

# Resting Dead Space Fraction as Related to Clinical Characteristics, Lung Function, and Gas Exchange in Male Patients with Chronic Obstructive Pulmonary Disease

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**Background:** Measures of forced expired volume in one second % predicted (FEV<sub>1</sub>%), residual volume to total lung capacity ratio (RV/TLC) and diffusing capacity for carbon monoxide measurements (D<sub>L</sub>CO) are the standard lung function test for evaluating patients with chronic obstructive pulmonary disease (COPD). The dead space fraction (V<sub>D</sub>/V<sub>T</sub>) has been shown to be a robust marker of gas exchange abnormality. However, the use of V<sub>D</sub>/V<sub>T</sub> has gradually become less common. As V<sub>D</sub>/V<sub>T</sub> measured at rest (V<sub>D</sub>/V<sub>T</sub>R) has been successfully used in non-COPD conditions, it was hypothesized that in COPD the V<sub>D</sub>/V<sub>T</sub>R was more sensitive than the standard lung function test in correlation with clinical characteristics and gas exchange. This study aimed to test the hypothesis and to identify the variables relevant to V<sub>D</sub>/V<sub>T</sub>R.

**Methods:** A total of 46 male subjects with COPD were enrolled. Clinical characteristics included demographic data, oxygen-cost diagram (OCD), and image studies for pulmonary hypertension. The standard lung function was obtained. To calculate V<sub>D</sub>/V<sub>T</sub>, invasive arterial blood gas and pulmonary gas exchange (PGX) were measured. The variables relevant to V<sub>D</sub>/V<sub>T</sub>R were analyzed by multiple linear regression.

**Results:** Compared to lung function, V<sub>D</sub>/V<sub>T</sub>R was more frequently and significantly related to smoking, carboxyhemoglobin level, pulmonary hypertension and P<sub>a</sub>CO<sub>2</sub> (all p < 0.05) whereas FEV<sub>1</sub>% was more related to lung function test, P<sub>a</sub>O<sub>2</sub> and OCD score. V<sub>D</sub>/V<sub>T</sub>R and FEV<sub>1</sub>% were highly related to resting gas exchange but RV/TLC and D<sub>L</sub>CO% were not. Cigarette consumption, the equivalent for CO<sub>2</sub> output, arterial oxyhemoglobin saturation, and the product of tidal volume and inspiratory duty cycle were identified as the parameters relevant to V<sub>D</sub>/V<sub>T</sub>R with a power of 0.72.

**Conclusion:** Compared to lung function test, V<sub>D</sub>/V<sub>T</sub>R is more related to clinical characteristics and is a comprehensive marker of resting gas exchange. Further studies are warranted to provide a noninvasive measurement of V<sub>D</sub>/V<sub>T</sub>R.

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**Keywords:** obstructive airway disease, residual volume and total lung capacity ratio, diffusing capacity of lung, dead space and tidal volume ratio, cigarette consumption, carboxyhemoglobin, pulmonary hypertension

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## Background

The severity of chronic obstructive pulmonary disease (COPD) is usually graded by forced expired volume in one second % predicted (FEV<sub>1</sub>%).<sup>1</sup> Despite mMRC and acute exacerbation being related to the risk assessment of COPD, the power of

correlations of FEV<sub>1</sub>% with the clinical outcomes is not robust,<sup>2–4</sup> and lung volume such as the residual volume to total lung capacity ratio (RV/TLC) and diffusing capacity measurements (D<sub>L</sub>CO) provide additional information.<sup>5–8</sup>

The dead space to tidal volume ratio at rest or at peak exercise or change during exercise ( $V_D/V_{T,R}$ ,  $-P$ , and  $-C$ ) indicating the severity of ventilation/perfusion ( $V/Q$ ) mismatch<sup>9</sup> can serve as a marker of physiological change in patients with COPD in a various clinical conditions.<sup>8,10–15</sup> However, exercise testing is labor consuming and costly and in diseases other than COPD, the  $V_D/V_T$  has been successfully used in non-exercise conditions.<sup>16–20</sup>

It was hypothesized that the  $V_D/V_{T,R}$  was more significant than the standard lung function test in correlation with clinical characteristics and gas exchange (ie, all variables relevant to oxygen and CO<sub>2</sub> tensions and their differences in arterial blood and alveoli) in patients with COPD. This study aimed to test the hypothesis by correlation analysis and to identify variables of demographics, symptom scores, images for pulmonary hypertension, lung function, and gas exchange relevant to  $V_D/V_{T,R}$  by multiple regression analysis.

## Methods

### Study Design

In this observational cross-sectional study, we measured demographic characteristics, cigarette smoking history, functional activity and pulmonary hypertension determined by image studies, and lung function in subjects with COPD at a university teaching hospital. Resting pulmonary gas exchange (PGX) and arterial blood gas (ABG) were measured simultaneously. The local Institutional Review Board of Chung Shan Medical University Hospital (CS16174) approved this study. This study was conducted in compliance with the Declaration of Helsinki.

### Subjects

Subjects aged  $\geq 40$  years with COPD were enrolled. Anthropometric measurements, cigarette consumption, and functional activity were recorded. Male adult subjects who underwent lung function testing were enrolled if their forced expired volume in one second (FEV<sub>1</sub>)/forced vital capacity (FVC) was  $< 0.7$ .<sup>1</sup> The diagnosis of COPD was made according to the Global Initiative for Chronic Lung Disease (GOLD) criteria.<sup>1</sup> As few female subjects met the

criteria of COPD in Taiwan (4%),<sup>2</sup> for simplicity they were not included in this study. Subjects with a body mass index  $\leq 18 \text{ kg}\cdot\text{m}^{-2}$  or  $\geq 32 \text{ kg}\cdot\text{m}^{-2}$ , any other chronic diseases including uncontrolled diabetes mellitus, uncontrolled hypertension, anemia (hemoglobin  $< 13 \text{ g}\cdot\text{dL}^{-1}$  in males), or with laboratory findings of cardiovascular, hematological, metabolic or neuromuscular diseases or acute illnesses in the recent 1 month were not enrolled. Uncontrolled hypertension means having hypertension but no or inadequate treatment so that the blood pressure remained high (ie,  $> 140/90 \text{ mm Hg}$ ).<sup>21</sup> Signed informed consent was obtained from each participant. Some of the participants were enrolled in other studies.<sup>22,23</sup>

## Measurements

### Demographic Data and Functional Activity

Age, height, weight, body mass index, triceps skinfold, mid-arm circumference, and cigarette consumption were recorded. The oxygen cost diagram (OCD) was used to evaluate the participants' functional activity. The OCD a 100-mm long vertical line with everyday activities listed alongside the line, above which breathlessness limited the participants. The distance from zero was measured and scored.

### Image Study

Chest radiography was obtained within one month of enrolling in the study. The hila thoracic ratio (HTR), cardiac thoracic ratio, and the diameter of anterior descending pulmonary artery (ADPA) on the standing posterior-anterior chest radiograph were measured as these variables were reported to represent pulmonary hypertension.<sup>24</sup> The chest radiographs were evaluated by an experienced pulmonologist without knowing the clinical information and the average values were recorded for analysis.

Two-dimensional echocardiography was performed by an experienced cardiologist who was unaware of the clinical data and lung function. Parasternal, apical, and subcostal studies were conducted.<sup>25,26</sup>

### Pulmonary Function Testing

Pre-test preparation was followed the standard guide and bronchodilators were not administered within 3 h for short-acting beta-agonists and 12 h for long-acting beta-agonists before the tests.<sup>27–29</sup> FEV<sub>1</sub>, FVC, TLC, RV, and D<sub>L</sub>CO were measured using spirometry, body plethysmography, and the single-breath technique (MasterScreenTM Body; Carefusion, Wuerzburg, Germany), respectively, in accordance with the currently recommended standards by

ATS/ERS task force.<sup>30,31</sup> The best of three technically satisfactory readings was used.<sup>30,32,33</sup> All of the spirometry data were obtained before and after inhaling a standard dose of fenoterol HCl. Post-dose measurements were performed 15 minutes after inhalation. Static lung volume data and  $D_LCO$  data were obtained before inhaling fenoterol.

Maximum inspiratory pressure at the mouth indicating inspiratory muscle strength and maximum expiratory pressure indicating expiratory muscle strength at the mouth were measured.<sup>34</sup>

### Pulmonary Gas Exchange and $V_D/V_T$ Measurement

Each subject completed PGX measured at a 2-min complete rest.  $VO_2$  (mL/min),  $CO_2$  output ( $VCO_2$ ) (mL/min), and minute ventilation ( $V_E$ ) were continuously measured and the data at the last 15 seconds were averaged and reported (MasterScreen CPX™, Carefusion, Wuerzburg, Germany). The physiological  $V_D/V_T$  was measured ( $V_D/V_T$ ) using a standard formula as follows:<sup>35</sup>

$$V_D/V_T = (P_aCO_2 - P_ECO_2)/P_aCO_2 - V_{Dm}/V_T \quad (1)$$

where  $P_aCO_2$  was arterial  $PCO_2$  and  $P_ECO_2 = VCO_2/V_E \times (P_B - 47\text{mmHg})$  and  $P_B$  was barometric pressure measured daily and  $V_{Dm}$  was the dead space of mouth piece and pneumotachograph as the manufacture reported.<sup>36</sup> Artery blood samples were drawn at the brachial artery and heparinized at rest. The sample was immediately placed on ice and then analyzed for pH,  $PCO_2$ , and  $PO_2$  with body temperature correction (model 278, CIBA-Corning, Medfield, MA, USA).

### Statistical Analysis

Data were summarized as mean  $\pm$  standard deviation. Pearson's or Spearman correlation coefficients were used when appropriate for quantifying the pair-wise relationships among the variables of interest. Multiple linear regression analysis was used to select important parameters of  $V_D/V_T$ . All possible regression algorithms were performed using the candidate variables with  $p$  values  $< 0.35$  in univariate analysis. The Student's  $t$ -test was used for comparisons between two groups. The chi-square test or Fisher exact test was used to compare the proportions between the two groups. All statistical analyses were performed using SAS statistical software (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at  $p < 0.05$ . Marginal significance was set at  $0.05 \leq p \leq 0.1$ .

## Results

Fifty-seven patients were enrolled, of whom 10 were excluded because two subjects did not meet the inclusion criteria and another two met the exclusion criteria and six subjects declined to participate (Figure 1). The remaining 46 male subjects with COPD were enrolled after excluding one subject whose arterial blood gas analysis was not obtained (mean age  $65.2 \pm 5.8$  years) (Tables 1–3). In Tables 1–3, some data were missing in one to six subjects because of technical failure or no measurements. Most of the patients had GOLD stages II and III, hyperinflation of lung and static air trapping, high  $V_D/V_{TR}$ , and impaired diffusing capacity, inspiratory muscle strength and peak flow, and hyperventilation with normoxemia and normocapnia.

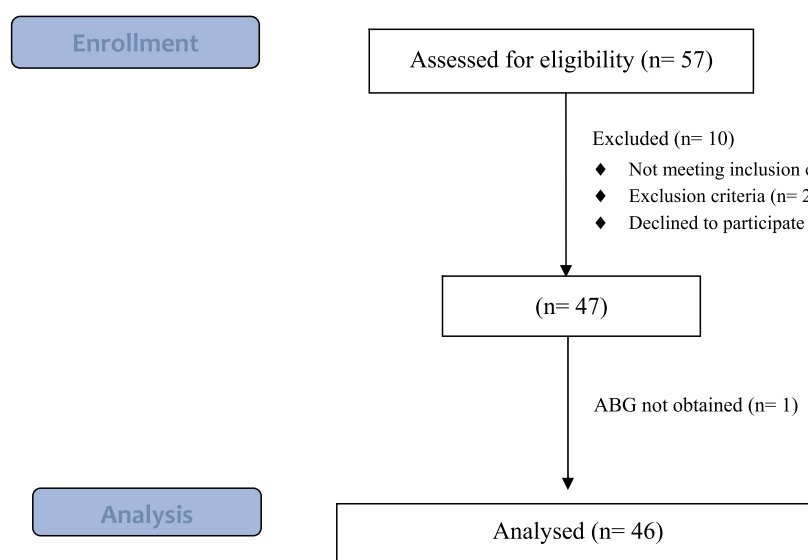
Compared to the standard lung function test,  $V_D/V_T$  R was more frequently (Table 4,  $p < 0.0001$ ) and significantly related to cigarette consumption, carboxyhemoglobin level, and pulmonary hypertension (all  $p < 0.05$ ) and these associated factors were not related to  $FEV_1\%$ , RV/TLC, and  $D_LCO\%$  (all  $p = \text{NS}$ ). In contrast,  $FEV_1\%$  and RV/TLC were more related to lung function as expected and  $D_LCO\%$  was singly and mildly related to RV/TLC.  $V_D/V_T$  R and  $FEV_1\%$  were correlated with the resting gas exchange whereas RV/TLC and  $D_LCO\%$  were not.

Multiple linear regression analysis revealed that cigarette consumption and HTR were positively related to  $V_D/V_T$  R whereas the height was negatively related to  $V_D/V_T$  R (Table 5). When PGX data were added in analysis, the HTR and height were replaced by  $VE/VCO_2$ , the product of  $V_T$  and inspiratory duty cycle ( $V_{TIDC}$ ), and  $SpO_2$  where  $VE/VCO_2$  was positively related to  $V_D/V_{TR}$  whereas  $V_{TIDC}$  and  $SpO_2$  were negatively related to  $V_D/V_T$  R. Cigarette consumption and the three PGX variables were highly related to  $V_D/V_{TR}$  with a power of 0.72.

## Discussion

In this study, compared to  $FEV_1\%$ , RV/TLC, and  $D_LCO\%$ ,  $V_D/V_{TR}$  was a unique marker for male patients with COPD (Table 4).  $V_D/V_{TR}$  was related to cigarette consumption, carboxyhemoglobin, and pulmonary hypertension, whereas the standard lung function was not. Using statistical technique for evaluation of  $V_D/V_{TR}$ , cigarette consumption,  $VE/VCO_2$ ,  $V_{TIDC}$  and  $SpO_2$  were the four contributors (Table 5,  $r^2 = 0.72$ ).

Regarding lung function,  $D_LCO\%$ , KCO, and  $V_A/TLC$  have been related to  $V_D/V_{TR}$  and  $V_D/V_{TP}$  in the literature



**Figure 1** Flow diagram. A total of 57 subjects with chronic obstructive pulmonary disease were screened. After excluding 10 subjects, the remaining 46 were retained for analysis after further excluding another one subject whose arterial blood gas data was not obtained.

( $r = -0.20$ – $-0.60$ ,  $p < 0.05$  –  $<0.01$ ) where KCO is  $D_LCO$  divided by alveolar volume ( $V_A$ ).<sup>7</sup> The  $V_A$  and  $V_A/TLC$  were related to lung volumes and airway obstruction, respectively (all  $p < 0.05$  –  $<0.01$ ),<sup>7</sup> suggesting that  $D_LCO$ , KCO, and  $V_A$  are related to poor communication of airways “that would be indicative of high ventilation-perfusion areas (~alveolar dead space)”.<sup>7</sup> Hence, it was expected that  $RV/TLC$  was related to  $V_D/V_{TR}$  and thus measuring  $V_D/V_{TR}$  is redundant. However, in this study,  $V_D/V_{TR}$  was not correlated with the lung function variables suggesting that  $V_D/V_T$  and lung hyperinflation, air trapping or diffusing capability might be different components in physiology.<sup>22</sup>  $V_D/V_{TR}$  was correlated with cigarette consumption, carboxyhemoglobin, and pulmonary hypertension measured by chest radiography (Table 4). Thus,  $V_D/V_{TR}$  may offer additional information to lung function test, whereas  $FEV_1\%$ ,  $RV/TLC$ , and  $D_LCO\%$  were more related to lung function test (Table 4).

Tobacco smoking is the key preventable risk factor for the development of COPD and the pathogenesis of emphysema. The duration of cigarette consumption associated with the development of COPD is considered to be  $\geq 20$  pack-years.<sup>1,37</sup> Emphysema with a tissue-to-airway progression pattern<sup>37</sup> was related to an increased  $V_D/V_T$ .<sup>15</sup> Although cigarette consumption is thought to contribute to an increased  $V_D/V_T$  as found in this study, their relationship may not be necessary through the mechanism of emphysema. This was noted that  $RV/TLC$  was not related to  $V_D/V_{TR}$  in this study. Further studies are warranted to elucidate the

relationship between cigarette consumption, emphysema, and  $V_D/V_T$ . Furthermore, carboxyhemoglobin level is modestly related to cigarette smoking ( $r = 0.28$ ,  $p = 0.06$ ) and was mildly correlated with  $V_D/V_{TR}$  ( $r = 0.35$ ,  $p = 0.02$ ) in the current study. It was consistent with a previous report that carboxyhemoglobin was positively correlated with  $VE/VCO_2$  and rapid breathing and inversely with  $VO_{2max}\%$  and expandable volume excursion.<sup>38</sup> Of note, carboxyhemoglobin level and  $V_D/V_{TR}$  were not in a cause–effect relationship and that carboxyhemoglobin was not correlated with  $D_LCO\%$  in the current study does not exclude that carboxyhemoglobin can affect  $D_LCO$  in normal subjects. The findings indicate that the lung pathology of COPD plays a more important role than carboxyhemoglobin in relation to  $D_LCO$ .

Regarding chest radiography, a  $HTR \geq 0.36$  and diameter of the right ADPA  $\geq 1.8$  cm have been reported to be markers of pulmonary hypertension in COPD.<sup>24</sup> COPD is usually complicated with pulmonary hypertension in the later stages. Although there was discordance between radiographic and hemodynamic measures of pulmonary arterial pressure, HTR and diameter of the right ADPA were modestly correlated with increased  $V_D/V_{TR}$  in this study (Table 4,  $r = 0.33$  and  $0.34$ , both  $p < 0.05$ ).

In normal subjects, age and height have been positively related to  $V_D/V_{TR}$  whereas weight has been negatively related to  $V_D/V_{TR}$ , and  $V_D/V_{TR}$  has been reported to be smaller in females.<sup>39</sup> However, in this study, in subjects with COPD, height was negatively related to  $V_D/V_{TR}$ . The

**Table 1** Demographic Data, Symptom Score, Blood Tests, Chest Radiography, and Echocardiography (n = 46)

	n	Mean	SD
Age, year	46	65.2	5.8
Height, cm	46	165.0	6.4
Weight, kg	46	60.4	11.2
Body mass index, kg/m <sup>2</sup>	46	22.12	3.53
Smoke, py	46	42.3	19.2
OCD, cm	46	7.0	1.4
Triceps, mm	44	6.4	2.6
Mid-arm, cm	44	27.3	3.4
Borg, A.U.	46	0.05	0.19
Hemoglobin, g/dL	46	14.8	1.5
Albumin, g/dL	40	4.2	0.4
GPT, IU/L	40	21.1	16.8
Bilirubin, direct, mg/dL	42	0.25	0.29
Creatinine, mg/dL	42	1.09	0.20
Na <sup>+</sup> , mmol/L	41	140.5	2.4
K <sup>+</sup> , mmol/L	40	4.3	0.5
Sugar, mg/dL	41	98.8	14.7
Cholesterol, mg/dL	43	182.2	36.6
Hila-thoracic ratio	44	0.36	0.04
Cardiac-thoracic ratio	41	0.44	0.06
ADPA, cm	46	1.62	0.33
Apical 4 EDRV, cm <sup>2</sup>	42	13.5	3.7
Apical 4 ESRV, cm <sup>2</sup>	42	7.8	1.8
Subcostal 4 EDRV, cm <sup>2</sup>	42	14.2	3.3
Subcostal 4 ESRV, cm <sup>2</sup>	42	7.6	2.1
Right ventricle wall, mm	42	6.0	2.0

**Abbreviations:** A.U., absolute unit; ADPA: anterior descending pulmonary artery of the right lung; apical four chamber view; end-diastolic right ventricle area (EDRV), end-systolic right-ventricle area (ESRV); subcostal four-chamber view; long and short axes view: the right ventricle free wall thickness at an end-diastolic phase between the tricuspid annulus and the papillary muscle.

reason for this discrepancy is not clear, but it is probably due to the high correlation between height and weight in this study in an analysis a posteriori ( $r = 0.51$ ,  $p = 0.0003$ ). A higher weight is probably beneficial against the development of emphysema and stage 4 disease of COPD<sup>40</sup> and thus negatively related to  $V_D/V_T$  (Table 4,  $r = -0.27$ ,  $p = 0.08$ ), while sarcopenia or low lean body mass may predispose to the development of emphysema (multi-organ loss of tissue, MOLT phenotype).<sup>41</sup> Another possible reason is that the lung pathology of COPD outweighs the contribution of height to  $V_D/V_T$  as normal subjects do.

$VE/VCO_2$  has been reported to be strongly related to  $V_D/V_T$  when the data involve healthy subjects and those with COPD at rest and during submaximal exercise.<sup>7</sup> This is attributed to the Bohr-Enghoff equation in which  $VE/VCO_2$  and  $V_D/V_T$  are mathematically related at a given level of  $P_aCO_2$ . A high  $VE/VCO_2$  and high  $P_{a-ET}$

**Table 2** Lung Function

Variables	n	Mean	SD
Total lung capacity, TLC, L	46	6.5	1.0
TLCpred, %	46	135	21
Functional residual capacity, FRC, L	46	4.8	1.0
FRCpred, %	46	162	34
Inspiratory capacity, L	46	1.7	0.5
Residual volume, RV, L	46	3.8	0.9
RV/TLC, %	46	58	9
$D_LCO$ , mL/min/mmHg	45	15.8	5.6
$D_LCO$ pred, %	45	69	22
Forced vital capacity, FVC, L	46	2.5	0.7
FVCpred, %	46	81	21
FEV <sub>1</sub> , L	46	1.2	0.5
FEV <sub>1</sub> pred, %	46	50	19
GOLD, I, II, III, IV, n (%)			
3 (6.5), 18 (39.1), 19 (41.3), 6 (13.0)			
FEV <sub>1</sub> /FVC, %	46	49	13
Slow vital capacity, SVC, L	46	2.7	0.7
SVCpred, %	46	89	22
MIP, cmH <sub>2</sub> O	43	68.4	18.6
MEP, cmH <sub>2</sub> O	43	103.7	22.6
PEFR, L/sec	46	2.9	1.3
PEFRpred, %	46	42	20

**Abbreviations:**  $D_LCO$ , the diffusion capacity of the lungs for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in one second; GOLD I-IV, global initiative for chronic obstructive lung disease stages; MIP, maximal inspiratory pressure; MEP, maximum expiratory pressure; PEFR, peak expiratory flow rate.

$CO_2$  explain 40–50% of high  $V_D/V_T$  in this study (Table 4,  $r = 0.64$  and  $0.67$ , both  $p < 0.0001$ ) compatible with that Lewis et al and Liu et al reported that  $V_D/V_T$  and  $P_{a-ET}CO_2$  were highly correlated ( $r = 0.76$ – $0.88$ ,  $p < 0.001$ ).<sup>42,43</sup> Compared to FEV<sub>1</sub>% in this study,  $V_D/V_T$  was more related to  $P_aCO_2$  at rest ( $r^2 = 0.24$  versus  $0.10$ ) whereas FEV<sub>1</sub>% was more related to  $P_aO_2$  and OCD.

Despite A-aDO<sub>2</sub> and  $S_pO_2$  being marginally correlated with  $V_D/V_T$  (Table 4,  $r = -0.28$  to  $-0.29$ , both  $p = 0.06$ ),  $S_pO_2$  was selected in multiple regression analysis. However, in COPD even in subjects with mild severity A-aDO<sub>2</sub> was positively related to  $V_D/V_T$ .<sup>10</sup> The discrepancy between these two studies in the  $V_D/V_T$  versus A-aDO<sub>2</sub> relationship might be due to poor correlation of  $V_D/V_T$  with  $P_aO_2$  where A-aDO<sub>2</sub> was highly negatively related to  $P_aO_2$  in this study ( $r = -0.66$ ,  $p < 0.0001$ ).

$V_T$  IDC probably represents expandable tidal volume excursion in a timely manner. When both  $V_T$  and IDC are large, the mean inspiratory flow ( $V_T$ /inspiratory time) can be favorably generated by the force of the inspiratory muscles. On the other hand, when  $V_T$  is large and IDC is small, the mean inspiratory flow is extremely high and



**Table 3** Cardiopulmonary Physiological Data, Arterial Blood Gases, Carboxyhemoglobin and Plasma Lactate Concentrations at Rest

Variables	n	Mean	SD
VO <sub>2</sub> /predicted maximum, %	46	16	3
VO <sub>2</sub> /kg, L/min/kg	46	4.1	0.8
VCO <sub>2</sub> , L/min	46	0.20	0.04
Respiratory exchange ratio	46	0.83	0.05
O <sub>2</sub> Pulse, mL/beat	46	3.1	0.7
VE/VCO <sub>2</sub>	46	53.5	10.0
VE/VO <sub>2</sub>	46	44.5	7.4
V <sub>D</sub> /V <sub>T</sub>	45	0.58	0.08
P <sub>a-ET</sub> CO <sub>2</sub> , mmHg	45	4.0	4.4
A-aDO <sub>2</sub> , mmHg	45	18.9	1.0
S <sub>P</sub> O <sub>2</sub> , %	45	95.3	2.6
VE, L/min	46	10.7	2.1
MVV, L/min	46	36.3	16.9
VE/MVV	46	0.35	0.16
Systolic blood pressure, mmHg	46	145.0	18.6
Diastolic blood pressure, mmHg	45	79.3	9.0
Heart rate, beat/min	46	80.6	13.2
pH	45	7.4	0.03
P <sub>a</sub> CO <sub>2</sub> , mmHg	45	40.6	6.4
P <sub>a</sub> O <sub>2</sub> , mmHg	45	79.2	10.1
HCO <sub>3</sub> <sup>-</sup> , mEq/L	45	24.7	1.9
Carboxyhemoglobin, %	45	1.3	0.9
Methemoglobin, %	43	0.25	0.08
Lactate, mmol/L	43	1.2	0.3

**Abbreviations:** VO<sub>2</sub>, oxygen uptake; VCO<sub>2</sub>, CO<sub>2</sub> output; Respiratory exchange ratio, CO<sub>2</sub> output and oxygen uptake ratio; O<sub>2</sub> Pulse, oxygen uptake divided by heart rate; V<sub>D</sub>/V<sub>T</sub>, dead space and tidal volume ratio; P<sub>a-ET</sub>CO<sub>2</sub>, arterial end-tidal CO<sub>2</sub> pressure gradient; A-aDO<sub>2</sub>, alveolar arterial oxygen pressure gradient; VE, minute ventilation; MVV, maximal voluntary ventilation; S<sub>P</sub>O<sub>2</sub>, hemoglobin saturation measured by pulse oximetry.

would be not biologically plausible. V<sub>T</sub>IDC is a variable firstly reported in the literature and its importance needs to be confirmed.

## Study Limitations

The number of cases in this study was small; however, it may be inevitable for an invasive study. The small number of cases may have caused insufficient power when performing correlation coefficient analysis on V<sub>D</sub>/V<sub>T</sub> R. However, the sample size of 46 achieved a power of 80% to detect a difference between a correlation of 0.4 and the null (no correlation) using a two-sided test with a significance level of 0.05.<sup>23</sup> As the power is related to type II error, nonsignificant test results should be interpreted more conservatively. All of the participants in this study were male, so using the results applied to females should be cautious. To investigate the relationship

**Table 4** Comparison of Correlation Coefficient (r) Between Resting Dead Space Fraction (V<sub>D</sub>/V<sub>T</sub>R) and Lung Function with Variables of Interest

	n	V <sub>D</sub> /V <sub>T</sub> R	FEV <sub>1</sub> %	RV/ TLC	D <sub>L</sub> CO %
		r	r	r	r
<b>Clinical parameters</b>					
Age	45	<b>0.30*</b>	0.04	0.04	0.02
Height	45	<b>-0.40**</b>	-0.04	-0.01	-0.17
Weight	45	-0.27 <sup>†</sup>	0.16	-0.15	<b>0.37**</b>
Body mass index	45	-0.12	-0.16	-0.16	<b>0.52<sup>†</sup></b>
Smoke, p-y	45	<b>0.32*</b>	-0.11	0.21	-0.01
OCD	45	0.08	<b>0.34*</b>	-0.14	0.03
Hemoglobin	45	<b>0.29*</b>	-0.16	-0.18	<b>0.31*</b>
Carboxyhemoglobin	45	<b>0.42**</b>	0.01	0.08	-0.16
Hila-thoracic ratio	44	<b>0.33*</b>	0.25 <sup>†</sup>	-0.22	0.00
ADPA diameter	45	<b>0.34*</b>	-0.06	-0.11	0.13
Number of significant correlation, n		10 <sup>#</sup>	2	1	3
<b>Lung function parameters</b>					
FRC%	45	0.02	-0.23	<b>0.48<sup>†</sup></b>	-0.24
RV/TLC	45	-0.04	<b>-0.66<sup>‡</sup></b>	1	<b>-0.31*</b>
D <sub>L</sub> CO%	45	0.05	0.25 <sup>†</sup>	<b>-0.31*</b>	1
Slow vital capacity%	45	0.10	<b>0.69<sup>‡</sup></b>	<b>-0.72<sup>‡</sup></b>	0.12
Forced vital capacity%	45	0.02	<b>0.75<sup>‡</sup></b>	<b>-0.64<sup>‡</sup></b>	0.05
FEV <sub>1</sub> %	45	-0.01	1	<b>-0.66<sup>‡</sup></b>	0.25 <sup>†</sup>
MIP	43	-0.19	0.13	-0.14	0.19
Post MIP	43	-0.28 <sup>†</sup>	-0.07	-0.02	0.30 <sup>†</sup>
Number of significant correlation, n		1 <sup>†</sup>	4	5	3
<b>Gas exchange parameters</b>					
P <sub>a-ET</sub> CO <sub>2</sub>	45	<b>0.67<sup>‡</sup></b>	-0.02	0.06	0.08
V <sub>E</sub> /V <sub>CO</sub> <sub>2</sub>	45	<b>0.64<sup>‡</sup></b>	<b>0.34*</b>	-0.19	-0.05
P <sub>a</sub> CO <sub>2</sub>	45	<b>0.49<sup>†</sup></b>	<b>-0.32*</b>	0.10	0.18
P <sub>a</sub> O <sub>2</sub>	45	-0.18	<b>0.44**</b>	-0.06	-0.08
AaDO <sub>2</sub>	45	-0.28 <sup>†</sup>	-0.25 <sup>†</sup>	0.02	-0.06
S <sub>P</sub> O <sub>2</sub>	45	-0.29 <sup>†</sup>	0.12	0.08	-0.17
Number of significant correlation, n		5	4	0	0

**Notes:** P<sub>a-ET</sub>CO<sub>2</sub>, V<sub>E</sub>/V<sub>CO</sub><sub>2</sub>, AaDO<sub>2</sub>, S<sub>P</sub>O<sub>2</sub>. Fisher exact test was used for comparison of V<sub>D</sub>/V<sub>T</sub>R versus 3 lung function tests, # and <sup>†</sup> indicating p = 0.0001 and 0.1, respectively; <sup>†</sup>Indicating modest correlation with 0.05 < p < 0.1, whereas \*, \*\*, <sup>‡</sup>Indicating significant correlation with p < 0.05, < 0.01, < 0.001, and < 0.0001, respectively; bolded numerals highlighting a significant correlation.

**Abbreviations:** FEV<sub>1</sub>, forced expired volume in one second %predicted; RV/TLC, residual volume to total lung capacity ratio; D<sub>L</sub>CO%, diffusing capacity for carbon monoxide % predicted; p-y, packyear; OCD, oxygen cost diagram; ADPA, anterior descending pulmonary artery; FRC, functional residual capacity; SVC, slow vital capacity; MIP, maximal inspiratory capacity.

between two or more variables, it is usually to adjust known factors that influence the dependent variables. We used % predicted of lung function variables instead of using the absolute measured values because lung function variables are obviously influenced by anthropometrics. In this context, the unwanted influences by anthropometrics were avoided and highlight the important

**Table 5** Risk Factors of Dead Space Fraction at Rest ( $V_D/V_{T-R}$ )

Variable	Equation	$r^2$	p
$V_D/V_{T-R_{stat}}$	$1.046 (\pm 0.279) - 0.0042 \times \text{height} (\pm 0.0015) + 0.0014 \times \text{smoke} (\pm 0.0006) + 0.491 \times \text{HTR} (\pm 0.276)$	0.33	0.001
	$0.942 (\pm 0.251) + 0.0012 \times \text{smoke} (\pm 0.0004) + 0.0048 \times \text{VE}/\text{VCO}_2 (\pm 0.0007) - 0.472 \times V_{T-IDC} (\pm 0.118) - 0.006 \times S_pO_2 (\pm 0.0027)$	0.72	< 0.0001

**Notes:**  $V_D/V_{T-R_{stat}}$  is the  $V_D/V_{T-R}$  obtained using multiple linear regression, smoke refers to cigarette consumption in pack-years, HTR is the hila-thoracic ratio in decimals measured from chest radiography, with the height in centimeters, and the numbers in parenthesis are standard errors.  $\text{VE}/\text{VCO}_2$  is the ventilatory equivalent for  $\text{CO}_2$  output,  $V_{T-IDC}$  is the product of tidal volume in liters, inspiratory duty cycle (IDC) in decimals, and  $S_pO_2$  is the oxyhemoglobin saturation measured with pulse oximetry. IDC is the ratio of inspiratory time of an entire respiratory cycle.

factors. This issue has been strongly recommended in a previous report that TLC, FRC, IC, IRV, ERV, RV, FVC, SVC, and FEV1 in liters and DLCO in mL/min/mmHg were omitted from correlation analysis.<sup>27</sup> As transcutaneous  $\text{PCO}_2$  ( $P_{tc}\text{CO}_2$ ) is a noninvasive measurement, it warrants further study to compare the study with that using  $P_{tc}\text{CO}_2$ .<sup>7,44</sup> Although using radioisotopes or applying the multiple inert gas elimination technique (MIGET) is the standard of measuring V/Q mismatch, these techniques are costly and the latter is not common in clinical practice whereas  $V_D/V_{T-R}$  measurement is practical and high  $V_D/V_{T-R}$  is consistent with high V/Q mismatch.<sup>9</sup>

## Clinical Implication

Compared to lung function test,  $V_D/V_{T-R}$  was more related to cigarette consumption and pulmonary hypertension and was a comprehensive variable of resting PGX. Whether or not it can serve as a prognosticator or can be applied in smoking cessation strategy warrants further studies.

## Conclusion

Compared to  $\text{FEV}_1\%$ ,  $\text{RV}/\text{TLC}$ , and  $\text{D}_L\text{CO}\%$ ,  $V_D/V_{T-R}$  is more related to smoking, carboxyhemoglobin, pulmonary hypertension, and  $\text{PaCO}_2$  whereas  $\text{FEV}_1\%$  is more related to  $\text{PaO}_2$  and oxygen-cost diagram score and thus should be considered when evaluating patients with COPD. Further studies are warranted to provide a noninvasive measurement of  $V_D/V_{T-R}$ .

## Author Contributions

MLC: initiated and designed the study, analyzed and interpreted the data, wrote and revised the manuscript, and approved the version to be published in *Inter J Gen Med.* and take responsibility and is accountable for the contents of the article. BYTH: analyzed and interpreted the data, critically reviewed the manuscript and approved the version to be published in *Inter J Gen Med.* and take

responsibility and is accountable for the contents of the article. IFL: analyzed and interpreted the data and revised and critically reviewed the manuscript and approved the version to be published in *Inter J Gen Med.* and take responsibility and is accountable for the contents of the article.

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The authors declare that there are no competing interests.

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