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ORIGINAL RESEARCH

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_1%), residual volume to total lung capacity ratio (RV/TLC) and diffusing capacity for carbon monoxide measurements (D_LCO) are the standard lung function test for evaluating patients with chronic obstructive pulmonary disease (COPD). The dead space fraction (V_D/V_T) has been shown to be a robust marker of gas exchange abnormality. However, the use of V_D/V_T has gradually become less common. As V_D/V_T measured at rest (V_D/V_TR) has been successfully used in non-COPD conditions, it was hypothesized that in COPD the V_D/V_TR 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_D/V_TR.

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_D/V_T, invasive arterial blood gas and pulmonary gas exchange (PGX) were measured. The variables relevant to V_D/V_TR were analyzed by multiple linear regression.

Results: Compared to lung function, V_D/V_TR was more frequently and significantly related to smoking, carboxyhemoglobin level, pulmonary hypertension and P_aCO_2 (all $p < 0.05$) whereas FEV_1% was more related to lung function test, P_aO_2 and OCD score. V_D/V_TR and FEV_1% were highly related to resting gas exchange but RV/TLC and D_LCO% were not. Cigarette consumption, the equivalent for CO_2 output, arterial oxyhemoglobin saturation, and the product of tidal volume and inspiratory duty cycle were identified as the parameters relevant to V_D/V_TR with a power of 0.72.

Conclusion: Compared to lung function test, V_D/V_TR 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_D/V_TR.

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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_1%).[1] Despite mMRC and acute exacerbation being related to the risk assessment of COPD, the power of

correlations of FEV_1% with the clinical outcomes is not robust,[2–4] and lung volume such as the residual volume to total lung capacity ratio (RV/TLC) and diffusing capacity measurements (D_LCO) provide additional information.[5–8]

The dead space to tidal volume ratio at rest or at peak exercise or change during exercise (V_D/V_TR, -P, and -C) indicating the severity of ventilation/perfusion (V/Q) mismatch[9] can serve as a marker of physiological change in patients with COPD in a various clinical conditions.[8,10–15] 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.[16–20]

It was hypothesized that the V_D/V_TR 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_2 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_TR 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 ≥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_1)/forced vital capacity (FVC) was <0.7.[1] The diagnosis of COPD was made according to the Global Initiative for Chronic Lung Disease (GOLD) criteria.[1] As few female subjects met the criteria of COPD in Taiwan (4%),[2] for simplicity they were not included in this study. Subjects with a body mass index ≤18 $kg \cdot m^{-2}$ or ≥32 $kg \cdot m^{-2}$, any other chronic diseases including uncontrolled diabetes mellitus, uncontrolled hypertension, anemia (hemoglobin <13 $g \cdot dL^{-1}$ 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 mm Hg).[21] Signed informed consent was obtained from each participant. Some of the participants were enrolled in other studies.[22,23]

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.[24] 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.[25,26]

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.[27–29] FEV_1, FVC, TLC, RV, and D_LCO 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.[30,31] The best of three technically satisfactory readings was used.[30,32,33] 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.[34]

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:[35]

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

where P_aCO_2 was arterial PCO_2 and $P_{\bar{E}}CO_2 = VCO_2/V_E \times (P_B - 47mmHg)$ and PB was barometric pressure measured daily and V_Dm was the dead space of mouth piece and pneumotachograph as the manufacture reported.[36] 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 ± 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_TR. 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 ± 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 = 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 S_PO_2 where VE/VCO_2 was positively related to V_D/V_TR whereas V_T IDC and S_PO_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 S_PO_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

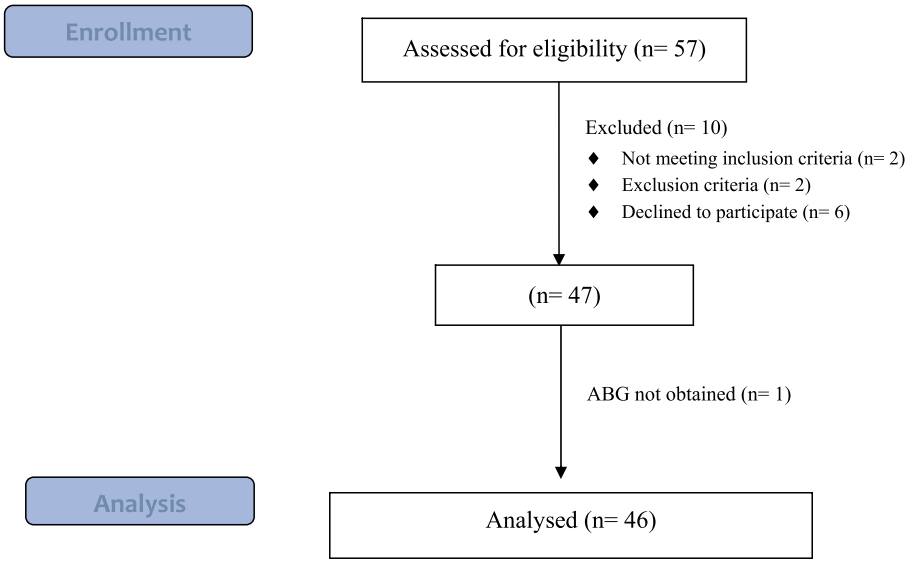

Figure 1 Flow diagram. A total of 57 subjects with chronic obstructive pulmonary disease were screened. After excluding 10 subjects, the remaining 46 were retained for analysis after further excluding another one subject whose arterial blood gas data was not obtained.

(r = –0.20–-0.60, p < 0.05 - <0.01) where KCO is D_LCO divided by alveolar volume (V_A).[7] The V_A and V_A/TLC were related to lung volumes and airway obstruction, respectively (all p < 0.05 - <0.01),[7] 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)".[7] 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.[22] 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 ≥20 pack-years.[1,37] Emphysema with a tissue-to-airway progression pattern[37] was related to an increased V_D/V_T.[15] 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_T R 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.[38] 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 ≥0.36 and diameter of the right ADPA ≥1.8 cm have been reported to be markers of pulmonary hypertension in COPD.[24] 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.[39] 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^2	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^+, mmol/L	41	140.5	2.4
K^+, 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^2	42	13.5	3.7
Apical 4 ESRV, cm^2	42	7.8	1.8
Subcostal 4 EDRV, cm^2	42	14.2	3.3
Subcostal 4 ESRV, cm^2	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.

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_1, L	46	1.2	0.5
FEV_1pred, %	46	50	19
GOLD, I, II, II, IV, n (%)	3 (6.5), 18 (39.1), 19 (41.3), 6 (13.0)		
FEV_1/FVC, %	46	49	13
Slow vital capacity, SVC, L	46	2.7	0.7
SVCpred, %	46	89	22
MIP, cmH_2O	43	68.4	18.6
MEP, cmH_2O	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_1, 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.

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[40] 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).[41] Another possible reason is that the lung pathology of COPD outweighs the contribution of height to V_D/V_TR 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.[7] 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 $P_{a–ET}CO_2$ explain 40–50% of high V_D/V_TR 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 $P_{a\text{-}ET}CO_2$ were highly correlated (r = 0.76–0.88, p < 0.001).[42,43] Compared to FEV_1% in this study, V_D/V_TR was more related to P_aCO_2 at rest (r^2 = 0.24 versus 0.10) whereas FEV_1% was more related to P_aO_2 and OCD.

Despite A-aDO_2 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_2 was positively related to V_D/V_T.[10] The discrepancy between these two studies in the V_D/V_TR versus A-aDO_2 relationship might be due to poor correlation of V_D/V_T R with P_aO_2 where A-aDO_2 was highly negatively related to P_aO_2 in this study (r = −0.66, p < 0.0001).

V_TIDC 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_2%predicted maximum, %	46	16	3
VO_2/kg, L/min/kg	46	4.1	0.8
VCO_2, L/min	46	0.20	0.04
Respiratory exchange ratio	46	0.83	0.05
O_2 Pulse, mL/beat	46	3.1	0.7
VE/VCO_2	46	53.5	10.0
VE/VO_2	46	44.5	7.4
V_D/V_T	45	0.58	0.08
$P_{a\text{-}ET}CO_2$, mmHg	45	4.0	4.4
A-aDO_2, mmHg	45	18.9	1.0
S_PO_2, %	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_aCO_2, mmHg	45	40.6	6.4
P_aO_2, mmHg	45	79.2	10.1
HCO_3^-, 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_2, oxygen uptake; VCO_2, CO_2 output; Respiratory exchange ratio, CO_2 output and oxygen uptake ratio; O_2 Pulse, oxygen uptake divided by heart rate; V_D/V_T, dead space and tidal volume ratio; $P_{a\text{-}ET}CO_2$, arterial end-tidal CO_2 pressure gradient; A-aDO_2, alveolar arterial oxygen pressure gradient; VE, minute ventilation; MVV, maximal voluntary ventilation; S_PO2, hemoglobin saturation measured by pulse oximetry.

would be not biologically plausible. V_TIDC 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_D/V_T 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.[23] 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 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 4 Comparison of Correlation Coefficient (r) Between Resting Dead Space Fraction (V_D/V_TR) and Lung Function with Variables of Interest

	n	V_D/V_T R	FEV_1%	RV/ TLC	D_LCO %
		r	r	r	r
Clinical parameters					
Age	45	**0.30***	0.04	0.04	0.02
Height	45	**-0.40****	-0.04	-0.01	-0.17
Weight	45	-0.27¶	0.16	-0.15	**0.37****
Body mass index	45	-0.12	-0.16	-0.16	**0.52**†**
Smoke, p-y	45	**0.32***	-0.11	0.21	-0.01
OCD	45	0.08	**0.34***	-0.14	0.03
Hemoglobin	45	**0.29***	-0.16	-0.18	**0.31***
Carboxyhemoglobin	45	**0.42****	0.01	0.08	-0.16
Hila-thoracic ratio	44	**0.33***	0.25¶	-0.22	0.00
ADPA diameter	45	**0.34***	-0.06	-0.11	0.13
Number of significant correlation, n		10#	2	1	3
Lung function parameters					
FRC%	45	0.02	-0.23	**0.48**†	-0.24
RV/TLC	45	-0.04	**-0.66**‡**	1	**-0.31***
D_LCO%	45	0.05	0.25¶	**-0.31***	1
Slow vital capacity%	45	0.10	**0.69**‡**	**-0.72**‡**	0.12
Forced vital capacity%	45	0.02	**0.75**‡**	**-0.64**‡**	0.05
FEV_1%	45	-0.01	1	**-0.66**‡**	0.25¶
MIP	43	-0.19	0.13	-0.14	0.19
Post MIP	43	-0.28¶	-0.07	-0.02	0.30¶
Number of significant correlation, n		1I	4	5	3
Gas exchange parameters					
$P_{aET}CO_2$	45	**0.67**‡**	-0.02	0.06	0.08
$V'_E/V'CO_2$	45	**0.64**‡**	**0.34***	-0.19	-0.05
P_aCO_2	45	**0.49**†**	**-0.32***	0.10	0.18
P_aO_2	45	-0.18	**0.44****	-0.06	-0.08
$AaDO_2$	45	-0.28¶	-0.25¶	0.02	-0.06
S_PO_2	45	-0.29¶	0.12	0.08	-0.17
Number of significant correlation, n		5	4	0	0

Notes: $P_{aET}CO_2$ $V'_E/V'CO_2$ $AaDO_2$ S_aO_2. Fisher exact test was used for comparison of V_D/V_TR versus 3 lung function tests, # and I indicating p = 0.0001 and 0.1, respectively; ¶Indicating modest correlation with 0.05< p 0.1, whereas *, **, †, ‡Indicating significant correlation with p <0.05, <0.01, <0.001, and <0.0001, respectively; bolded numerals highlighting a significant correlation.

Abbreviations: FEV_1, forced expired volume in one second %predicted; RV/TLC, residual volume to total lung capacity ratio; D_LCO%, 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.

Table 5 Risk Factors of Dead Space Fraction at Rest (V_D/V_TR)

Variable	Equation	r^2	p
V_D/V_TR_{stat}	1.046 (± 0.279) – 0.0042 X height (± 0.0015) + 0.0014 X smoke (± 0.0006) + 0.491 X HTR (± 0.276)	0.33	0.001
	0.942 (± 0.251) + 0.0012 X smoke (± 0.0004) + 0.0048 XVE/VCO_2 (± 0.0007) – 0.472 X V_TIDC (± 0.118) – 0.006 X S_PO_2 (± 0.0027)	0.72	< 0.0001

Notes: V_D/V_TR_{stat} is the V_D/V_TR 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.VE/VCO_2 is the ventilatory equivalent for CO_2 output, V_TIDC 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.[27] As transcutaneous PCO_2 ($P_{tc}CO_2$) is a noninvasive measurement, it warrants further study to compare the study with that using $P_{tc}CO_2$.[7,44] 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 measurement is practical and high V_D/V_T is consistent with high V/Q mismatch.[9]

Clinical Implication

Compared to lung function test, V_D/V_TR 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 FEV_1%, RV/TLC, and D_LCO%, V_D/V_TR is more related to smoking, carboxyhemoglobin, pulmonary hypertension, and P_aCO_2 whereas FEV_1% is more related to P_aO_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_TR.

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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Disclosure

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