}$) and its value adjusted with Jones' equation (P_JCO_{2peak}) have been used to calculate dead space fraction (and thus the corresponding $V_D/V_{TpeakET}$ and V_D/V_{TpeakJ} values, respectively),[14] and have been shown to be accurate in patients with heart failure during exercise.[15] However, these noninvasive estimations are not recommended for patients with lung disease.[16,17]

The ventilation and CO_2 output ratio at nadir is a non-invasive gas exchange parameter that has been suggested as a surrogate for V_D/V_{Tpeak}; however, the nadir values of minute ventilation and CO_2 output ratio between 28 and 39 cannot predict V_D/V_{Tpeak}.[18] Therefore, in patients with chronic obstructive pulmonary disease, other noninvasive methods to predict V_D/V_{Tpeak} need to be established, and the relationships between measured V_D/V_{Tpeak} and $V_D/V_{TpeakET}$ and V_D/V_{TpeakJ} need to be reappraised. Accordingly, this study aimed to

1. generate prediction equations for V_D/V_{Tpeak} and
2. appraise the differences among P_aCO_{2peak}, $P_{ET}CO_{2peak}$, and P_JCO_{2peak} in patients with chronic obstructive pulmonary disease.

2. Methods

2.1. Study design

We conducted this observational analytical cross-sectional study to investigate the relationship between P_aCO_2, $P_{ET}CO_2$, and P_JCO_2 and the corresponding V_D/V_{Tpeak} values in patients with chronic obstructive pulmonary disease at Chung Shan Medical University Hospital. Multiple linear regression was used to generate the prediction equations for V_D/V_{Tpeak}. Signed informed consent was obtained from all the participants.

2.2. Subjects

We enrolled patients with chronic obstructive pulmonary disease aged ≥40 years with a smoking history of ≥15 pack-years and with exertional dyspnea and/or leg fatigue. Chronic obstructive pulmonary disease was diagnosed according to the Global Initiative for Chronic Lung Obstructive Disease criteria: persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities caused by significant exposure to cigarette smoke.[19] The forced expired volume in one second (FEV_1)/forced vital capacity in each subject was <0.7.[19]

We excluded subjects with a body mass index $\leq 18\,kg\,m^{-2}$ or $\geq 32\,kg\,m^{-2}$ and those with uncontrolled diabetes mellitus, uncontrolled hypertension, anemia (hemoglobin $<13\,g\,dL^{-1}$ in men), cardiovascular, hematological, metabolic, or neuromuscular diseases, and an acute illness in the recent 1 month, as these factors may confound exercise performance. Female subjects were not included in this study because few women had chronic obstructive pulmonary disease in Taiwan,[20] and lung function parameters, anthropometric data, and exercise physiology used for multiple regression analysis were highly sex-related. If women had been included, the inequality in the sample size would have introduced bias when these factors were selected to generate the prediction equations for V_D/V_{Tpeak}.

2.3. Measurements

Demographic data and daily functional activities, including age, height, weight, body mass index, and cigarette consumption, were recorded. An oxygen cost diagram was used to evaluate the participants' functional activity. The participants were asked to indicate a point on an oxygen cost diagram, a 10-cm long vertical line with everyday activities listed alongside the line above which breathlessness limited them.[21] The distance from zero was measured and scored. Leisure activity was coded 1 to 4 according to hours of activity per week: 1 = ≤ 1 hour; 2 = 1 to 3 hours; 3 = 3 to 6 hours; 4 = ≥6 hours.[22]

Chest radiography and two-dimensional echocardiography Chest radiography was obtained within one month of enrollment in the study. The hilothoracic ratio, cardiothoracic ratio, and diameter of the anterior descending pulmonary artery on the standing posterior-anterior chest radiograph were measured.[23] The hila-thoracic ratio >36% and the diameter of anterior descending pulmonary artery >1.8 cm on the standing posterior-anterior chest radiograph were in favor of pulmonary hypertension. The chest radiographs were evaluated by two of the pulmonologists without knowing the clinical information and the average values were recorded for analysis. Two-dimensional echocardiography was performed by an experienced cardiologist who was blinded to the clinical data, lung function, and cardiopulmonary exercise test reports. Parasternal, apical, and subcostal examinations were conducted.[24] Cor pulmonale was defined as follows. Apical four–chamber view: end-diastolic right ventricle area (EDRV) $>15\,cm^2$, end-systolic right-ventricle area (ESRV) $>10\,cm^2$; subcostal four-chamber view: EDRV $>13\,cm^2$, ESRV $>8\,cm^2$; long and short axes view: the presence of paroxysmal intraventricular septum (IVS) with right ventricle enlargement; the right ventricle free wall thickness >4 mm at an end-diastolic phase between the tricuspid annulus and the papillary muscle.[22]

Pulmonary function testing A thorough physical examination was completed before the exercise testing. Pretest preparation and short-acting and long-acting beta bronchodilators were administered according to standard protocols.[25,26] FEV_1, forced vital capapcity, total lung capacity, residual volume, and diffusing capacity for carbon monoxide were measured using spirometry, body plethysmography, and the single-breath

technique (MasterScreen Body; Carefusion, Wuerzburg, Germany).[27,28] The best of the technically satisfactory readings was used.[27,29,30] All of the spirometry data were obtained 15 min before and after inhalation of 400 μg of fenoterol HCl. Static lung volume and diffusing capacity for carbon monoxide data were obtained before administering fenoterol. Maximum inspiratory pressure at the mouth, indicating inspiratory muscle strength, was measured at the residual volume with a nose clip in place (RPM, Micro Medical, Rochester, UK), and a forceful inspiratory maneuver leading to a sustained maximal effort for the best 1 to 3 seconds was calculated, followed by natural release upon fatigue.[22] Maximum expiratory pressure, indicating expiratory muscle strength at the mouth, was measured at total lung capacity.

Exercise testing with pulmonary gas exchange with arterial blood gases and V_D/V_T measurements: Each subject completed an incremental exercise test with pulmonary gas exchange measurements. Oxygen uptake (mL/min at standard temperature and pressure and dry, standard temperature, and pressure and dry), CO_2 output (mL/min at standard temperature and pressure and dry), minute ventilation (at body temperature, pressure, and water vapor saturation, L/min), and oxyhaemoglobin saturation (S_PO_2, %) were measured (MasterScreen CPX, Carefusion, Wuerzburg, Germany). Data from the last 15 seconds of each stage were averaged and reported.[23] The definition of maximum exercise has been reported in the literature if any of the following are reached:

1. heart rate reserve was of 15% or 15 beats/min of predicted maximum heart rate or less; predicted maximum heart rate = 220 − age;
2. respiratory exchange ratio was of 1.09 or greater;
3. blood bicarbonate level of <21 mmol/L;
4. a drop of 4 mmol/L or more in bicarbonate level from baseline level;
5. pH of arterial blood gas at peak exercise was of 7.35 or lower; or
6. pH of arterial blood gas at peak exercise decreased by 0.05 or more from rest.[22]

Brachial artery catheterization was performed, and blood samples were drawn and heparinized for each subject during peak exercise. The sample was immediately placed on ice and then analyzed with normal body temperature correction (model 278, CIBA-Corning, Medfield, MA). Three types of V_D/V_{Tpeak} were calculated using the standard Bohr's formula as follows[31]

$$V_D/V_T = (P_aCO_2 - P_{\bar{E}}CO_2)/P_aCO_2 - V_Dm/V_T \quad (1)$$

$$V_D/V_{TET} = (P_{ET}CO_2 - P_{\bar{E}}CO_2)/P_{ET}CO_2 - V_Dm/V_T \quad (2)$$

$$V_D/V_{TJ} = (P_JCO_2 - P_{\bar{E}}CO_2)/P_JCO_2 - V_Dm/V_T \quad (3)$$

where $P_{\bar{E}}CO_2 = CO_2$ output/minute ventilation $\times (P_B - 47$ mm Hg), P_B is the barometric pressure measured daily, and V_Dm is the dead space of the mouth piece and pneumotachograph, as reported by the manufacturer. $P_JCO_2 = 5.5 + 0.90 \times P_{ET}CO_2 - 0.0021 \times V_T$ (mL).

Blood cell and biochemical analyses Blood cell and biochemical analyses were conducted within one month before entering the study. Biochemical analyses included albumin, globulin, creatinine, sodium, potassium, glucose, cholesterol, triglyceride, aspartate and alanine aminotransferase, and bilirubin. Whole-blood lactate concentration was analyzed.

2.4. Statistical analysis

Data are summarized as mean ± standard deviation. As the primary aim of this study was to construct a predictive model for invasively measured V_D/V_{Tpeak} using noninvasive variables rather than to test the hypothesis of detecting an expected effect size in a clinical trial, our sample size consideration focused on the size needed to ensure stable and efficient regression coefficients. The sample size was thus estimated to be at least 6 to 15 subjects per variable based on at least 6 to 10 subjects per variable, the sum of 20 and 2 times the number of predictors, and 10 to 15 subjects per variable.[32] For each outcome variable, comparisons were performed *a priori* for each outcome variable. Pearson's or Spearman's correlation coefficients were used when appropriate to quantify pairwise relationships among the variables of interest. Multiple linear regression analysis was performed to generate a predictive equation for V_D/V_T. All possible regression algorithms were performed using candidate variables with P values <.35 in univariate analysis in a step-by-step manner. Although using candidate variables with P values <.157 has been suggested in the literature,[33] using candidate variables with P values <.35 would result in many more variables being included. Predictors that are highly correlated with others (i.e., a lower P-value) contribute little independent information, whereas predictors that are not significant in univariable analysis (i.e., a higher P-value) should not be excluded as candidates.[33] Our procedure included more variables, thus avoiding missing any potential candidates as far as possible. The final models were based on the highest adjusted r-square values; when models had similarly high adjusted r-square values, biological plausibility was considered. Studies often measure more predictors than can be used in a model, and thus, pruning is required.[33] Biological plausibility is a component of the reasoning method that can establish a cause-and-effect relationship between a biological factor and an adverse event. Hence, the possible candidate variables should meet any possible cause-and-effect relationship and should not be obtained from data mining. P-values were calculated using ANOVA with Tukey's correction for multiple comparisons to compare means across the three types of PCO_{2peak} and V_D/V_{Tpeak}. Correlation *post hoc* analyses were conducted when indicated. All statistical analyses were performed using the SAS statistical software (SAS Institute Inc, Cary, NC). Statistical significance was set at $P < .05$.

2.5. Ethics approval statement

The local institutional review board of Chung Shan Medical University Hospital (CS19014) approved this study. This study was conducted in compliance with the principles of the Declaration of Helsinki.

3. Results

A total of 46 male subjects with chronic obstructive pulmonary disease were enrolled (mean age 65.2 ± 5.8 years) (Table 1). Most of the enrolled subjects had moderate-to-severe chronic obstructive pulmonary disease, were normocapnic, and had borderline hypoxemia at rest (Table 1). At peak exercise, obstructive ventilatory limitation, mild hypercapnia, and hypoxemia were observed.

Table 1

Demographic data, image, lung function and peak exercise data.

	n	Mean	SD
Age, year	46	65.2	5.8
Body mass index, kg/m^2	46	22.12	3.53
Anterior descending pulmonary artery, cm	46	1.62	0.33
Apical four EDRV,* cm^2	42	13.5	3.7
Total lung capacity, TLC predicted, %	46	135	21
Residual Volume, RV predicted, %	46	200	55
RV/TLC, %	46	58	9
D_LCO pred, %	45	69	22
Slow vital capacity pred, %	46	94	43
Forced vital capacity, FVC predicted, %	46	81	21
FEV_1 pred, %	46	50	19
FEV_1/FVC, %	46	49	13
Maximal inspiratory pressure, %	43	63.8	17.2
Exercise:			
Oxygen uptake, L/min/kg	46	17.9	5.4
Respiratory exchange ratio	46	1.05	0.10
Oxygen pulse, mL/beat	46	8.1	2.4
Heart rate, beat/min	46	133.2	20.4
V_T/T_I, L/s	46	1.52	0.46
Ventilatory equivalent for CO_{2nadir}	46	35.0	6.9
Minute ventilation, L/min	46	38.6	12.3
P_aCO_2, mm Hg	44	46.1	7.8
V_D/V_T	43	0.44	0.10
$P_{a\text{-}ET}CO_2$, mm Hg	44	-0.55	5.04

D_LCO = the diffusion capacity of the lungs for carbon monoxide, FEV_1 = forced expiratory volume in one second, $P_{a\text{-}ET}CO_2$ = arterial end-tidal CO_2 pressure gradient, V_D/V_T = dead space and tidal volume ratio, V_T/T_I = tidal volume and inspiratory time in seconds ratio. Anterior descending pulmonary artery of the right lung ≥1.8 cm indicating pulmonary hypertension.

* Apical four chamber view, end-diastolic right ventricle area (EDRV) >15 cm, oxygen pulse = oxygen uptake divided by heart rate.

3.1. Prediction equation for V_D/V_{Tpeak}

In the multiple linear regression analysis, diffusion capacity for carbon monoxide and V_T/T_{Ipeak} were positively correlated with V_D/V_{Tpeak}, whereas SVC and heart rate and oxygen pulse at peak exercise were negatively correlated with V_D/V_{Tpeak} (Table 2, r^2 = 0.74). Table 3 shows the correlations between the selected variables and the variables of interest.

3.2. PCO_{2peak}s and the corresponding V_D/V_{Tpeak}s

The differences among P_aCO_2, $P_{ET}CO_2$, and P_JCO_2 at peak exercise were insignificant; therefore, the differences among V_D/V_{Tpeak}, $V_D/V_{TpeakET}$, and V_D/V_{TpeakJ} were also insignificant (Fig. 1; P = .63 and .57, respectively). The predictive powers of $V_D/V_{TpeakET}$ and V_D/V_{TpeakJ} in relation to V_D/V_{Tpeak} were similar to those of the prediction equation for V_D/V_{Tpeak} (Table 3 and Fig. 2; r^2 = 0.75 vs 0.74). The residual difference between V_D/V_{Tpeak} and V_D/V_{TpeakJ} is 0.01 ± 0.06 (Fig. 2).

4. Discussion

In this study, we established prediction equations for V_D/V_{Tpeak} with a predictive power of 0.74. Differences across the three types of PCO_2 were not significant; therefore, there were no significant differences across the three types of corresponding V_D/V_{Tpeak} values. The predictive power for V_D/V_{Tpeak} was similar when using the statistical method and when calculated using the $P_{ET}CO_{2peak}$ or P_JCO_{2peak}.

4.1. Prediction equation for V_D/V_{Tpeak}

In normal subjects, age and weight were positively correlated with V_D/V_{Tpeak}, whereas for females and taller individuals, V_D/V_{Tpeak} was lower.[13] However, in the multiple linear regression analysis for V_D/V_{Tpeak} in patients with chronic obstructive pulmonary disease in the current study, age, height, and weight were not selected (Table 2), and slow vital capacity (SVC), diffusing capacity of the lungs and mean tidal inspiratory flow, heart rate, and oxygen pulse at peak exercise were selected. The results indicated that the relationship between demographics and V_D/V_{Tpeak} in normal subjects was altered by lung pathology in patients with chronic obstructive pulmonary disease.

4.2. Slow vital capacity and heart rate and oxygen pulse at peak exercise

Slow vital capacity is different from forced vital capacity in that air trapping beyond the small airways cannot be expelled if breathing is forcefully exhaled. Hence, slow vital capacity was highly related to air trapping (residual volume/total lung capacity) and chronic obstructive pulmonary disease severity (Table 3, $|r|$ = 0.69 − 0.72). Increased V_D/V_T has been reported to occur secondary to an increase in functional residual capacity. However, V_D/V_{Tpeak} was not correlated with functional residual capacity % predicted in the current study but was correlated with residual volume/total lung capacity (r = 0.16 and 0.44, respectively). In brief, V_D/V_{Tpeak} was related to slow vital capacity rather than forced vital capacity owing to an air trapping effect.

Heart rate and oxygen pulse at peak exercise are indicators of exercise intensity and cardiovascular effort, and they were positively correlated with ventilatory and exercise capabilities in this study (Table 3, r = 0.36 − 0.69, P = .01 − < .0001). Hence, heart rate % predicted and oxygen pulse at peak exercise were negatively correlated with V_D/V_{Tpeak} in the univariate and multivariate analyses (Table 3, r = − 0.46 and −0.63, P = .002 and <.0001, respectively; Table 2). Oxygen pulse at peak exercise[34] and its curve patterns[35] are influenced by both central cardiovascular function[36] and air trapping and dynamic hyperinflation in patients with chronic obstructive pulmonary disease.[34,35]

Table 2

Multiple linear regression analysis of dead space fraction of tidal volume at peak exercise in male patients with chronic obstructive pulmonary disease.

V_D/V_{Tpeak} equation		r^2
(1)	1.1375 (± 0.0751) − 0.0333 × SVC (± 0.0176) + 0.0045 × D_LCO (± 0.0024) + 0.1346 × V_T/T_{Ipeak} (± 0.0359) − 0.0037 × HR_{peak} (± 0.0006) − 0.0492 × O_2P_{peak} (± 0.0067)	0.74

D_LCO = diffusing capacity for carbon monoxide in mL/min/mm Hg, HR_{peak} = peak heart rate, O_2P = peak oxygen pulse which was peak oxygen uptake in mL/min divided by peak heart rate in beats per minute, (±SE) = standard errors, P < .0001, SVC = slow vital capacity in liters, V_T/T_I = tidal volume in liters divided by inspiratory time in seconds indicating the mean inspiratory flow at peak exercise.

Table 3

Predictors of high dead space fraction at peak exercise (V_D/V_{Tpeak}) correlated with variables of interest.

SVC% predicted		
	r	*P*
RV/TLC	−0.72	<.0001
FEV_1%predicted	0.69	<.0001
Peak V_D/V_T		
FRC% predicted	0.16	NS
RV/TLC	0.44	.003
Peak HR %predicted	−0.46	.002
Peak O_2P, mL/beat	−0.63	<.0001
Peak HR% predicted		
Peak$\dot{V}_E/(20+20\times FEV_1)$	0.36	.01
Peak V_T/TLC	0.37	.01
Peak $\dot{V}O_2$%predicted	0.44	.002
Peak O_2P, mL/beat		
Peak$\dot{V}_E/(20+20*FEV_1)$	0.64	<.0001
Peak V_T/TLC	0.69	<.0001
Peak $\dot{V}O_2$%predicted	0.63	<.0001
Peak V_T/T_I		
SVC %predicted	0.37	.01
D_LCO %predicted	0.36	.016
Peak $\dot{V}O_2$%predicted	0.59	.0001
Peak O_2 pulse	0.69	<.0001
Peak V_D/V_T	−0.49	.0007
Peak RR/V_T	−0.48	.0006
RV/TLC	−0.58	<.0001
FRC %predicted	−0.32	.03
FVC %predicted	0.35	.02
FEV_1%predicted	0.51	.0003
MIP, cm H_2O	0.5	.0006
$\dot{V}_E$	**0.95**	<.0001
V_T/TLC	0.74	<.0001
HR %predicted	0.46	.001
D_LCO% predicted		
V_D/V_{Tpeak}	−0.38	.01

D_LCO = diffusing capacity for carbon monoxide, FEV_1 = forced expired volume in one second, FRC = functional residual capacity, FVC = forced expiratory capacity, HR = heart rate, MIP = maximal inspiratory pressure, O_2P = oxygen pulse defined by oxygen uptake divided by heart rate, RR/V_T = shallow breathing index, RR = respiratory rate, RV/TLC = residual volume and total lung capacity ratio, SVC = slow vital capacity, T_I = inspiratory time, TLC = total lung capacity, $\dot{V}_E$ = minute ventilation, $\dot{V}O_2$ = oxygen uptake, V_T = tidal volume.

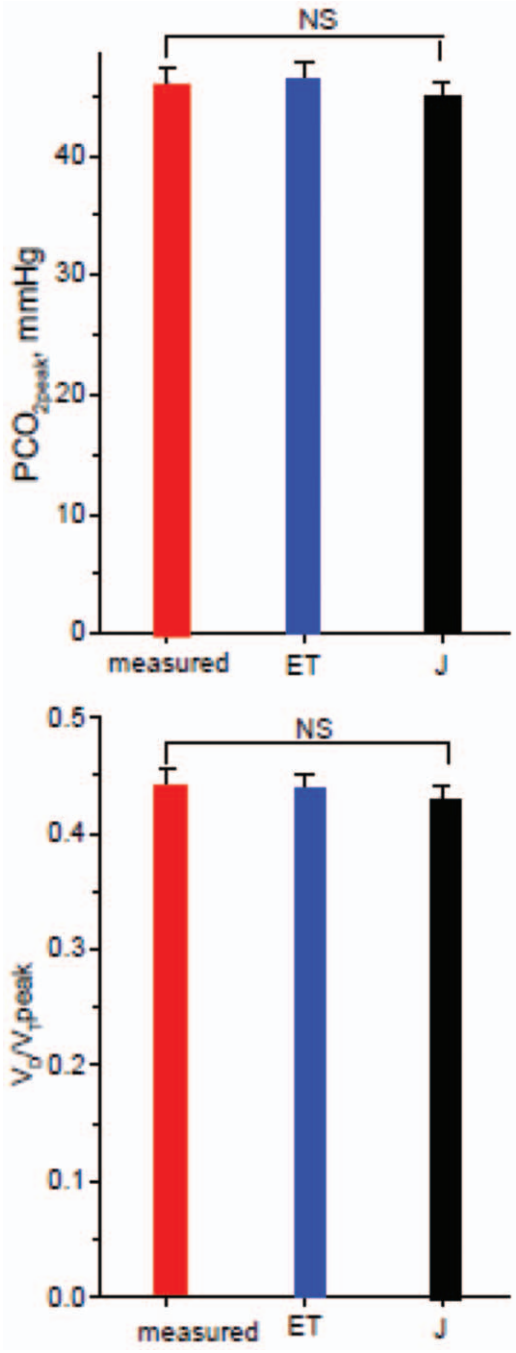

Figure 1. Three types of PCO_2 and dead space fraction of tidal volume (V_D/V_T) at peak exercise in patients with chronic obstructive pulmonary disease. Upper panel: analysis of variance was conducted across three types of PCO_2. (1) Measured: Arterial PCO_2 (P_aCO_2); (2) ET: end-tidal PCO_2 ($P_{ET}CO_2$); and (3) J: P_JCO_2 using Jones' equation (P = .63). Lower panel: analysis of variance across the three types of corresponding V_D/V_{Tpeak} (P = .57).

4.3. Tidal inspiratory flow at peak exercise and diffusion capacity for carbon monoxide

In univariate analysis, tidal inspiratory flow at peak exercise and diffusion capacity for carbon monoxide were negatively related to V_D/V_{Tpeak} (Table 3, $r = -0.49$ and -0.38, respectively). In the multiple regression analysis, tidal inspiratory flow at peak exercise and diffusion capacity for carbon monoxide were "positively" related to V_D/V_{Tpeak}. Because the correlations among the independent variables were significant, their contributions to the dependent variables may have affected each other and even changed the direction of the correlation. In this study, V_T/T_{Ipeak} was correlated with slow vital capacity % predicted, diffusion capacity for carbon monoxide % predicted, and oxygen pulse and heart rate at peak exercise (Table 3, $r = 0.36 - 0.69$).

Tidal inspiratory flow at peak exercise represents the mean tidal inspiratory flow during peak exercise, and should be a beneficial indicator of ventilation. Hence, in the univariate analysis, it was positively correlated with spirometry data in % predicted, diffusion capacity for carbon monoxide % predicted, and maximum inspiratory pressure, and oxygen uptake % predicted, minute ventilation, tidal volume, and their related derivatives, and heart rate % predicted at peak exercise ($r = 0.35 - 0.95$, $P = 0.02 - < .0001$), whereas it was negatively correlated with V_D/V_{Tpeak}, shallow breathing index, functional residual capacity % predicted, and residual volume/total lung capacity (Table 3, $r = -0.32 - 0.58$, $P = .03 - < .0001$).

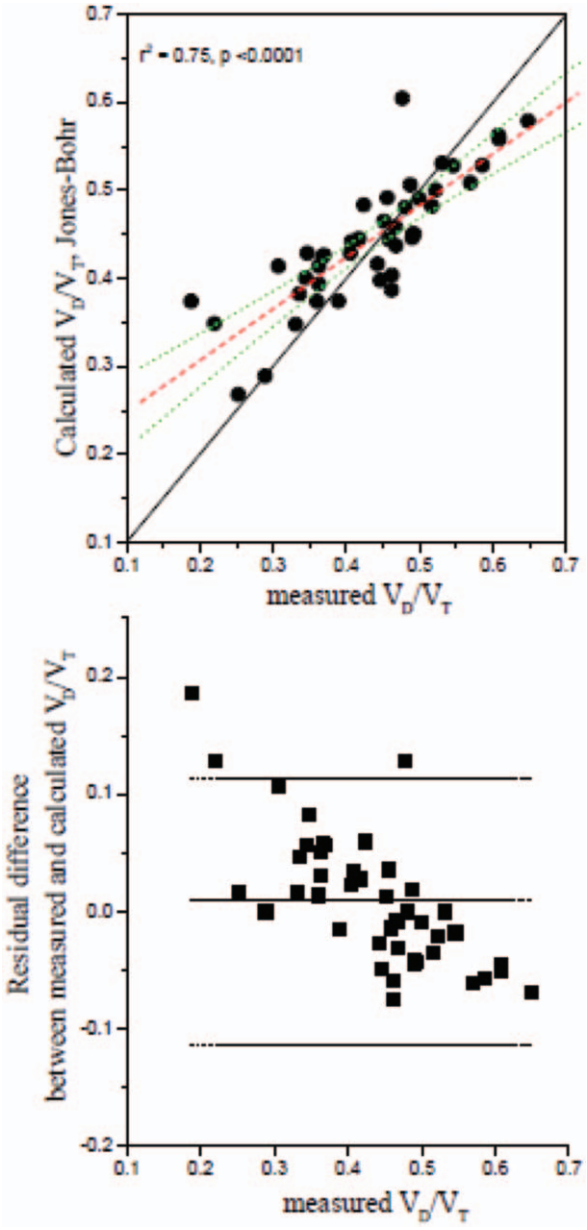

Figure 2. The relationship between the measured dead space fraction (V_D/V_{Tpeak}) and calculated V_D/V_T using Jones' equation adjusted for P_aCO_2 (P_JCO_{2peak} and V_D/V_{TpeakJ}) at peak exercise. Upper panel: scatter plot of measured V_D/V_{Tpeak} and calculated V_D/V_{TpeakJ}. Calculated V_D/V_{TpeakJ} used PCO_{2peakJ} to replace P_aCO_{2peak}. The diagonal solid line indicates the line of identity, the solid line indicates the regression line, and the dotted lines indicated 95% confidence intervals. Lower panel: Bland-Altman plot showed the residual difference between calculated V_D/V_{TpeakJ} and measured V_D/V_{Tpeak}. The solid line indicates the mean, and dotted lines indicate ± 1.96 SD.

Diffusion capacity for carbon monoxide should also be a beneficial indicator of gas exchange; however, it has been shown to be a specific but insensitive predictor during exercise. Hence, diffusion capacity for carbon monoxide was negatively correlated with V_D/V_{Tpeak} in univariate analysis (Table 3, $r=-0.38$, $P=.01$). This is consistent with a previous report, in which diffusion capacity for carbon monoxide % predicted was found to be negatively related to dead space fraction at rest and during peak exercise.[37]

4.4. Types of PCO_{2peak} and V_D/V_{Tpeak}

Lewis et al reported that, in 68 patients with exertional dyspnea, $V_D/V_{TpeakET}$ and V_D/V_{TpeakJ} identified only 50% and 57% of those with abnormal V_D/V_{Tpeak}, respectively.[16] In addition, Liu et al reported that $P_{ET}CO_2$ was correlated with P_aCO_2 with a standard error of estimate as high as 2.3 mm Hg in only 7 patients with chronic obstructive pulmonary disease in whom arterial blood gas was repeatedly sampled at rest and during exercise ($r=0.76$).[38] In addition, Zimmerman et al reported that in 35 patients referred for the evaluation of dyspnea, the mean difference between V_D/V_{Tpeak} and V_D/V_{TpeakJ} significantly increased by 4% ± 6% in response to exercise at ~50% of $\dot{V}O_{2peak}$.[17] They suggested that V_D/V_{TpeakJ} underestimated the measured V_D/V_{Tpeak} and that V_D/V_{TpeakJ} was no better than $V_D/V_{TpeakET}$.[16,17,38] In the current study, there were no significant differences in the PCO_{2peak} and the corresponding V_D/V_{Tpeak} values across the three types (both p = NS). The discrepancies between the current study and previous reports may be because the involved data were obtained from subjects at different stages of exercise and from subjects with different diseases. However, only one previous study investigated patients with chronic obstructive pulmonary disease alone, and the sample size was small.[38]

4.5. Limitations

The number of cases was small in this study because of the invasive procedures. Hence, it was not appropriate to split the dataset for the cross-validation of the derived prediction equations. However, future cross-validation studies using predictive equations are warranted. It may be argued that measuring V_D/V_{Tpeak} was redundant, as minute ventilation and CO_2 output ratio and minute ventilation and O_2 uptake ratio, their nadir values, slopes, and intercepts during exercise, provide a very good approximation of the "wasted" ventilation, and that this coupled with $P_{ET}CO_{2peak}$ and breathing reserve is usually sufficient to understand the causes of a patient's breathlessness. However, the relationships between airflow obstruction, minute ventilation and CO_2 output ratio, its slope and intercept, dead space fraction, and dead space remain controversial.[39] Nevertheless, an minute ventilation and CO_2 output ratio value between 28 and 39 has been shown to be a poor predictor of V_D/V_{Tpeak}.[18] In patients with pulmonary hypertension and chronic obstructive pulmonary disease, inhaled iloprost improves minute ventilation and CO_2 output ratio, but not dead space fraction.[40] In patients with chronic obstructive pulmonary disease and heart failure overlap, increased slope, nadir, or end-exercise of minute ventilation and CO_2 output ratio has been related to capillary PCO_2 but not dead space fraction.[4] However, the nadir of minute ventilation and CO_2 output ratio has been reported to be strongly related to V_D/V_{Tpeak} when the data involve healthy subjects and those with chronic obstructive pulmonary disease at rest and during submaximal exercise.[37] Nevertheless, the nadir of minute ventilation and CO_2 output ratio was not selected for the multiple regression analysis in this study. Except for the contribution of neural control to breathing, V_D/V_T explains the nadir of minute ventilation and CO_2 output ratio because both factors are mathematically related. The reason why the nadir of minute ventilation and CO_2 output ratio was not selected may be the much greater contributions of slow vital capacity, diffusion capacity for carbon monoxide % predicted and tidal inspiratory flow, heart rate % predicted, and oxygen

pulse at peak exercise to V_D/V_{Tpeak}. Recently, a study reported that transcutaneous PCO_2 may reflect P_aCO_2 and may be used to calculate dead space fraction during rest and exercise, but not during recovery in patients with chronic obstructive pulmonary disease.[41] Lastly, the Harris-Benedict estimated resting dead space fraction has been reported to be a better predictor of mortality in patients with acute respiratory distress syndrome than the other three estimates of predicted measured dead-space fraction, namely the Siddiki estimate, Penn State estimate, and direct estimate from physiological variables.[8] The first three approaches require predicting energy expenditure, and the last approach is used to derive an equation that includes the Murray lung injury score and positive end-expiratory pressure level.[8] However, it is not clear whether these equations are appropriate for predicting dead space fraction during peak exercise, even though volumetric capnography has been successfully used in patients with cystic fibrosis during submaximal exercise.[42] Moreover, different techniques to measure alveolar PCO_2 and $P\bar{E}CO_2$, such as using a Douglas bag, indirect calorimetry, and volumetric capnography in patients with acute respiratory distress syndrome, have been shown to result in clinically relevant mean and individual differences in calculated dead space fraction.[43] Further studies on these approaches during peak exercise are required.

4.6. Future directions

Further studies on our prediction equations and the corresponding $V_D/V_{TpeakET}$ and V_D/V_{TpeakJ} ratios are warranted. Using predicted types of V_D/V_{Tpeak} to evaluate subjects with chronic obstructive pulmonary disease is simple and noninvasive and may thus expand its clinical application to evaluate lung pathophysiology, treatment response, and patient-centered outcomes.

5. Conclusion

Our prediction equations showed high predictive power for V_D/V_{Tpeak} and a small residual difference between the measured V_D/V_{Tpeak} and calculated V_D/V_{Tpeak} with and without using the Jones and Bohr equations to adjust the $P_{ET}CO_{2peak}$. We believe that these equations can be used to predict V_D/V_{Tpeak} and may lead to changes in practice guidelines regarding the use of $P_{ET}CO_{2peak}$ or P_JCO_{2peak} to calculate V_D/V_{Tpeak} in patients with chronic obstructive pulmonary disease. These non-invasive methods may approximate the measured V_D/V_{Tpeak} and thus may add information to lung function tests; however, further studies are warranted to confirm their validity.

Supplementary: http://links.lww.com/MD2/A891

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References

[1] Wasserman K, Hansen JE, Sue DY. Wasserman K, et al. Measurements during integrative cardiopulmonary exercise testing. Principles of exercise testing and interpretation Philadelphia: Lippincot Williams & Wilkins; 2005;76–110.
[2] Wasserman K, Hansen JE, Sue DY. Wasserman K, et al. Physiology of exercise. Principles of exercise testing and interpretation Philadelphia: Lippicott Williams & Wilkins; 2005;10–65.
[3] Elbehairy AF, Ciavaglia CE, Webb KA, et al. Pulmonary gas exchange abnormalities in mild chronic obstructive pulmonary disease. Implications for dyspnea and exercise intolerance. Am J Respir Crit Care Med 2015;191:1384–94.
[4] Rocha A, Arbex FF, Sperandio PA, et al. Excess ventilation in chronic obstructive pulmonary disease-heart failure overlap. Implications for dyspnea and exercise intolerance. Am J Respir Crit Care Med 2017;196:1264–74.
[5] Cigarroa CL, van den Bosch SJ, Tang X, et al. Measurement of dead space fraction upon ICU admission predicts length of stay and clinical outcomes following bidirectional cavopulmonary anastomosis. Pediatr Crit Care Med 2018;19:23–31.
[6] Bhalla AK, Belani S, Leung D, et al. Higher dead space is associated with increased mortality in critically ill children. Crit Care Med 2015;43:2439–45.
[7] Morales-Quinteros L, Schultz MJ, Bringue J, et al. Estimated dead space fraction and the ventilatory ratio are associated with mortality in early ARDS. Ann Intensive Care 2019;9:128.
[8] Beitler JR, Thompson BT, Matthay MA, et al. Estimating dead-space fraction for secondary analyses of acute respiratory distress syndrome clinical trials. Crit Care Med 2015;43:1026–35.
[9] Granchi T, Lemere A, Mashruwala N, et al. Increased ratio of dead space to tidal volume in subjects with inhalation injury. Respir Care 2020;65:1555–60.
[10] Shostak E, Schiller O, Merzbach A, et al. Alveolar dead-space fraction and arterial saturation predict postoperative course in Fontan patients. Pediatr Crit Care Med 2020;21:e200–6.
[11] Songur Yucel Z, Metin Aksu N, Akkas M. The combined use of end-tidal carbon dioxide and alveolar dead space fraction values in the diagnosis of pulmonary embolism. Pulmonology 2020;26:192–7.
[12] Godinas L, Sattler C, Lau EM, et al. Dead-space ventilation is linked to exercise capacity and survival in distal chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant 2017;36:1234–42.
[13] Gläser S, Ittermann T, Koch B, et al. Influence of smoking and obesity on alveolar-arterial gas pressure differences and dead space ventilation at rest and peak exercise in healthy men and women. Respir Med 2013;107:919–26.
[14] Lumb AB, Nunn JF. Lumb AB. Distribution of pulmonary ventilation and perfusion. Nunn's Applied Respiratory Physiology Edinburgh: Butterworth Heinemann; 2000;163–99.
[15] Van Iterson EH, Olson TP. Use of 'ideal' alveolar air equations and corrected end-tidal PCO2 to estimate arterial PCO2 and physiological dead space during exercise in patients with heart failure. Int J Cardiol 2018;250:176–82.
[16] Lewis DA, Sietsema KE, Casaburi R, et al. Inaccuracy of noninvasive estimates of VD/VT in clinical exercise testing. Chest 1994;106:1476–80.
[17] Zimmerman MI, Miller A, Brown LK, et al. Estimated vs actual values for dead space/tidal volume ratios during incremental exercise in patients evaluated for dyspnea. Chest 1997;106:131–6.

[18] Roman MA, Casaburi JD, Porszasz J, et al. Noninvasive assessment of normality of VD/VT in clinical cardiopulmonary exercise testing utilizing incremental cycle ergometry. Eur J Appl Physiol 2013;113:33–40.
[19] GOLD Committees. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Disclosure forms for GOLD Committees are posted on the GOLD Website, www.goldcopd.org. 2020. Accessed December 25, 2020.
[20] Huang TH, Hsiue TR, Lin SH, et al. Comparison of different staging methods for COPD in predicting outcomes. Eur Respir J 2018;51: pii: 1700577.
[21] Chuang ML, Lin IF, Lee CY. Clinical assessment tests in evaluating patients with chronic obstructive pulmonary disease: a cross-sectional study. Medicine (Baltimore) 2016;95:e5471.
[22] Chuang ML, Lin IF. Clinical characteristics and lung function in chronic obstructive pulmonary disease complicated with impaired peripheral oxygenation. Intern Emerg Med 2014;9:633–40.
[23] Chuang ML, Huang SF, Su CH. Cardiovascular and respiratory dysfunction in chronic obstructive pulmonary disease complicated by impaired peripheral oxygenation. Int J Chron Obstruct Pulmon Dis 2015;10:329–37.
[24] Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008 The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Europ Heart J 2008;29:2388–442.
[25] Chuang ML, Lin IF. Investigating the relationships among lung function variables in chronic obstructive pulmonary disease in men. Peer J 2019;7: e7829.
[26] Chuang ML, Lin IF, Wasserman K. The body weight-walking distance product as related to lung function, anaerobic threshold and peak VO2 in COPD patients. Respir Med 2001;95:618–26.
[27] Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–38.
[28] Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511–22.
[29] ATS/ERS SATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med 2002;166:518–624.
[30] Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J 2005;26:153–61.
[31] Wasserman K, Hansen JE, Sue DY. Wasserman K, et al. Calculations, formulas, and examples. Principles of Exercise Testing and Interpretation Philadelphia: Lippincot Williams & Wilkins; 2005;556–65.
[32] Chow S-C, Shao J, Wang H. Sample size Calculations in Clinical Research. 2nd ed.Boca Raton, FL: Chapman & Hall/CRC; 2008.
[33] Royston P, Moons KG, Altman DG, et al. Prognosis and prognostic research: developing a prognostic model. BMJ 2009;338:b604.
[34] Vassaux C, Torre-Bouscoulet L, Zeineldine S, et al. Effects of hyperinflation on the oxygen pulse as a marker of cardiac performance in COPD. Eur Respir J 2008;32:1275–82.
[35] Chuang ML, Lin IF, Huang SF, et al. Patterns of oxygen pulse curve in response to incremental exercise in patients with chronic obstructive pulmonary disease: an observational study. Sci Rep 2017; 7:10929.
[36] Degani-Costa LH, Nery LE, Rodrigues MT, et al. Does oxygen pulse trajectory during incremental exercise discriminate impaired oxygen delivery from poor muscle oxygen utilisation? ERJ Open Res 2019;5: 00108-2018.
[37] Mahut B, Chevalier-Bidaud B, Plantier L, et al. Diffusing capacity for carbon monoxide is linked to ventilatory demand in patients with chronic obstructive pulmonary disease. COPD 2012;9:16–21.
[38] Liu Z, Vargas F, Stansbury D, et al. Comparison of the end-tidal arterial PCO2 gradient during exercise in normal subjects and in patients with severe COPD. Chest 1995;107:1218–24.
[39] Chuang ML. Mechanisms affecting exercise ventilatory inefficiency-airflow obstruction relationship in male patients with chronic obstructive pulmonary disease. Respir Res 2020;21:206.
[40] Dernaika TA, Beavin M, Kinasewitz GT. Iloprost improves gas exchange and exercise tolerance in patients with pulmonary hypertension and chronic obstructive pulmonary disease. Respiration 2010;79: 377–82.
[41] Cao M, Stringer WW, Corey S, et al. Transcutaneous PCO2 for exercise gas exchange efficiency in chronic obstructive pulmonary disease. COPD 2021;18:16–25.
[42] Parazzi PLF, Marson FAL, Ribeiro M, et al. Correlation between parameters of volumetric capnography and spirometry during a submaximal exercise protocol on a treadmill in patients with cystic fibrosis and healthy controls. Pulmonology 2019;25:21–31.
[43] Doorduin J, Nollet JL, Vugts MP, et al. Assessment of dead-space ventilation in patients with acute respiratory distress syndrome: a prospective observational study. Crit Care 2016;20:121.