Journal of
Clinical Medicine

MDPI

Article

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

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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_{Dpeak}% (8%), the V_DDH_{peak}% was 15% and the V_DEELV_{peak}% was 78%. Both were higher than those of the healthy controls. In the COPD group, the V_DDH_{peak}% and V_DEELV_{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 ($R^2 \approx 0.50$). 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_DDH 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 ≥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 ≤18 kg/m^2 or ≥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_LCO) 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_LCO 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. V_{O2peak} was symptom-limited peak V_{O2}, because V_{O2max}, which was the plateau of V_{O2}, 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]. $EELV_{rest}\% = 0.7235 - 1.0053 \times V_{Trest}\%$; $EELV_{AT}\% = 0.9877 - 2.0132 \times V_{T\ AT}\%$; $EELV_{peak}\% = 0.9491 - 1.35178 \times V_{Tpeak}\%$; 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]: $V_D/V_T = (P_aCO_2 - P_{\bar{E}}CO_2)/P_aCO_2 - V_{Dm}/(V_T - V_{Dm})$, where $P_{\bar{E}}CO_2 = VCO_2/V_E \times (P_B - 47\ mmHg)$ and PB 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).

Table 1. Demographics and lung function in 80 male subjects with 46 subjects of chronic obstructive pulmonary disease (COPD) and 34 healthy subjects.

	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	2.7	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
D_LCO% 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
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_aCO_2, mmHg	40.6	6.4	NA	NA	NA
P_aO_2, mmHg	79.3	10.1	NA	NA	NA
S_PO_2, %	95.3	2.6	97.2	1.2	<0.0001

TLC: total lung capacity, RV: residual volume, IC: inspiratory capacity, D_LCO: 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, S_PO_2: oxyhemoglobin saturation measured with pulse oximetry. NA: not available or not applicable.

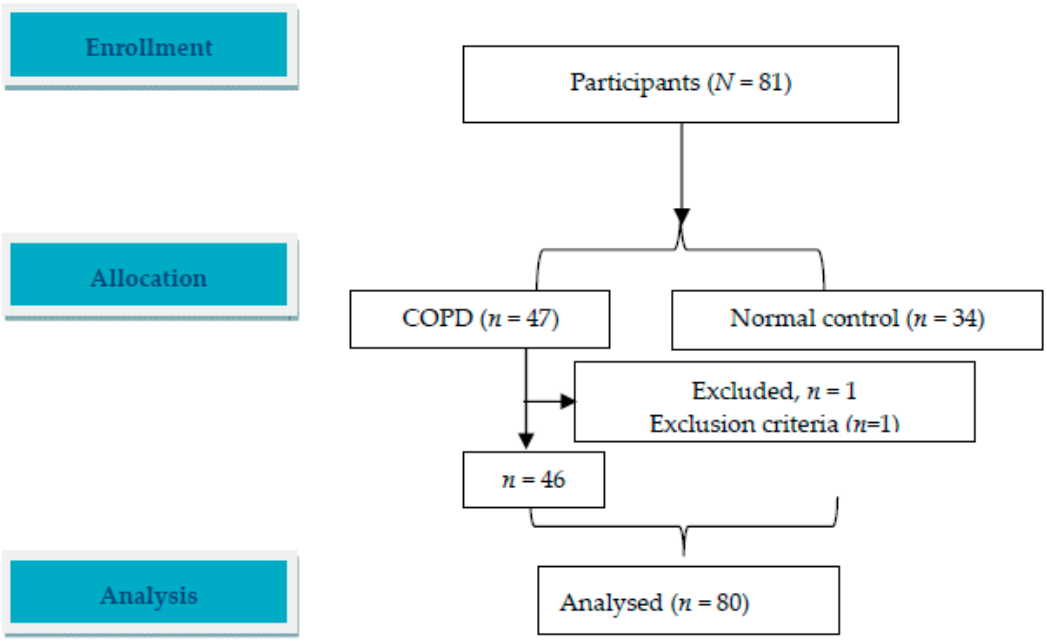

Figure 1. Flow diagram. A total of 81 participants with chronic obstructive pulmonary disease and healthy controls were screened.

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	**SD**	**Mean**	**SD**	
Work rate, watts	91.8	42.9	146.6	34.7	<0.0001
% predicted	69	30	115.9	22.9	<0.0001
Oxygen uptake (VO_2), mL/min	1073	355	1708	402	<0.0001
% predicted	69.3	20.9	90.7	19.4	<0.0001
Anaerobic threshold, mL/min	489	137	1018	302	<0.0001
%V_{O2max} predicted, %	31.1	8.0	53.0	11.8	<0.0001
Respiratory exchange ratio	1.05	0.10	1.16	0.14	0.0003
Cardiac frequency, b/min	133	20	149	17	0.0002
% predicted max, %	81.3	12.0	94.7	9.6	<0.0001
Oxygen pulse, mL/min	8.1	2.4	11.5	2.5	<0.0001
% predicted	85.3	23.5	96.7	22.9	0.03
Minute ventilation $V_E/V_{O2nadir}$	36.9	8.0	28.2	3.9	<0.0001
S_PO_2,%	91.0	5.8	96.8	1.2	<0.0001
V_E, L/min	38.6	12.3	70.4	18.0	<0.0001
V_E/MVV	1.16	0.36	0.63	0.15	<0.0001
Breathing frequency, breath/min	32.6	5.9	36.6	9.3	0.03
Tidal volume (V_T), L	1.19	0.35	1.96	0.42	<0.0001
V_T/total lung capacity (TLC)	0.19	0.05	0.32	0.05	<0.0001
Dead space volume (V_D)/V_T	0.43	0.10	0.19 *	0.07	NA
pH	7.32	0.04	NA		NA
P_aCO_2, mmHg	46.1	7.8	NA		NA
P_aO_2, mmHg	71.0	16.7	NA		NA

Oxygen pulse = VO_2/cardiac frequency; oxyhemoglobin saturation measured with pulse oximetry—S_PO_2; maximum voluntary ventilation—MVV; * from Reference [2]. NA: not applicable or not available.

3.1. The % of TLC: EELV%, DH%, V_D%, V_T%, V_DDH%, V_DEELV%, and V_TEELV% (or End-Inspiratory Lung Volume, EILV)

In the COPD group, $EELV_{rest}$% was 63% ± 2% and $EELV_{peak}$ 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_{peak}% was 7% ± 7% as compared with 1% ± 10% in the healthy group ($p = 0.03$). In the COPD group, V_{Drest}% was 5% ± 1% and V_{Dpeak}% 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_{peak}% was similar to V_{Dpeak}% at peak exercise (7% ± 7% vs. 8% ± 2%, $p = 0.61$).

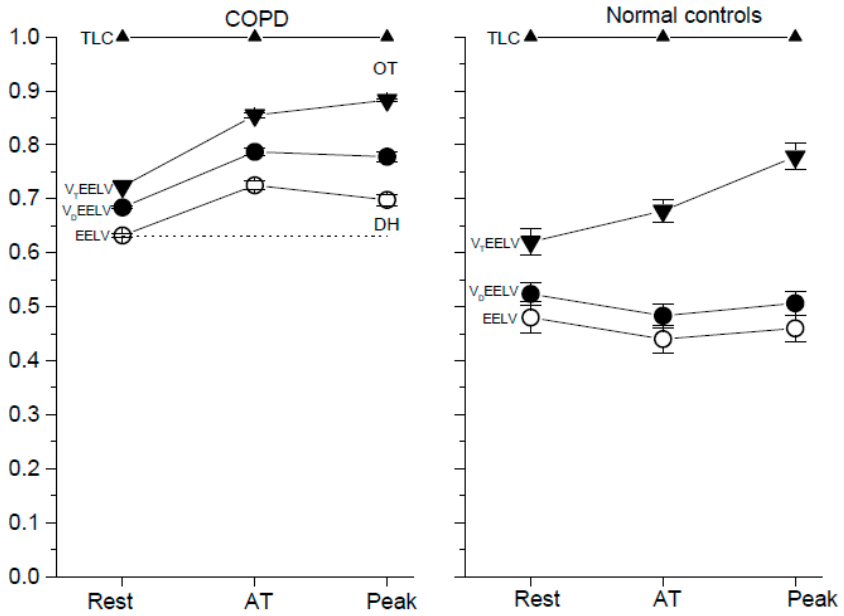

Figure 2. The % of total lung capacity (TLC, upward triangles) at rest, anaerobic threshold (AT) and peak exercise. Left panel COPD group and right panel normal controls. Open circles, end-expiratory lung volume (EELV); solid circles, dead space volume (V_D) plus EELV; down triangles, tidal volume (V_T) 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_TEELV at rest, $p < 0.01$ and V_TEELV 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_DEELV at AT versus V_DEELV at peak exercise, $p = 0.046$, which was insignificant.

After combining V_D with DH (V_DDH%), $V_D DH_{rest}$% was 5% ± 1% and $V_D DH_{peak}$% 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_D with EELV (V_DEELV%), $V_D EELV_{rest}$% was 68% ± 1% and $V_D EELV_{peak}$% 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_T with EELV (V_TEELV% or EILV%), $V_T EELV_{rest}$% was 72% ± 0% and $V_T EELV_{peak}$% 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_{Dpeak}% was moderately positively correlated with V_{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 (VO_2), minute ventilation (V_E), and dyspnea at peak exercise in 46 patients with COPD.

Peak	V_D%	VO_2	V_E	ΔBorg/ΔVO_2
EELV%	−0.67 †	−0.62 †	−0.75 †	0.66 †
DH%	−0.61 †	−0.69 †	−0.78 †	0.72 †
V_D%	1	0.26 *	0.46 **	−0.19
V_T%	0.66 †	0.62 †	0.76 †	−0.67 †
V_DDH%	−0.68 †	−0.74 †	−0.74 †	0.78 †
V_DEELV%	−0.47 **	−0.74 †	−0.74 †	0.78 †
V_TEELV%	−0.68 †	−0.60 †	−0.71 †	0.63 †

%: variable divided by TLC, EELV: end-expiratory lung volume, DH: dynamic hyperinflation indicating EELV at peak exercise subtracting resting EELV, V_DDH: combing dead space (V_D) and DH, V_T: tidal volume, Δ: change. * $0.05 > p \leq 0.1$, ** $p \leq 0.01$, † $p \leq 0.0001$.

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

In the % of TLC, V_DEELV$_{peak}$% and V_DDH$_{peak}$% showed the best correlations with ΔBorg/ΔVCO_2 and, and a similar strength of correlation with V_{Epeak} (Table 3). The higher the V_DDH$_{peak}$% and V_DEELV$_{peak}$%, the higher the dyspnea score and the lower the VO_{2peak}% and V_{Epeak}.

3.4. V_{Tpeak}% versus V_D/V_{Tpeak}

In the COPD group, V_{Trest}% was 9% ± 2% and V_{Tpeak}% 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 V_T% and V_D/V_T 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, V_D and DH (V_DDH) and V_D and EELV (V_DEELV) could be combined. Secondly, we found that in the patients with COPD, V_D and DH were similar in size, and that V_DEELV$_{rest}$ accounted for 68% of the TLC and V_DEELV$_{peak}$ accounted for up to 78%. Third, compared to DH$_{peak}$% and EELV$_{peak}$%, V_DDH$_{peak}$% and V_DEELV$_{peak}$% were more closely related to dyspnea and exercise capacity and had a similar power in relation to ventilation capability. Lastly, V_{Tpeak}%, a recently reported marker of DH$_{peak}$ [11], was moderately negatively correlated with V_D/V_{Tpeak}. To the best of our knowledge, these findings have not previously been published.

4.1. The % of TLC

The importance of EELV$_{peak}$% has been reported when the EELV$_{peak}$ is ≥75% of TLC, a threshold value which can maximize the sensitivity and specificity of detecting ≤5.5 mL/heartbeat change in oxygen pulse (ΔO_{2P}) and ≤10,000 oxygen uptake efficiency slope (OUES) during exercise [25], where ΔO_{2P} and OUES are markers of cardiovascular function. In addition to EELV$_{peak}$% >75% [25], the reciprocal IC$_{peak}$/TLC <25% [26] has also been associated with lower O_{2P} and exercise capacity in patients with severe COPD. IC$_{peak}$/TLC <23% has also been associated with lower O_{2P} and exercise capacity in patients with severe COPD [27]. Although OUES was not measured in this study, our previous study reported that IC$_{peak}$/TLC was significantly correlated with O_{2P} and ΔO_{2P} (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 V_T 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_DEELV "buoyed" the expandable basic lung volume above its position, meaning that V_T 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 DH_{peak} but not included V_{Dpeak}. In this study, V_DDH_{peak}% and V_DEELV_{peak}% were slightly better than DH_{peak}% and $EELV_{peak}$% with regards to the correlation with $\Delta Borg/\Delta VO_2$ and VO_{2peak}% and had a similar power with regards to the correlation with V_{Epeak} (Table 3). Therefore, it could be reasonable to combine V_{Dpeak} with DH_{peak} and to combine V_{Dpeak} with $EELV_{peak}$. In this study, V_DEELV_{peak}%, an unfavorable lung volume, was elevated to as high as 78% ± 6% of TLC.

In the patients with COPD in this study, although V_{Dpeak}% was small as compared with $EELV_{peak}$% but similar to DH_{peak}% in size, V_DDH_{peak}% accounted for 15% of TLC. The majority of the increase in physiological V_D must have come from alveolar V_D, as the increase in anatomical V_D was estimated to be only 12 mL and 20 mL in the COPD and control groups, respectively, based on the estimation that anatomical V_D would increase 20 mL per liter increase in EELV [1]. Hence, the remaining increase in physiological V_D must have come from alveolar V_D, 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 V_T% were moderately positively correlated and V_T% and EELV% were highly negatively correlated ($r = -0.83$, $p < 0.0001$) [11]. V_D% was positively correlated with V_T% because V_D is calculated by V_D/V_T multiplied by V_T. Hence, the larger the V_T, the larger the V_D, and the smaller the EELV. It is clear that V_D 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 V_D is small. Interestingly, V_D% 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. V_T% 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, V_T%, an inverse marker of DH [11], was inversely correlated with V_D/V_T ($R^2 \approx 0.50$) (see the Appendix A Table A2). However, Mahut et al. reported that V_D/V_{Tpeak} was only mildly correlated to DH ($r = -0.45$, $p = 0.004$) [10], where DH was represented by IC_{peak}% 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., IC_{peak}% predicted versus V_T%. Predicted IC data were obtained from the general population, whereas V_T% was directly measured in the participants. In addition, Mahut et al. reported that the alveolar volume (V_A)/TLC ratio was significantly correlated with V_D/V_{Trest} but much less significantly correlated with V_D/V_{Tpeak} (see the Appendix A Table A1) [10]. V_A is usually measured using the single breath helium dilution method at rest and is equal to TLC − V_D [34]. Therefore, V_A would underestimate TLC in subjects with poorly communicating airways or disequilibrium of ventilation. V_A/TLC measured at rest cannot reflect DH_{peak}, so that it was poorly correlated with V_D/V_{Tpeak}. Moreover, in this study, the relationship between V_T% 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 V_{Tpeak}% and V_D/V_{Tpeak} with increasing exercise intensity could be due to the common factor V_{Tpeak}

being highly constrained at peak exercise. The stronger relationship between V_T% and V_D/V_T after pooling different stages of exercise is comparable to a previous study in which V_E/VCO_2 was used instead of V_T% in healthy subjects and patients with COPD [3].

Nevertheless, Paoletti et al. reported that $V_{Tpeak}/FEV_1 > 1$ (or $V_{Tpeak}/IC = 0.96 \pm 0.05$), emphysema, the slope of V_E/VCO_2, and $P_{ET}CO_{2peak}$ 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 $V_{Tpeak}/FEV_1 > 1$ or elevated V_{Tpeak}/IC was due to DH occurring at peak exercise in patients with severe emphysema, which is comparable with our study and another study using V_{Tpeak}/SVC to assess the severity of emphysema evaluated with HRCT [36] (Figure 3). However, it has been reported that the change in V_D/V_T from rest to peak exercise was not related to the severity of emphysema [35]. In the current study, $V_{Tpeak}/FEV_1 > 1$ and V_{Tpeak}/SVC were correlated with V_{Tpeak}%, respectively (Figure 3, r = −0.36 and 0.66, $p = 0.001$, $p < 0.0001$), however neither were correlated with V_D/V_{Tpeak}. Nevertheless, V_{Tpeak}% was correlated with V_D/V_{Tpeak} (r = −0.64, $p < 0.0001$), suggesting that V_{Tpeak}% could be more powerful than V_{Tpeak}/FEV_1 and V_{Tpeak}/SVC (Figure 3).

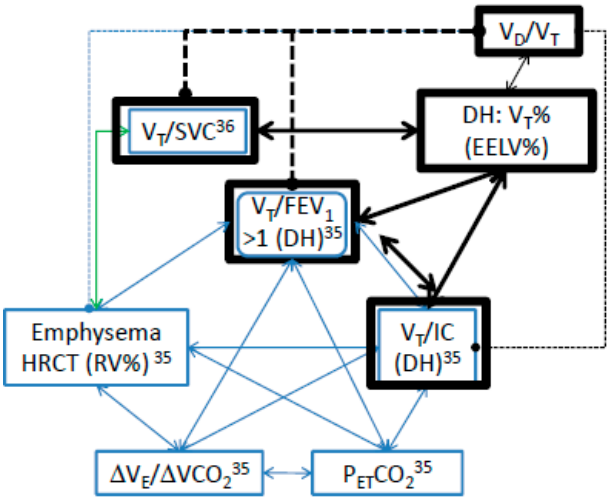

Figure 3. Relationships among dynamic hyperinflation (DH) variables and relationships between DH variables and dead space fraction (V_D/V_T) in patients with chronic obstructive pulmonary disease. Black bolded boxes, from this study; blue boxes, from References [35,36]. Solid lines, significantly correlated; dashed lines, not significantly correlated. Black lines, from this study; blue lines, from reference [35]; green line, from reference [36]. V_T%, tidal volume and total lung capacity (TLC) ratio; EELV%, end-expiratory lung volume and TLC ratio; V_T/SVC, V_T and slow vital capacity ratio; V_T/FEV_1, V_T and forced expired volume in one second ratio; HRCT, high resolution computed tomography; RV%, residual volume predicted %; Δ V_E/Δ VCO_2, slope of minute ventilation and CO_2 output; $P_{ET}CO_2$, end-tidal CO_2 pressure.

4.3. Clinical Implications of V_DDH_{peak}% and V_DEELV_{peak}%, and V_{Tpeak}%

Since DH may not occur in all COPD patients [31–33], as V_DDH_{peak}% and V_DEELV_{peak}% are substantially larger and slightly more related to dyspnea [31] and exercise capacity than DH% and EELV%, and as V_{Tpeak}% 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 FEV_1/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_DDH. 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_aCO_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_LCO	diffusing capacity for carbon monoxide
VO_2	oxygen uptake
VCO_2	CO_2 output
V_E	minute ventilation
$P_{\bar{E}}CO_2$	mixed expired CO_2 pressure
PB	barometric pressure
V_{Dm}	breathing valve dead space
ΔBo$\rho\gamma/\Delta$ ςO_2	slope of Borg score and oxygen uptake
$\Delta O_{2\Pi}$	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
$V_{E\ peak}$/MVC% [10]	NA	0.32
$IC_{\ peak}$% predicted [10]	NA	−0.45
V_E/VCO_2 [3]	0.78 **	NA
KCO [10]	−0.52	−0.43
D_LCO% predicted [10]	NA*	NA*
PaO_2peak [10]	NA	−0.66
$Borg_{peak}/\%VO_{2peak}$ [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_LCO/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.

References

1. Lumb, A.B.; Nunn, J.F. Distribution of pulmonary ventilation and perfusion. In *Nunn's Applied Respiratory Physiology*, 5th ed.; Lumb, A.B., Ed.; Butterworth Heinemann: Edinburgh, UK, 2000; pp. 163–199.
2. Wasserman, K.; Hansen, J.E.; Sue, D.Y.; Stringer, W.W.; Whipp, B.J. Physiology of exercise. In *Principles of Exercise Testing and Interpretation*, 4th ed.; Wasserman, K., Ed.; Lippicott Williams & Wilkins: Philadelphia, PA, USA, 2005; pp. 10–65.
3. Elbehairy, A.F.; Ciavaglia, C.E.; Webb, K.A.; Guenette, J.A.; Jensen, D.; Mourad, S.M.; Neder, J.A.; O'Donnell, D.E. Pulmonary Gas Exchange Abnormalities in Mild Chronic Obstructive Pulmonary Disease. Implications for Dyspnea and Exercise Intolerance. *Am. J. Respir. Crit. Care Med.* **2015**, *191*, 1384–1394. [CrossRef] [PubMed]
4. O'Donnell, D.E. Hyperinflation, dyspnea, and exercise inteolerance in in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2006**, *3*, 180–184.
5. O'Donnell, D.E.; Revill, S.M.; Webb, K.A. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2001**, *164*, 770–777. [CrossRef] [PubMed]
6. O'Donnell, D.E.; Webb, K.A. Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. *Am. Rev. Respir. Dis.* **1993**, *148*, 1351–1357. [CrossRef]
7. Guenette, J.A.; Chin, R.C.; Cory, J.M.; Webb, K.A.; O'Donnell, D.E. Inspiratory Capacity during Exercise: Measurement, Analysis, and Interpretation. *Pulm. Med.* **2013**, *2013*, 956081. [CrossRef]
8. Casanova, C.; Cote, C.; De Torres, J.P.; Aguirre-Jaime, A.; Marin, J.M.; Pinto-Plata, V.; Celli, B.R. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2005**, *171*, 591–597. [CrossRef]
9. Chuang, M.L.; Huang, S.F.; Su, C.H. Cardiovascular and respiratory dysfunction in chronic obstructive pulmonary disease complicated by impaired peripheral oxygenation. *Int. J. Chron. Obstruct. Pulm. Dis.* **2015**, *10*, 329–337. [CrossRef]
10. Mahut, B.; Chevalier-Bidaud, B.; Plantier, L.; Essalhi, M.; Callens, E.; Graba, S.; Gillet-Juvin, K.; Valcke-Brossollet, J.; Delclaux, C. Diffusing capacity for carbon monoxide is linked to ventilatory demand in patients with chronic obstructive pulmonary disease. *COPD* **2012**, *9*, 16–21. [CrossRef]
11. Chuang, M.L.; Hsieh, M.J.; Lin, I.F. Developing a New Marker of Dynamic Hyperinflation in Patients with Obstructive Airway Disease—An observational study. *Sci. Rep.* **2019**, *9*, 7514. [CrossRef]
12. GOLD Committees. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (revised 2015). *Disclosure Forms for GOLD Committees Are Posted on the GOLD Website.* Available online: www.goldcopdorg (accessed on 31 July 2015).
13. Chuang, M.L.; Lin, I.F.; Lee, C.Y. Clinical assessment tests in evaluating patients with chronic obstructive pulmonary disease—A cross-sectional study. *Medicine* **2016**, *95*, e5471. [CrossRef]
14. Chuang, M.L.; Lin, I.F. Investigating the relationships among lung function variables in chronic obstructive pulmonary disease in men. *PeerJ* **2019**, *7*, e7829. [CrossRef] [PubMed]
15. Chuang, M.L.; Lin, I.F.; Wasserman, K. The body weight-walking distance product as related to lung function, anaerobic threshold and peak VO2 in COPD patients. *Respir. Med.* **2001**, *95*, 618–626. [CrossRef] [PubMed]
16. Graham, B.L.; Steenbruggen, I.; Miller, M.R.; Barjaktarevic, I.Z.; Cooper, B.G.; Hall, G.L.; Hallstrand, T.S.; Kaminsky, D.A.; McCarthy, K.; McCormack, M.C.; et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am. J. Respir. Crit. Care Med.* **2019**, *200*, e70–e88. [CrossRef] [PubMed]
17. Quanjer, P.H.; Stanojevic, S.; Cole, T.J.; Baur, X.; Hall, G.L.; Culver, B.H.; Enright, P.L.; Hankinson, J.L.; Ip, M.S.; Zheng, J.; et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *Eur. Respir. J.* **2012**, *40*, 1324–1343. [CrossRef] [PubMed]
18. Stanojevic, S.; Graham, B.L.; Cooper, B.G.; Thompson, B.R.; Carter, K.W.; Francis, R.W.; Hall, G.L. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur. Respir. J.* **2017**, *50*, 1700010. [CrossRef] [PubMed]
19. Chuang, M.L.; Lee, C.H.; Lin, I.F. Using the oxygen-cost diagram in ramp-slope selection for dyspneic patients. *Intern. Med.* **2010**, *49*, 1325–1332. [CrossRef]

20. Faisal, A.; Alghamdi, B.J.; Ciavaglia, C.E.; Elbehairy, A.F.; Webb, K.A.; Ora, J.; Neder, J.A.; O'Donnell, D.E. Common Mechanisms of Dyspnea in Chronic Interstitial and Obstructive Lung Disorders. *Am. J. Respir. Crit. Care Med.* **2016**, *193*, 299–309. [CrossRef]
21. O'Donnell, D.E.; Chau, L.K.; Webb, K.A. Qualitative aspects of exertional dyspnea in patients with interstitial lung disease. *J. Appl. Physiol.* **1998**, *84*, 2000–2009. [CrossRef]
22. Casaburi, R.; Rennard, S.I. Exercise limitation in chronic obstructive pulmonary disease. The O'Donnell threshold. *Am. J. Respir. Crit. Care Med.* **2015**, *191*, 873–875. [CrossRef]
23. Chuang, M.L.; Lin, I.F.; Vintch, J.R.E.; Ho, B.J.; Chao, S.W.; Ker, J.J.W. Significant exercise-induced hypoxaemia with equivocal desaturation in patients with chronic obstructive pulmonary disease. *Intern. Med. J.* **2006**, *36*, 294–301. [CrossRef]
24. Wasserman, K.; Hansen, J.E.; Sue, D.Y.; Stringer, W.W.; Whipp, B.J. Calculations, formulas, and examples. In *Principles of Exercise Testing and Interpretation*, 4th ed.; Wasserman, K., Ed.; Lippincot Williams & Wilkins: Philadelphia, PA, USA, 2005; pp. 556–565.
25. Tzani, P.; Aiello, M.; Elia, D.; Boracchia, L.; Marangio, E.; Olivieri, D.; Clini, E.; Chetta, A. Dynamic hyperinflation is associated with a poor cardiovascular response to exercise in COPD patients. *Respir. Res.* **2011**, *12*, 150. [CrossRef] [PubMed]
26. Vassaux, C.; Torre-Bouscoulet, L.; Zeineldine, S.; Cortopassi, F.; Paz-Díaz, H.; Celli, B.R.; Pinto-Plata, V.M. Effects of hyperinflation on the oxygen pulse as a marker of cardiac performance in COPD. *Eur. Respir. J.* **2008**, *32*, 1275–1282. [CrossRef]
27. Zhang, Y.; Sun, X.G.; Yang, W.L.; Tan, X.Y.; Liu, J.M. Inspiratory fraction correlates with exercise capacity in patients with stable moderate to severe COPD. *Respir. Care.* **2013**, *58*, 1923–1930. [CrossRef] [PubMed]
28. Chuang, M.L.; Lin, I.F.; Huang, S.F.; Hsieh, M.J. Patterns of Oxygen Pulse Curve in Response to Incremental Exercise in Patients with Chronic Obstructive Pulmonary Disease—An Observational Study. *Sci. Rep.* **2017**, *7*, 10929. [CrossRef] [PubMed]
29. Xu, Y.; Yamashiro, T.; Moriya, H.; Tsubakimoto, M.; Tsuchiya, N.; Nagatani, Y.; Matsuoka, S.; Murayama, S. Hyperinflated lungs compress the heart during expiration in COPD patients: A new finding on dynamic-ventilation computed tomography. *Int. J. Chron. Obstruct. Pulm. Dis.* **2017**, *12*, 3123–3131. [CrossRef] [PubMed]
30. O'Donnell, D.E.; Webb, K.A. The major limitation to exercise performance in COPD is dynamic hyperinflation. *J. Appl. Physiol.* **2008**, *105*, 753–755, discussion 755–757. [CrossRef] [PubMed]
31. Guenette, J.A.; Webb, K.A.; O'Donnell, D.E. Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? *Eur. Respir. J.* **2012**, *40*, 322–329. [CrossRef]
32. O'Donnell, D.E.; Elbehairy, A.F.; Berton, D.C.; Domnik, N.J.; Neder, J.A. Advances in the Evaluation of Respiratory Pathophysiology during Exercise in Chronic Lung Diseases. *Front. Physiol.* **2017**, *8*, 82. [CrossRef]
33. Vogiatzis, I.; Georgiadou, O.; Golemati, S.; Aliverti, A.; Kosmas, E.; Kastanakis, E.; Geladas, N.; Koutsoukou, A.; Nanas, S.; Zakynthinos, S.; et al. Patterns of dynamic hyperinflation during exercise and recovery in patients with severe chronic obstructive pulmonary disease. *Thorax* **2005**, *60*, 723–729. [CrossRef]
34. Miller, A. Diffusing capacity for CO. In *Pulmonary Function Tests in Clinical & Occupational*, 4th ed.; Miller, A., Ed.; Grune & Stratton, Inc.: Orlando, FL, USA, 1986; pp. 133–159.
35. Paoletti, P.; De Filippis, F.; Fraioli, F.; Cinquanta, A.; Valli, G.; Laveneziana, P.; Vaccaro, F.; Martolini, D.; Palange, P. Cardiopulmonary exercise testing (CPET) in pulmonary emphysema. *Respir. Physiol. Neurobiol.* **2011**, *179*, 167–173. [CrossRef]
36. Miniati, M.; Catapano, G.A.; Monti, S.; Mannucci, F.; Bottai, M. Effects of emphysema on oxygen uptake during maximal exercise in COPD. *Intern. Emerg. Med.* **2013**, *8*, 41–47. [CrossRef] [PubMed]
37. Andersson, M.; Stridsman, C.; Rönmark, E.; Lindberg, A.; Emtner, M. Regional blood flow during periodic acceleration. *Respir. Med* **2015**, *109*, 1048–1057. [CrossRef] [PubMed]
38. Gore, S.; Blackwood, J.; Guyette, M.; Alsalaheen, B. Validity and Reliability of Accelerometers in Patients with COPD: A Systematic Review. *J. Cardiopulm. Rehabil. Prev.* **2018**, *38*, 147–158. [CrossRef]
39. Hirabayashi, G.; Ogihara, Y.; Tsukakoshi, S.; Daimatsu, K.; Inoue, M.; Kurahashi, K.; Maruyama, K.; Andoh, T. Effect of pressure-controlled inverse ratio ventilation on dead space during robot-assisted laparoscopic radical prostatectomy: A randomised crossover study of three different ventilator modes. *Eur. J. Anaesthesiol.* **2018**, *35*, 307–314. [CrossRef]

40. Diaz, O.; Villafranca, C.; Ghezzo, H.; Borzone, G.; Leiva, A.; Milic-Emili, J.; Lisboa, C. Breathing pattern and gas exchange at peak exercise in COPD patients with and without tidal flow limitation at rest. *Eur. Respir. J.* **2001**, *17*, 1120–1127. [CrossRef] [PubMed]
41. Diaz, O.; Villafranca, C.; Ghezzo, H.; Borzone, G.; Leiva, A.; Milic-Emil, J.; Lisboa, C. Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. *Eur. Respir. J.* **2000**, *16*, 269–275. [CrossRef] [PubMed]
42. Lewis, D.A.; Sietsema, K.E.; Casaburi, R.; Sue, D.Y. Inaccuracy of noninvasive estimates of VD/VT in clinical exercise testing. *Chest* **1994**, *106*, 1476–1480. [CrossRef] [PubMed]
43. Zimmerman, M.I.; Miller, A.; Brown, L.K.; Bhuptani, A.; Sloane, M.F.; Teirstein, A.S. Estimated vs actual values for dead space/tidal volume ratios during incremental exercise in patients evaluated for dyspnea. *Chest* **1997**, *106*, 131–136. [CrossRef]