Combining Dynamic Hyperinflation with Dead Space Volume during Maximal Exercise in Patients with Chronic Obstructive Pulmonary Disease

Ming-Lung Chuang

1 Division of Pulmonary Medicine and Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung 40201, Taiwan; yuan1007@ms36.hinet.net; Tel.: +886-4-2473-9595 (ext. 34718)

2 School of Medicine, Chung Shan Medical University, Taichung 40201, Taiwan

Received: 17 March 2020; Accepted: 13 April 2020; Published: 15 April 2020

Abstract: Physiological dead space volume (V_D) and dynamic hyperinflation (DH) are two different types of abnormal pulmonary physiology. Although they both involve lung volume, their combination has never been advocated, and thus their effect and implication are unclear. This study aimed (1) to combine V_D and DH, and (2) investigate their relationship and clinical significance during exercise, as well as (3) identify a noninvasive variable to represent the V_D fraction of tidal volume (V_D/V_T).

Forty-six male subjects with chronic obstructive pulmonary disease (COPD) and 34 healthy male subjects matched for age and height were enrolled. Demographic data, lung function, and maximal exercise were investigated. End-expiratory lung volume (EELV) was measured for the control group and estimated for the study group using the formulae reported in our previous study. The V_D/V_T ratio was measured for the study group, and reference values of V_D/V_T were used for the control group. In the COPD group, the DH_peak/total lung capacity (TLC, DH_peak%) was 7% and the EELV_peak% was 70%. After adding the V_D_peak% (8%), the V_D/DH_peak% was 15% and the V_D/EELV_peak% was 78%. Both were higher than those of the healthy controls. In the COPD group, the V_D/DH_peak% and V_D/EELV_peak% were more correlated with dyspnea score and exercise capacity than that of the DH_peak% and EELV%, and had a similar strength of correlation with minute ventilation. The V_Tpeak/TLC (V_Tpeak%), an inverse marker of DH, was inversely correlated with V_D/V_T (R^2 ≈ 0.50). Therefore, we recommend that V_D should be added to DH and EELV, as they are physiologically meaningful and V_Tpeak% represents not only DH but also dead space ventilation. To obtain V_D, the V_D/V_T must be measured. Because obtaining V_D/V_T requires invasive arterial blood gases, further studies on noninvasive predicting V_D/V_T is warranted.

Keywords: incremental exercise test; plethysmography; diffusing capacity; air trapping; tidal volume and total lung capacity ratio; end-expiratory lung volume

1. Introduction

In the alveolar dead space (V_D) of the three component (Riley) model [1], if alveolar V_D exists, residual volume is expected to increase, potentially causing air trapping and hyperinflation of the lung. However, the physiological V_D refers to ventilation not involved in gas exchange and involved in unperfused or underperfused alveoli [2] and includes anatomical and alveolar V_Ds [1]. Acute dynamic hyperinflation (DH) refers to a temporary increase in operating lung volume above the resting value, i.e., end-expiratory lung volume at peak exercise (EELV_peak) [3–6] minus resting EELV (EELV_rest) [7]. Because the definitions of alveolar V_D and DH are different, physiological V_D would not cause DH, and thus their relationship is unclear.

The physiological V_D/tidal volume ratio (V_D/V_T) can be calculated using the Bohr-Enghoff equation [2]. Therefore, V_D can be considered to be a part of V_T, and anatomical V_D can be assumed.
to occur at the beginning of $V_T$. Accordingly, as EELV is immediately followed by tidal breathing, beginning $V_D$ not included in EELV should be added.

In patients with chronic obstructive pulmonary disease (COPD), the $V_D/V_T$ is often highly increased at rest and usually mildly decreased during exercise as compared with normal subjects. This phenomenon has been hypothesized to be due to a small increase in $V_D$ and a small expansion in $V_T$, as $V_T$ is constrained by DH. $V_T$ “floats” above DH and is concomitantly limited by the ceiling of total lung capacity (TLC) and causes reductions in inspiratory reserve volume and O’Donnell threshold [8]. This is in contrast to healthy subjects, in whom a small change in $V_D$ and a large increase in $V_T$ are usually noted.

Although the definition and mechanism of $V_D$ and DH are quite different, both are volumes; DH, i.e., EELV$_{peak}$ minus EELV$_{rest}$ has been reported to be correlated with the $V_D/V_T$ ratio [3,9,10] (see the Appendix A Table A1), and EELV$_{peak}$ has been shown to be inversely related to $V_{Tpeak}/TLC$ ($V_{Tpeak}\%$) [11]. Hence, the aims of this study were as follows: (1) to combine $V_D$ with DH; (2) to investigate the relationship between DH and $V_D$; (3) to investigate the relationship between $V_D$ and dyspnea, exercise capacity, and ventilation capability; and (4) to investigate the relationship between $V_D/V_{Tpeak}$ and $V_{Tpeak}\%$ during maximal exercise in order to find a surrogate for $V_D/V_{Tpeak}$, which is an invasive variable. This study could help clinicians better understand the relative positions of EELV, DH, $V_D$, and $V_T$ in TLC, and show that $V_D$ and DH together are unfavorable lung volumes during exercise [9,10]. Using the easily calculated $V_{Tpeak}\%$ during exercise, testing could possibly reflect the invasively measured $V_D/V_{Tpeak}$, and thus clinicians could use the $V_{Tpeak}\%$ as an indicator of DH and also $V_D/V_{Tpeak}$. To the best of our knowledge, this is the first study to integrate the concept of dead space ventilation and DH during exercise.

2. Methods

2.1. Study Design

In this observational cross-sectional study, we analyzed lung function data and cardiopulmonary exercise with inspiratory capacity maneuver data from subjects with COPD and healthy controls at the Chung Shan Medical University hospital. The relationships between $V_{Tpeak}\%$ and $V_D/V_T$ were investigated in the subjects with COPD. $V_D$, $V_T$, and EELV as $\%$ of TLC were illustrated using percentages. Signed informed consent was obtained from each participant. The local Institutional Review Board of the institution (CS16174) approved this study, which was conducted in compliance with the Declaration of Helsinki.

2.2. Subjects

Subjects aged $\geq$40 years without any chronic diseases including uncontrolled diabetes mellitus, uncontrolled hypertension, anemia (hemoglobin $<$13 g/dL), and no acute illnesses in the recent period of 1 month were enrolled. Anthropometric measurements, leisure/sports activities, and cigarette smoking were recorded. Subjects with a body mass index $\leq$18 kg/m$^2$ or $\geq$32 kg/m$^2$ or with laboratory findings of cardiovascular, hematological, metabolic, or neuromuscular diseases were excluded. All of the participants performed lung function and cardiopulmonary exercise tests (CPET). Subjects who did not have sufficient motivation to perform CPET were also excluded.

2.2.1. Study Group

Male adult subjects who underwent spirometry, plethysmography, and diffusing capacity were enrolled if their forced expired volume in one second (FEV$_1$)/forced expired capacity (FVC) was $<$0.7 [12]. The diagnosis of COPD was made according to the global initiative for chronic obstructive lung disease (GOLD) criteria [12]. As few female subjects met the criteria of COPD, they were not included in this study.
2.2.2. Control Group

A group of healthy subjects was recruited among the hospital staff and from the local community through personal contacts. Healthy male subjects reported no chronic diseases.

2.3. Measurements

2.3.1. Functional Daily Activity

The oxygen cost diagram (OCD) was used to evaluate the participants’ functional activity. The participants were asked to indicate a point on an OCD, a 100 mm long vertical line with everyday activities listed alongside the line, above which breathlessness limited them [13]. The distance from zero was measured and scored.

2.3.2. Pulmonary Function Testing

Cigarette smoking, drinking coffee, tea, or alcohol, and taking medications were not permitted 24 h before any test. Bronchodilators were not administered within 3 h for short-acting beta agonists and 12 h for long-acting beta agonists before the tests [14,15]. FEV$_1$, TLC, residual volume (RV), and diffusing capacity for carbon monoxide (D$_L$CO) were measured using spirometry, body plethysmography, and the single-breath technique, respectively, in accordance with the currently recommended standards [16–18]. All of the spirometry data were obtained before and after inhaling a standard dose of fenoterol HCl. Post-dose measurements were performed 15 min after inhalation. Static lung volume data and D$_L$CO data were obtained before inhaling fenoterol. Simple volume calibration was conducted and accuracy checks for body plethysmograph mouth flow and pressure and box pressure were performed as reported previously [14,15].

2.3.3. Cardiopulmonary Exercise Testing (CPET)

Each subject completed an incremental exercise test using a cycle ergometer to the limit of the symptom. Work rate was selected at a rate of 5–20 W/min based on a derived protocol formula according to the oxygen-cost diagram scores [19]. Oxygen uptake (VO$_2$) (mL/min), CO$_2$ output (VCO$_2$) (mL/min), and minute ventilation (V$_E$) were continuously measured. VO$_2$max was symptom-limited peak VO$_2$, because VO$_2$max, which was the plateau of VO$_2$, was likely not attained in the participants with COPD. The ratio of compartment of TLC and TLC was remarked as the % of TLC such as EELV%, DH%, V$_D$%, and V$_T$%. A dyspnea score was obtained using the Borg scale by asking the patients about their dyspnea levels while they were performing the ramp-pattern exercise at the end of each minute and at peak exercise.

2.3.4. Dynamic Inspiratory Capacity (IC) Measurement

The techniques used for performing and accepting IC measurements of our previous study [11] were modified from a previous report [7]. Dynamic IC was measured at the end of a steady-state resting baseline, near the middle of loaded exercise (supposed to be near anaerobic threshold, AT), and near peak exercise. Dynamic IC near AT was measured approximately 5–6 min after the start of loaded exercise. EELV was calculated as TLC minus dynamic IC [5,6,20,21]. DH referred to end-expiratory lung volume at AT or peak exercise (EELV$_{AT}$ or peak) minus resting EELV (EELV$_{rest}$). In this study, EELV was estimated for subjects with COPD using the formulae from the data of our previous report [11]. EELV$_{rest}$% = 0.7235 – 1.0053 × V$_{Trest}$%; EELV$_{AT}$% = 0.9877 – 2.0132 × V$_{TAT}$%; EELV$_{peak}$% = 0.9491 – 1.35178 × V$_{Tpeak}$%; O’Donnell threshold (OT) = TLC - EELV - V$_{Tpeak}$ (see O’Donnell threshold in Reference [22]).

2.3.5. V$_D$/V$_T$ Calculation

Brachial artery blood samples were drawn via an arterial catheter connected to a pressure transducer within the last 15 s of each minute after the start of exercise to the peak of exercise [23].
At rest, near the anaerobic threshold, and at the peak of exercise, the physiological \( V_{D}/V_T \) was calculated using a standard formula as follows [24]: 

\[
V_{D}/V_T = (P_{a}CO_2 - P_{\bar{R}}CO_2)/P_{a}CO_2 - V_{Dm}/(V_T - V_{Dm}),
\]

where 

\[
P_{\bar{R}}CO_2 = VCO_2/V_E \times (P_B - 47 \text{ mmHg})
\]

and \( P_B \) is barometric pressure measured daily and \( V_{Dm} \) is breathing valve dead space. Hemoglobin and biochemistry data were provided. In normal subjects, mean values of \( V_{D}/V_T \) are 0.30 ± 0.08 at rest, 0.20 ± 0.07 at AT, and 0.19 ± 0.07 at peak [2].

### 2.4. Statistical Analysis

Data were summarized as mean ± standard deviation. The sample size was estimated to be at least 17 for each group when the population mean difference in \( V_{D}/V_T \) was 0.1 with a standard deviation for the normal and COPD groups of 0.1 and with a significance level of 0.05 and a power of 0.8. The unpaired t-test was used to compare the means between two groups. The paired t-test was used to compare two related means between two different time points with Bonferroni correction. Pearson’s correlation coefficients were further used when appropriate for quantifying the pairwise relationships among the interested variables. All statistical analyses were performed using SAS statistical software 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at \( p < 0.05 \) and \( p < 0.017 \) for Bonferroni correction.

### 3. Results

A total of 81 male subjects were enrolled, including 46 subjects (mean age 65.2 ± 5.8 years) with COPD after excluding one subject due to poor motivation, and 34 healthy subjects matched for age and height (mean age 62.2 ± 9.2 years) (Table 1 and Figure 1). Most of the COPD subjects had GOLD stages II and III with hyperinflation and air trapping, normocapnia, and borderline hypoxemia at rest and could perform daily brisk walking on the level. Compared to the healthy controls during exercise, most of the COPD subjects had mildly impaired exercise capacity due to ventilatory limitation with poor lung expansion, significant oxyhemoglobin desaturation, and exercise hyperventilation (Table 2).

| COPD | Normal Controls |
|------|-----------------|
| Mean | SD | Mean | SD | \( p \) |
| --- | --- | --- | --- | --- |
| Age, years | 65.2 | 5.8 | 62.2 | 9.2 | 0.10 |
| Height, cm | 165.0 | 6.4 | 167.0 | 5.3 | 0.14 |
| Weight, kg | 60.4 | 11.2 | 69.2 | 8.9 | 0.0002 |
| Body mass index, kg/m\(^2\) | 22.1 | 3.5 | 24.8 | 7.4 | 0.0003 |
| Cigarette smoke, pack-year | 42.3 | 19.2 | 4.7 | 17.4 | <0.0001 |
| Oxygen cost diagram, cm | 7.0 | 1.4 | 8.3 | 1.0 | <0.0001 |
| TLC% predicted, % | 135 | 21 | 97 | 11 | <0.0001 |
| RV% predicted, % | 200 | 55 | 101 | 17 | <0.0001 |
| RV/TLC | 0.58 | 0.09 | 0.39 | 0.06 | <0.0001 |
| IC% predicted, % | 92 | 27 | 99 | 17 | 0.15 |
| DL\(_{CO}\)% predicted, % | 69 | 22 | 106 | 16 | <0.0001 |
| FVC% predicted, % | 81 | 21 | 101 | 13 | <0.0001 |
| FEV\(_1\)% predicted, % | 50 | 19 | 103 | 13 | <0.0001 |
| GOLD, I, II, III, IV, n | 3, 18, 19, 6 | NA | NA | NA |
| FEV\(_1\)/FVC | 0.49 | 0.13 | 0.93 | 0.28 | <0.0001 |
| Hemoglobin, g/dL | 14.8 | 1.5 | 14.6 | 1.2 | 0.78 |
| Creatinine, mg/dL | 1.1 | 0.2 | 1.0 | 0.3 | 0.25 |
| Na\(^+\), meq/L | 140.5 | 2.4 | 138.4 | 2.2 | 0.73 |
| K\(^+\), meq/L | 4.3 | 0.5 | 4.1 | 0.4 | 0.52 |
| Albumin, mg/dL | 4.2 | 0.4 | NA | NA | NA |
| pH | 7.40 | 0.03 | NA | NA | NA |
| P\(_a\)CO\(_2\), mmHg | 40.6 | 6.4 | NA | NA | NA |
| P\(_a\)O\(_2\), mmHg | 79.3 | 10.1 | NA | NA | NA |
| Sp\(_O2\), % | 95.3 | 2.6 | 97.2 | 1.2 | <0.0001 |

TLC: total lung capacity, RV: residual volume, IC: inspiratory capacity, DL\(_{CO}\): diffusing capacity for carbon monoxide, FVC: forced vital capacity, FEV\(_1\): forced expired volume in one second., GOLD: global initiative for chronic obstructive lung disease, Sp\(_O2\): oxyhemoglobin saturation measured with pulse oximetry. NA: not available or not applicable.
Figure 1. Flow diagram. A total of 81 participants with chronic obstructive pulmonary disease and healthy controls were screened.

Table 2. Cardiopulmonary exercise test at peak exercise in male subjects with chronic obstructive pulmonary disease (COPD) (n = 46) and male healthy subjects (n = 34).

|                        | COPD   | Normal Controls | p      |
|------------------------|--------|-----------------|--------|
|                        | Mean   | Mean            | SD     |<0.0001|
| Work rate, watts       | 91.8   | 146.6           | 42.9   |<0.0001|
| % predicted            | 69     | 115.9           | 30     |<0.0001|
| Oxygen uptake (VO₂)    | 1073   | 1708            | 355    |<0.0001|
| % predicted            | 69.3   | 90.7            | 20.9   |<0.0001|
| Anaerobic threshold, mL/min| 489 | 1018            | 137    |<0.0001|
| %VO₂max Predicted, %   | 31.1   | 53.0            | 8.0    |<0.0001|
| Respiratory exchange ratio | 1.05 | 1.16            | 0.10   |<0.0001|
| Cardiac frequency, b/min| 133   | 149             | 20     |<0.0001|
| % predicted max, %     | 81.3   | 94.7            | 12.0   |<0.0001|
| Oxygen pulse, mL/min   | 8.1    | 11.5            | 2.4    |<0.0001|
| % predicted            | 85.3   | 22.9            | 23.5   |<0.0001|
| Minute ventilation Vₖ/V₀₂nadir | 36.9 | 28.2           | 8.0    |<0.0001|
| S_pO₂, %               | 91.0   | 96.8            | 5.8    |<0.0001|
| Vₑ, L/min              | 38.6   | 70.4            | 12.3   |<0.0001|
| Vₑ/MVV                 | 1.16   | 0.63            | 0.36   |<0.0001|
| Breathing frequency, breath/min | 32.6 | 36.6           | 5.9    |<0.0001|
| Tidal volume (V₉), L   | 1.19   | 1.96            | 0.35   |<0.0001|
| V₉/total lung capacity (TLC) | 0.19 | 0.32           | 0.05   |<0.0001|
| Dead space volume (V₃)/V₉ | 0.43 | 0.19           | 0.10   |<0.0001|
| pH                     | 7.32   | NA              | 0.04   |NA      |
| P_aCO₂, mmHg           | 46.1   | NA              | 7.8    |NA      |
| P_aO₂, mmHg            | 71.0   | NA              | 16.7   |NA      |

Oxygen pulse = VO₂/cardiac frequency; oxyhemoglobin saturation measured with pulse oximetry—S_pO₂; maximum voluntary ventilation—MVV; * from Reference [2]. NA: not applicable or not available.
3.1. The % of TLC: EELV%, DH%, VD%, VT%, VDEELV%, and VTEELV% (or End-Inspiratory Lung Volume, EILV)

In the COPD group, EELV\textsubscript{rest}% was 63% ± 2% and EELV\textsubscript{peak} was 70% ± 7% as compared with 48% ± 13% and 46% ± 13% in the healthy group (Figure 2, group comparisons, both \( p < 0.0001 \)). Hence, DH\textsubscript{peak}% was 7% ± 7% as compared with 1% ± 10% in the healthy group (\( p = 0.03 \)). In the COPD group, VD\textsubscript{rest}% was 5% ± 1% and VD\textsubscript{peak}% was 8% ± 2% as compared with 4% ± 2% and 6% ± 1% in the healthy group (Figure 2, group comparisons: \( p < 0.01 \) and \( p < 0.0001 \)). In the COPD group, DH\textsubscript{peak}% was similar to VD\textsubscript{peak}% at peak exercise (7% ± 7% vs. 8% ± 2%, \( p = 0.61 \)).

![Figure 2](image-url)

Figure 2. The % of total lung capacity (TLC, upward triangles) at rest, anaerobic threshold (AT) and peak exercise. Left panel COPD group and right panel normal controls. Open circles, end-expiratory lung volume (EELV); solid circles, dead space volume (VD) plus EELV; down triangles, tidal volume (VT) plus EELV (i.e., end-inspiratory lung volume, EILV); vertical bars, standard error of estimate; OT, O’Donnell threshold; DH, dynamic hyperinflation indicating EELV at AT or peak exercise minus EELV at rest; dashed line, EELV at rest. Comparisons of each compartment between COPD patients and normal controls at rest, AT and peak exercise, respectively, all \( p < 0.0001 \) except V\textsubscript{T}EELV at rest, \( p < 0.01 \) and V\textsubscript{T}EELV at peak exercise, \( p < 0.001 \). In COPD patients, comparisons of each compartments of TLC between two time points, all \( p < 0.0001 \) except EELV at AT versus EELV at peak exercise, \( p < 0.001 \) and V\textsubscript{D}EELV at AT versus V\textsubscript{D}EELV at peak exercise, \( p = 0.046 \), which was insignificant.

After combining V\textsubscript{D} with DH (V\textsubscript{D}DH%), V\textsubscript{D}DH\textsubscript{rest}% was 5% ± 1% and V\textsubscript{D}DH\textsubscript{peak}% was 15% ± 5% in the COPD group as compared with 4% ± 2% and 7% ± 10% in the healthy group (group comparisons, both \( p < 0.01 \)). After combining V\textsubscript{D} with EELV (V\textsubscript{DEELV}%), V\textsubscript{DEELV}\textsubscript{rest}% was 68% ± 1% and V\textsubscript{DEELV}\textsubscript{peak}% was 78% ± 6% in the COPD group as compared with 52% ± 13% and 52% ± 13% in the healthy group (group comparisons, both \( p < 0.0001 \)). After combining V\textsubscript{T} with EELV (V\textsubscript{T}EELV% or EILV%), V\textsubscript{T}EELV\textsubscript{rest}% was 72% ± 0% and V\textsubscript{T}EELV\textsubscript{peak}% was 88% ± 2% in the COPD group as compared with 62% ± 13% and 78% ± 14% in the healthy group (group comparisons, \( p < 0.01 \) and \( p < 0.001 \), respectively).

3.2. Relationships among the Compartments of TLC

V\textsubscript{Dpeak}% was moderately positively correlated with V\textsubscript{Tpeak}% (Table 3, \( r = 0.66, p < 0.0001 \)) and moderately negatively correlated with the other compartments at peak exercise (\( r = -0.47 \) to −0.68, \( p < 0.01 \) to <0.0001).
Table 3. Relationships among the compartments of total lung capacity (TLC) and correlations of seven components of total lung capacity (TLC) with oxygen uptake (VO2), minute ventilation (VE), and dyspnea at peak exercise in 46 patients with COPD.

| Peak              | VD%      | VO2     | VE      | ∆Borg/∆VO2 |
|-------------------|----------|---------|---------|------------|
| EELV%             | -0.67†   | -0.62†  | -0.75†  | 0.66†      |
| DH%               | -0.61†   | -0.69†  | -0.78†  | 0.72†      |
| VD%               | 1        | 0.26*   | 0.46**  | -0.19      |
| VT%               | 0.66†    | 0.62†   | 0.76†   | -0.67†     |
| VD-DH%            | -0.68†   | -0.74†  | -0.74†  | 0.78†      |
| VD-EELV%          | -0.47**  | -0.74†  | -0.74†  | 0.78†      |
| VT-EELV%          | -0.68†   | -0.60†  | -0.71†  | 0.63†      |

%: variable divided by TLC, EELV: end-expiratory lung volume, DH: dynamic hyperinflation indicating EELV at resting EELV, VD-DH: combing dead space (VD) and DH, VT: tidal volume, ∆: change.

*0.05 > p ≤ 0.1, ** p ≤ 0.01, † p ≤ 0.0001.

3.3. Relationships between the % of TLC and Oxygen Uptake, Minute Ventilation, and Dyspnea

In the % of TLC, VD-EELVpeak% and VD-DHpeak% showed the best correlations with ∆Borg/∆VO2 and, a similar strength of correlation with VEpeak (Table 3). The higher the VD-DHpeak% and VD-EELVpeak%, the higher the dyspnea score and the lower the VO2peak% and VEpeak.

3.4. VTpeak% versus VD/VTpeak

In the COPD group, VTpeak% was 9% ± 2% and VDpeak% was 18% ± 5% as compared with 13% ± 7% and 32% ± 54% in the healthy group (Figure 2, group comparisons p < 0.01 and p < 0.0001). In the COPD group, there was a negatively significant relationship between VT% and VD/VT at rest, anaerobic threshold, and peak exercise, and this was stronger as the exercise intensity increased (see the Appendix A Table A2, r = −0.34 to −0.64, p = 0.02 to p < 0.0001). When pooling the data of these two variables at the three time points together, the relationship was much closer (r = −0.72, p < 0.0001).

4. Discussion

There are four main findings in this study. First, VD and DH (VD-DH) and VD and EELV (VD-EELV) could be combined. Secondly, we found that in the patients with COPD, VD and DH were similar in size, and that VD-EELVrest accounted for 68% of the TLC and VD-EELVpeak accounted for up to 78%. Third, compared to DHpeak% and EELVpeak%, VD-DHpeak% and VD-EELVpeak% were more closely related to dyspnea and exercise capacity and had a similar power in relation to ventilation capability. Lastly, VTpeak%, a recently reported marker of DHpeak [11], was moderately negatively correlated with VD/VTpeak. To the best of our knowledge, these findings have not previously been published.

4.1. The % of TLC

The importance of EELVpeak% has been reported when the EELVpeak is ≥75% of TLC, a threshold value which can maximize the sensitivity and specificity of detecting ≤5.5 mL/heartbeat change in oxygen pulse (ΔO2p) and ≤10,000 oxygen uptake efficiency slope (OUES) during exercise [25], where ΔO2p and OUES are markers of cardiovascular function. In addition to EELVpeak% >75% [25], the reciprocal ICpeak/TLC <25% [26] has also been associated with lower O2p and exercise capacity in patients with severe COPD. ICpeak/TLC >23% has also been associated with lower O2p and exercise capacity in patients with severe COPD [27]. Although OUES was not measured in this study, our previous study reported that ICpeak/TLC was significantly correlated with O2p and ΔO2p (r = 0.35–0.36, both p < 0.05) [28]. These results support an interaction between hyperinflation and decreased cardiac function that can contribute to exercise limitation in these patients. A greater amount of trapped gas in the lung increases the intrinsic positive end-expiratory pressure, and this compresses the heart and
impedes venous return causing further heart impairment [25,26]. It has recently been reported that this compression can occur even at rest [29].

DH has been shown to increase with exercise in patients with COPD [3–6,9,10,20–22], and thus EELV caused failure of VT to expand, as in the healthy subjects in this study (0.6 ± 0.31 L versus 1.12 ± 0.57 L, \( p < 0.0001 \)). A high level of \( V_{D} \) EELV “buoyed” the expandable basic lung volume above its position, meaning that VT had limited room to expand downwards so that it could not help but invade upwards to the OT or near its limit (Figure 2). In COPD, decreased OT [3,22] and increased DH have been reported to be possible causes of exercise limitation [30], although some studies have questioned whether DH occurs in all COPD patients [31–33]. These previous studies have measured DHpeak but not included VDpeak. In this study, VD_DHpeak% and VD_EELVpeak% were slightly better than DHpeak% and EELVpeak% with regards to the correlation with ∆Borg/∆VO₂ and VO₂peak% and had a similar power with regards to the correlation with VEpeak (Table 3). Therefore, it could be reasonable to combine VD_DPeak with DHpeak and to combine VD_DPeak with EELVpeak%. In this study, VD_EELVpeak%, an unfavorable lung volume, was elevated to as high as 78% ± 6% of TLC.

In the patients with COPD in this study, although VD_DPeak% was small as compared with EELVpeak% but similar to DH_peak% in size, VD_DHpeak% accounted for 15% of TLC. The majority of the increase in physiological VT must have come from alveolar VD, as the increase in anatomical VT was estimated to be only 12 mL and 20 mL in the COPD and control groups, respectively, based on the estimation that anatomical VT would increase 20 mL per liter increase in EELV [1]. Hence, the remaining increase in physiological VT must have come from alveolar VD, which is strongly influenced by lung pathology but less influenced by other factors such as age, sex, body size (1 mL of physiological dead space per pound of weight reported by Radford), posture, low cardiac output, pulmonary emboli, and posture [1].

\( V_D \) % and EELV% were moderately negatively correlated (Table 3). This is because \( V_D \) % and VT% were moderately positively correlated and VT% and EELV% were highly negatively correlated (\( r = -0.83, p < 0.0001 \)) [11]. VT% was positively correlated with VT% because VT is calculated by \( V_D/V_T \) multiplied by VT. Hence, the larger the VT, the larger the VD, and the smaller the EELV. It is clear that VT is different from EELV and DH in the direction of correlation, that these volumes can be combined, and that the combinations are more related to exercise capacity and exertional dyspnea sensation, although VT is small. Interestingly, VT% alone was poorly related to exercise tolerance and dyspnea. However, the relationships between DH% and EELV% versus exercise tolerance and dyspnea were slightly improved after adding \( V_D \) % (Table 3).

4.2. VT% versus \( V_D/V_T \)

\( V_D/V_T \) has been reported to be the most consistent gas exchange abnormality in smokers with only mild abnormalities in spirometry [3]. However, invasive methods to obtain arterial blood gases are needed to measure \( V_D/V_T \). In this study, VT%, an inverse marker of DH [11], was inversely correlated with \( V_D/V_T \) (R² = 0.50) (see the Appendix A Table A2). However, Mahut et al. reported that \( V_D/V_T \) was only mildly correlated to DH (\( r = -0.45, p = 0.004 \)) [10], where DH was represented by ICpeak% predicted [10]. This difference in correlation between DH and \( V_D/V_T \) in these two studies could be due to the different criteria used for DH, i.e., ICpeak% predicted versus VT%. Predicted IC data were obtained from the general population, whereas VT% was directly measured in the participants. In addition, Mahut et al. reported that the alveolar volume (VA)/TLC ratio was significantly correlated with \( V_D/V_T \) (R² = 0.50) but much less significantly correlated with \( V_D/V_T \) peak (see the Appendix A Table A1) [10]. VA is usually measured using the single breath helium dilution method at rest and is equal to TLC – \( V_D \) [34]. Therefore, VA would underestimate TLC in subjects with poorly communicating airways or disequilibrium of ventilation. VA/TLC measured at rest cannot reflect DHpeak, so that it was poorly correlated with \( V_D/V_T \) peak. Moreover, in this study, the relationship between VT% and \( V_D/V_T \) was strongest when data at rest, anaerobic threshold, and peak exercise were pooled (see the Appendix A Table A2, \( r = -0.72, p < 0.0001 \)). The mechanism underpinning the stronger relationship between VTpeak% and \( V_D/V_T \) peak with increasing exercise intensity could be due to the common factor VTpeak.
being highly constrained at peak exercise. The stronger relationship between VT\% and VD/VT after pooling different stages of exercise is comparable to a previous study in which VE/VCO2 was used instead of VT\% in healthy subjects and patients with COPD [3].

Nevertheless, Paoletti et al. reported that VTpeak/FEV1 > 1 (or VTpeak/IC = 0.96 ± 0.05), emphysema, the slope of VE/VCO2, and PETCO2peak values were colinear [35] (Figure 3). In their study, the patients with COPD had high RV\% predicted and high emphysema score measured with high resolution computed tomography (HRCT). They hypothesized that VTpeak/FEV1 > 1 or elevated VTpeak/IC was due to DH occurring at peak exercise in patients with severe emphysema, which is comparable with our study and another study using VTpeak/SVC to assess the severity of emphysema evaluated with HRCT [36] (Figure 3). However, it has been reported that the change in VT/VT from rest to peak exercise was not related to the severity of emphysema [35]. In the current study, VTpeak/FEV1 > 1 and VTpeak/SVC were correlated with VTpeak\%, respectively (Figure 3, r = −0.36 and 0.66, p = 0.001, p < 0.0001), however neither were correlated with VD/VTpeak. Nevertheless, VTpeak\% was correlated with VD/VTpeak (r = −0.64, p < 0.0001), suggesting that VTpeak\% could be more powerful than VTpeak/FEV1 and VTpeak/SVC (Figure 3).

Figure 3. Relationships among dynamic hyperinflation (DH) variables and relationships between DH variables and dead space fraction (VD/VT) in patients with chronic obstructive pulmonary disease. Black bolded boxes, from this study; blue boxes, from References [35,36]. Solid lines, significantly correlated; dashed lines, not significantly correlated. Black lines, from this study; blue lines, from reference [35]; green line, from reference [36]. VT\%, tidal volume and total lung capacity (TLC) ratio; EELV\%, end-expiratory lung volume and TLC ratio; VT/SVC, VT and slow vital capacity ratio; VT/FEV1, VT and forced expired volume in one second ratio; HRCT, high resolution computed tomography; RV\%, residual volume predicted \%; Δ VE/Δ VCO2, slope of minute ventilation and CO2 output; PETCO2, end-tidal CO2 pressure.

4.3. Clinical Implications of VD\%DHpeak\% and VDEELVpeak\%, and VTpeak\%

Since DH may not occur in all COPD patients [31–33], as VD\%DHpeak\% and VDEELVpeak\% are substantially larger and slightly more related to dyspnea [31] and exercise capacity than DH\% and EELV\%, and as VTpeak\% can be obtained easily and noninvasively, these three markers could potentially be used to evaluate the effect of bronchodilator or lung volume reduction surgery on dyspnea and exercise tolerance.

5. Study Limitations

Airflow obstruction should be defined as a FEV1/VC ratio below the fifth percentile (z-score −1.645) of the distribution of a reference population [17] according to the 2019 ATS-ERS technical statement [16].
In the present study, the use of GOLD criteria to define COPD could have introduced age, sex, and height selection bias. However, the severity of most of the subjects with COPD in this study had GOLD stages II–IV (93.5%), and thus the likelihood of underdiagnosing COPD was small. Although OCD is not a commonly used tool to evaluate physical activity for patients with COPD, previous studies have suggested that the OCD and the COPD assessment test should be used simultaneously when undertaking clinical evaluations of patients with COPD, and that the OCD in ramp-slope selection should be used for dyspneic patients when undertaking CPET [13,19]. However, the International Physical Activity Questionnaire and accelerometry could also be helpful in this case [37,38]. A novel analytical method reported calculating shunt $V_D$ by subtracting respiratory $V_D$ (i.e., anatomical $V_D$ and alveolar $V_D$) from physiological $V_D$ [39]. We did not calculate shunt $V_D$, as this method is sophisticated and the shunt $V_D$ level was expected to be small. Tidal flow limitation measured with negative expiratory pressure has been shown to play a role in reducing the IC at rest, during which tidal flow limitation constrains $V_T$ expansion during exercise thereby causing an elevation in $V_D/V_T$ at peak exercise [40]. Although tidal flow limitation was not measured in this study, it can be anticipated to occur in the subjects with more severe airflow obstruction and higher air trapping with a lower IC [41]. In the COPD group in this study, EELV was estimated using the formulae reported in our previous study [11], and thus the estimated DH% and EELV% values may not be exactly the same as the measured data. In the healthy controls, data on $V_D/V_T$ at rest, AT, and peak exercise were retrieved from reference subjects, as it was difficult to obtain permission from our Institutional Review Boards to perform arterial catheterization for exercise testing. The emphysematous phenotype could be related to $V_D$DH. However, as there were relatively few subjects and emphysema was not evaluated using HRCT in this study, further studies are warranted to address these issues. Lastly, $V_D$ cannot be obtained without using invasive method in patients with COPD, and thus its clinical implication could be limited. Studies to investigate the development of a novel noninvasive method to obtain $V_D$ or $V_D/V_T$ are warranted. Finally, using Jones’ and Bohr’s equations to estimate $V_D/V_T$ in subjects with COPD is not suitable, as $P_{ET}CO_2$ used in the equations cannot be used as a surrogate for $P_{a}CO_2$ or alveolar $PCO_2$ [42,43].

6. Conclusions

Although the definitions of $V_D$ and DH are quite different, this study shows the utility of their combination, and that it could play a role in physiology with regards to the evaluation of exertional dyspnea and exercise capacity in subjects with COPD. In addition, $V_T$% was significantly correlated with $V_D/V_T$, suggesting that $V_T$% is not only a convenient marker for DH as reported previously, but also a potential noninvasive marker for $V_D/V_T$.

Author Contributions: M.-L.C. initiated and designed the study, analyzed and interpreted the data, wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: The study was supported in part by the Minister of Science and Technology, Taiwan (MOST 106-2314-B-040-025). The funding body had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Conflicts of Interest: The author declares no competing financial interests.

Abbreviations

$V_D$ Dead space
DH dynamic hyperinflation
EELV end-expiratory lung volume
$V_D/V_T$ dead space/tidal volume ratio
COPD chronic obstructive pulmonary disease
OT O’Donnell’s threshold
TLC total lung capacity
CPET cardiopulmonary exercise tests
IC inspiratory capacity
FEV$_1$ forced expired volume in one second
FVC forced expired capacity
GOLD global initiative for chronic obstructive lung disease
OCD oxygen cost diagram
RV residual volume
D$_L$CO diffusing capacity for carbon monoxide
VO$_2$ oxygen uptake
VCO$_2$ CO$_2$ output
V$_E$ minute ventilation
P$_E$CO$_2$ mixed expired CO$_2$ pressure
PB barometric pressure
V$_{Dm}$ breathing valve dead space
ΔBo/ΔO$_2$ slope of Borg score and oxygen uptake
ΔO$_2$Π oxygen pulse
V$_A$ alveolar volume
V$_E$/VCO$_2$ ventilatory equivalent for CO$_2$ output
P$_{ET}$CO$_2$ end-tidal CO$_2$ pressure
HRCT high resolution computed tomography
SVC slow vital capacity

Appendix A

Table A1. Summary of the correlation coefficient (r) between the dead space fraction (V$_D$/V$_T$) and some physiological variables reported by Mahut et al. [10] and Elbehairy et al. [3].

| r     | V$_D$/V$_T$  |
|-------|--------------|
|       | Rest | Peak |
| V$_A$/TLC [10] | −0.6 | −0.2 |
| V$_E$/MVC% [10] | NA | 0.32 |
| IC$_\text{peak}$% predicted [10] | NA | −0.45 |
| V$_E$/VCO$_2$ [3] | 0.78 ** | NA |
| KCO [10] | −0.52 | −0.43 |
| D$_L$CO% predicted [10] | NA* | NA* |
| PaO$_2$/peak [10] | NA | −0.66 |
| Borg$_{\text{peak}}$/%VO$_2$/peak [10] | NA | 0.33 |

V$_A$, alveolar volume measured during diffusing capacity for carbon monoxide (DLCO) measurement; TLC, total lung capacity; IC, inspiratory capacity; V$_E$, minute ventilation; CO$_2$, CO$_2$ output; KCO, the diffusing constant of Krogh, i.e., D$_L$CO/V$_A$ without considering barometric pressure, where V$_A$ is alveolar volume in BTPS equal to TLC measured by single breath helium dilution method after subtracting anatomic dead space [34]; Borg, Borg score.

* p < 0.05 reported in reference [10], but r values are not reported, ** data involving rest and submaximal exercise in healthy subjects and mild COPD subjects. NA: not available.

Table A2. Pearson correlations (r) pairwise deletion between dead space and tidal volume ratio (V$_D$/V$_T$) and tidal volume and total lung capacity ratio (V$_T$%) at different phases of exercise test in participants with chronic obstructive pulmonary disease.

| V$_T$% | V$_D$/V$_T$  |
|--------|--------------|
|        | Rest | AT  | Peak | All |
| Rest   | −0.34 * | -   | -    | -   |
| AT     | -    | −0.47 ** | -    | -   |
| Peak   | -    | -    | −0.64 † | -   |
| All    | -    | -    | −0.72 † | -   |

AT: anaerobic threshold, * p < 0.05, ** p < 0.01, † p < 0.0001, All: V$_T$% at rest, AT, and peak and V$_D$/V$_T$ at rest, AT, and peak were pooled together.
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