Tidal volume expandability affected by flow, dynamic hyperinflation, and quasi-fixed inspiratory time in patients with COPD and healthy individuals

Ming-Lung Chuang[1,2] ⓘ

Abstract

Exertional dyspnea (ED) and impaired exercise performance (EP) are mainly caused by dynamic hyperinflation (DH) in chronic obstructive pulmonary disease (COPD) patients by constraining tidal volume expansion at peak exercise ($V_{T_{peak}}$). As $V_{T_{peak}}$ is the product of inspiratory time (T_{Ipeak}) and flow (V_T/T_{Ipeak}), it was hypothesized that $V_{T_{peak}}$ and $V_{T_{peak}}$/total lung capacity ($V_{T_{peak}}/TLC$) may be affected by T_{Ipeak} and V_T/T_{Ipeak}. Hence, the study investigated the (1) effect of T_{Ipeak} and V_T/T_{Ipeak} on $V_{T_{peak}}$ expansion, (2) factors associated with T_{Ipeak}, expiratory time (T_{Epeak}), V_T/T_{Ipeak}, and $V_{T_{peak}}/TLC$, and (3) relationships between V_T/T_{Ipeak} and $V_{T_{peak}}/TLC$ with ED and EP in COPD patients and controls. The study enrolled 126 male stable COPD patients and 33 sex-matched controls. At peak exercise, T_{Ipeak} was similar in all subjects (COPD versus controls, mean ± SD: 0.78 ± 0.17 s versus 0.81 ± 0.20 s, p = NS), whereas the COPD group had lower V_T/T_{Ipeak} (1.71 ± 0.49 L/s versus 2.58 ± 0.69 L/s, p < .0001) and thus the COPD group had smaller $V_{T_{peak}}$ (1.31 ± 0.34 L versus 2.01 ± 0.45 L, p < .0001) and $V_{T_{peak}}/TLC$ (0.22 ± 0.06 vs 0.33 ± 0.05, p < .0001). T_{Ipeak}, T_{Epeak}, and V_T/T_{Ipeak} were mainly affected by exercise effort, whereas $V_{T_{peak}}/TLC$ was not. T_{Epeak}, V_T/T_{Ipeak}, and $V_{T_{peak}}/TLC$ were inversely changed by impaired lung function. T_{Ipeak} was not affected by lung function. Dynamic hyperinflation did not occur in the controls, however, $V_{T_{peak}}/TLC$ was strongly inversely related to DH ($r = -0.79$) and moderately to strongly related to lung function, ED, and EP in the COPD group. There was a slightly stronger correlation between $V_{T_{peak}}/TLC$ with ED and EP than V_T/T_{Ipeak} in the COPD group ($|r| = 0.55$–0.56 vs 0.38–0.43). In summary, T_{Ipeak} was similar in both groups and the key to understanding how flow affects lung expansion. However, the DH volume effect was more important than the flow effect on ED and EP in the COPD group.

Keywords

Inspiratory time, tidal inspiratory flow, breathing pattern, dynamic hyperinflation, exertional dyspnea, exercise capacity, tidal volume and total lung capacity ratio

Key points

1. Inspiratory time at peak exercise (T_{Ipeak}) was related to exercise effort in both the COPD and control groups. T_{Ipeak} was not affected by lung function and was similar in all subjects. Thus, tidal volume expansion was flow dependent. T_{Ipeak} is the key to understanding that flow is also involved in lung expansion.

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2. Expiratory time at peak exercise (T_{Epeak}) and mean tidal inspiratory flow (V_T/T_{Ipeak}) were also related to exercise effort in the two groups. However, the relationships were reduced by impaired lung function.
3. Tidal volume at peak exercise and total lung capacity ratio (V_{Tpeak}/TLC), an inverse marker of dynamic hyperinflation (end-expiratory lung volume/TLC), occurred only in the COPD group and was related to exercise effort. There was a slightly stronger correlation between V_{Tpeak}/TLC with exertional dyspnea and exercise performance than V_T/T_{Ipeak} in the COPD group.

Introduction

Exertional dyspnea (ED) and exercise intolerance in patients with chronic obstructive pulmonary disease (COPD) can be caused by many factors, however it is most likely to be caused by dynamic lung hyperinflation (DH).[1] This has been attributed to the volume effect of DH in constraining the expansion of inspiratory capacity and inspiratory reserve volume (IRV),[2] in which it cannot be overcome by forced expiratory effort.[3] Hence, tidal volume (V_T) cannot expand normally. As V_T is a product of inspiratory time (T_I) and flow (or ventilation) (V_T/T_I), V_T may be affected accordingly.

Inspiratory muscles of COPD patients are usually weak as shown by maximal inspiratory pressure, and they need to make a similar effort to healthy individuals at peak exercise[3,4] to meet a given V_T. This effort has to be completed within a shortened T_I due to a conversely prolonged expiratory time (T_E) caused by expiratory flow limitation. In this context, power of the weak inspiratory muscles must be escalated to facilitate tidal inspiratory flow,[5] or a given level of V_T cannot be achieved. This scenario is detrimental, as inspiration is more energy consuming than expiration.[6] Therefore, getting air in rather than out too slowly is usually a problem in patients with COPD. In addition, different time constants (τ) of alveolar units due to heterogeneous distribution are critical to ventilation, as they cause a reduction in ventilation even though the static lung volumes are the same.[7] Thus, in addition to the effect of DH on ventilation and symptoms in patients with COPD, T_I and V_T/T_I may also be important factors.

However, T_I and T_E values have seldom or even not been reported, even though time ratios such as T_I and total breathing cycle time ratio (i.e. inspiratory duty cycle, IDC) and T_I and T_E ratio (I: E) have been reported.[2–4,8–14] Given that the ratios at rest and peak exercise are quite different between normal and COPD subjects,[2,5,8] they do not reveal T_I, and so changes in V_T/T_I cannot be deduced from these reports.[4,8,9,12,14] Nevertheless, most variables of interest have been reported during the expiratory phase, such as τs

for alveolar units, spirometry, and expiratory flow limitation during exercise.[13,15,16]

T_{Ipeak} has been shown to have clinical value in patients with COPD before and after lung transplantation.[5] We hypothesized that reduced V_T/T_{Ipeak} with normal T_{Ipeak} in patients with COPD compared to healthy individuals may partially explain the reduced expansion of V_{Tpeak} and decreased V_{Tpeak}/total lung capacity (V_{Tpeak}/TLC). To test this hypothesis, we investigated differences between healthy individuals and patients with COPD at peak exercise in (1) V_{Tpeak} expansion affected by T_{Ipeak} (time effect) and/or V_T/T_{Ipeak} (flow effect), and (2) the factors associated with T_{Ipeak}, T_{Epeak}, V_T/T_{Ipeak}, and V_{Tpeak}/TLC, and compared (3) the relationships between V_T/T_{Ipeak} and V_{Tpeak}/TLC with ED and exercise performance (EP).

Methods

Study design

This was an observational cross-sectional comparative study. Lung function testing and cardiopulmonary exercise testing were performed. Signed informed consent was obtained from each participant, and the local Institutional Review Board (CS2-21018) approved this study.

Subjects

The study enrolled healthy and COPD subjects from this institution. The inclusion criteria were: (1) age 40–80 years; (2) body mass index 18–30 kg/m^2; and (3) male sex. Only male subjects were enrolled because few females have COPD in Taiwan.

Participants with COPD had respiratory symptoms, risk factors and a post-bronchodilator forced expired volume in one second (FEV_1)/forced vital capacity (FVC) of < 0.7 and no significant post-bronchodilator effect (increase in FEV_1 >12% and 200 mL from baseline) in accordance with the Global Initiative for Chronic Obstructive Lung Disease criteria.[17] All patients were clinically stable for 1 month prior to undergoing the tests. Patients were excluded if they had significant comorbidities including electrolyte imbalance, congestive heart failure, diabetes mellitus or significant chronic diseases or had participated in any physical training program before entry of this study.

Healthy subjects were recruited among the hospital staff and the local community through personal contacts. They were free of known significant acute and chronic diseases and were excluded if they had abnormal lung function, complete blood cell and biochemical tests, chest radiography, or electrocardiography during the screening phase of study.

Protocols and measurements

Pulmonary function testing. FEV_1, total lung capacity (TLC), and residual volume (RV) were measured by spirometry and body plethysmography. The best of three technically satisfactory readings was used, where it included acceptable back-extrapolated volume, a sharp peak of expiratory curve which occurred close to the start of expiration, acceptable end of forced expiration (i.e. expiratory time $\geq$ 6 s or a plateau of expiration curve reached), and reproducibility of the expiratory curve.[18] All lung function data were obtained after inhaling 400 µg of fenoterol HCl. Diffusing capacity of lung for carbon monoxide (D_LCO) was measured by the single-breath technique. Maximum inspiratory and expiratory pressures (MIP and MEP) were both performed on three occasions. The best result was recorded for analysis.

Cardiopulmonary exercise testing. After 3-min rest period, each patient began a 3-min period of unloaded cycling followed by a ramp-pattern exercise test to the limit of their tolerance. Work rate was selected at a slope of 5–20 W/min according to pre-determined fitness.

Twelve-lead electrocardiography, heart rate, oxyhemoglobin saturation (S_PO_2), oxygen uptake ($V'O_2$, ml/min), carbon dioxide output (ml/min), V'_E (L/min), breathing frequency (B_f, breath/min), and T_I and T_E in seconds were measured. The modified Borg scores were obtained every 2 minutes during the loaded exercise. Borg measured at peak exercise was divided by peak $V'O_2$% predicted to scale dyspnea.[19]

Maximum exercise is considered achieved by either one of the following: (1) heart rate reserve is 15% or 15 beats/min of predicted maximal heart rate or less; predicted maximum heart rate = 220 – age; (2) respiratory exchange ratio is 1.09 or greater.[20,21] Breathing reserve (BR) of < 30%, where BR = $1-V'_E$/MVV (maximum voluntary ventilation)[22] and a decrease in S_PO_2 by $\geq$3% from unloading to peak exercise[23] were also considered to indicate maximal effort, as these criteria indicate that physiological limitations had been reached by the COPD subjects. For comparisons between two groups of subjects during exercise, exercise stage was set at the same level. Thus, the exercise stages were at rest, unloaded, AT if determinate, and peak exercise. Exercise effort was defined as to what extent the level of maximum exercise was achieved at symptom-limited peak exercise, i.e. the higher the exercise effort, the more the maximum exercise criteria or the higher the exercise intensity achieved.

Dynamic inspiratory capacity measurement.[24] Dynamic inspiratory capacity (IC) was measured at the end of a steady-state resting baseline, unloaded cycling, the middle of loaded exercise, and the end of peak exercise. End-expiratory lung volume (EELV) was calculated as TLC minus dynamic IC.

Statistical analysis

The raw data as the file "Supplement data" was uploaded. Data was summarized as mean ± standard deviation. Unpaired-t test or Wilcoxon rank-sum test was used to compare the means or medians of the two sets of data of two patient groups when appropriate. Bivariate relationships were described by Pearson's correlation coefficients. All statistical analyses were performed using NCSS statistical software. Statistical significance was set at a two-sided $p \leq 0.05$.

Results

A total of 126 participants with COPD and 33 normal controls were enrolled after excluding 50 subjects with reasons shown in Figure 1. The COPD group was older and more symptomatic and had poorer lung function (Table 1) and exercise capacity than the controls as expected (Table 2).

Comparisons of the COPD group and control group at peak exercise showed that T_I was similar (p = NS), T_E was greater (p = .01), V_T/T_I was slower (p < .0001), V_T and V_T/TLC were smaller (both p < .0001), and EELV/TLC was greater (p < .0001) (Table 2 and Figure 2). When the COPD group was separated into subjects with a resting IC % predicted < 80% and those with a resting IC % predicted $\geq$ 80%, the former group had higher EELV/TLC (p < .01) and lower V_T/TLC (p < .01) and V_T/T_I (p < .01) at peak exercise (Table 3).

T_{Ipeak} and T_{Epeak} were related to exercise effort in all subjects, however, both relationships were weaker in the COPD group (Table 4). In contrast, T_{Ipeak} was not related to lung function in any of the subjects, however, T_{Epeak} was significantly related to impaired lung function (|r| = 0.25–0.53, all $p \leq$ .01).

V_T/T_{Ipeak} was not related to lung function or ED in the controls, however V_T/T_{Ipeak} was related to lung function and ED in the COPD group (Table 5). V_T/T_{Ipeak} was strongly related to exercise effort (r = 0.56–0.95) in the controls, however the correlations were reduced in the COPD group (r = 0.39–0.86). V_T/T_{Ipeak} was not related to RSBI and V_{Tpeak}/TLC in the controls, however it was related to RSBI and V_{Tpeak}/TLC in the COPD group (|r| = 0.39–0.60). Interestingly, V_T/T_{Ipeak}, V_T/T_{Epeak}, and minute ventilation were strongly inter-related in all subjects (r = 0.71–0.98).

Volume expansion at peak exercise/TLC was not related to lung function, ED or exercise effort in the controls, however all of these correlations were significant in the COPD group (Table 6, |r| = 0.47–0.79, all p < .001). In comparisons of the correlations of V_{Tpeak}/TLC and V_T/T_{Ipeak} with ED and VO_{2peak}% in the COPD group, V_{Tpeak}/TLC was mildly higher than V_T/T_{Ipeak} (Tables 5 and 6, |r| = 0.55 and 0.56 vs 0.38 and 0.43).
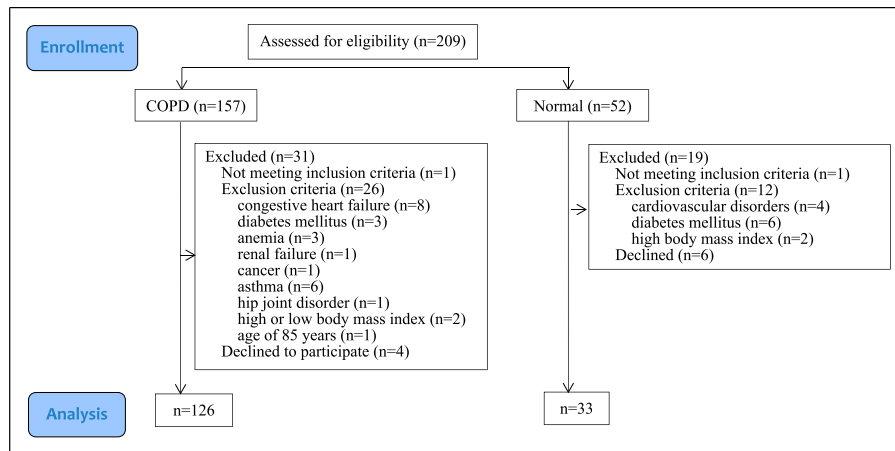
Figure 1. Flow chart. A total of 209 subjects were assessed for eligibility. 126 subjects with chronic obstructive pulmonary disease (COPD) and 33 healthy subjects were enrolled. All of the participants with COPD had respiratory symptoms, risk factors and a post-bronchodilator forced expired volume in one second (FEV_1)/forced vital capacity (FVC) of < 0.7 without a significant post-bronchodilator effect. Healthy subjects were recruited among the hospital staff and the local community through personal contacts. They were free of known significant diseases. A total of 50 subjects were excluded due to the reasons shown. For details about the inclusion and exclusion criteria of the participants, please refer to the text.

Discussion

The study found that T_{Ipeak} was similar in the COPD and control groups, whereas V_{Tpeak} and V_{Tpeak}/TLC were larger in the control group, suggesting that V_T/T_{Ipeak} plays a role in lung expansion during exercise (flow effect). Nevertheless, V_{Tpeak}/TLC decreased in the COPD group as $EELV_{peak}/TLC$ increased (volume effect of DH) only in the COPD group. T_{Epeak}, V_T/T_{Ipeak} and V_{Tpeak}/TLC were related to ED and exercise capacity in the COPD group, whereas the associations with V_{Tpeak}/TLC were stronger (Tables 4−6). In the control group, V_{Tpeak}/TLC was not related to ED or exercise capacity because they did not have DH. The associations of T_{Epeak}, V_T/T_{Ipeak}, and V_{Tpeak}/TLC with lung function were stronger in those whose lung function was impaired. T_I, T_E, $V'O_2$, V'_E, V_T/T_I, B_f, RSBI, BR%, and V_T at peak exercise were exercise effort-related variables in the controls (Tables 4−5); however, the associations were weaker in those whose lung function was impaired.

Volume expansion at peak exercise was related to T_I in all subjects, however the correlation was stronger in the controls, in whom V_T expandability was not influenced by a reduced flow or DH effect as the healthy individuals were assumed to have normal lung volumes and flow. In contrast, it was more related to flow than T_{Ipeak} in the COPD group (Tables 4 and 5, V_{Tpeak} correlated with T_{Ipeak}, r = 0.27 versus V_{Tpeak}/TLC correlated with V_T/T_{Ipeak}, r = 0.60) due to the deranged lung pathophysiology − the flow effect. All subjects had a similar T_{Ipeak} (approximately 0.8 s − the time effect), and thus V_T and V_{Tpeak}/TLC were smaller in the COPD group (Figure 2). Nevertheless, V_{Tpeak}/TLC in the COPD group was also constrained by the elevated EELV/

TLC, resulting in a smaller V_{Tpeak}/TLC − the volume effect (Table 6, r = −0.79).

Although the prolonged T_E caused by expiratory flow limitation may have shortened T_I in the COPD group,[5] T_I was similar to and B_f was lower than the values in the controls (Figure 2 and Table 2). This is in contrast to a previous study which reported that T_I was shorter and B_f was similar.[2] This discrepancy may be because the COPD patients in the previous study had lower FEV_1% (37% versus 56.5%) and B_f at peak exercise (30.7 vs 36.4 breaths/min), and because the normal control group contained female participants (40% versus 0%).[2] However, regardless of the difference in T_{Ipeak} in the COPD patients between these two studies, V_T/T_{Ipeak} was even lower, and thus V_{Tpeak} was also lower.[2] However, in another study comparing 11 patients with mild COPD and 11 matched normal subjects, T_I and V_T/T_I at peak exercise were similar between the two groups, whereas V_T was different.[25] The paradoxical relationships across the three factors raises concerns about a type II error. Therefore, T_{Ipeak} and V_T/T_{Ipeak} can provide additional information to DH with regards to constraining V_{Tpeak} expandability in COPD patients, especially for those with moderate to severe COPD. Elevated V_D/V_T plays a role in patients with mild COPD, as V_T/T_{Ipeak} can increase and V_{Tpeak} compensates to allow normal expansion.[25]

Despite the value of T_I in pulmonary mechanics, breathing-related times i.e. B_f, T_I, T_E, total cycle time, I:E ratio, and IDC have seldom been reported together in one study,[2–4,8–14] and therefore the underpinning pathophysiology may be overlooked. Hyperoxia improves ED not only by decreasing ventilatory demand and DH,[8] but also by decreasing B_f.[8,14] The decrease in B_f may prolong T_I, and thus V_T would be

Table 1. Demographic, lung function, blood tests, and peak exercise data in the subjects with COPD and normal controls.

	COPD (n = 126)		Control (n = 33)		p value
	Mean	SD	Mean	SD	
Age, years	68.1	7.8	61.8	9.0	≤.001
Height, cm	164.7	5.6	166.7	5.2	.06
Body mass index, kg/m^2	22.8	3.2	24.8	2.7	≤.01
Cigarette smoke, p-y	52.0	28.3	2.9	9.7	<.0001
Oxygen-cost diagram, cm	7.1	1.3	8.3	1.0	<.0001
mMRC§, A.U.	1		0		<.0001
CAT, A.U.	6.0	6.9	0.5	1.0	<.0001
hs-CRP, mg/dL	1.99	3.99	0.16	0.23	≤.01
Lung function					
MIP% predicted, %	62.0	16.8	NA	NA	NA
MEP% predicted, %	51.5	16.9	NA	NA	NA
PEFR% predicted, %	49.0	21.2	104.0	18.2	<.0001
FEV$_1$% predicted‖, %	56.5	18.4	102.7	12.8	<.0001
FEV$_1$/FVC, %	52.9	11.4	79.8	5.7	<.0001
TLC% predicted, %	114.5	22.6	97.2	10.6	<.0001
RV/TLC, %	55.7	9.5	38.7	6.4	<.0001
IC% predicted, %	79.5	24.2	104.5	18.6	<.0001
FRC% predicted, %	136.5	33.6	96.0	16.2	<.0001
D$_L$CO% predicted, %	76.3	24.5	106.2	15.4	<.0001

Abbreviations: CAT, COPD assessment test; DLCO, diffusing capacity of lung for carbon monoxide; EELV: end-expiratory lung volume; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FRC: functional residual capacity; hs-CRP, high-sensitivity C reactive protein; IC, inspiratory capacity; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; mMRC, modified Medical Research Council; PEFR, peak expiratory flow rate; RV: residual volume; TLC, total lung capacity. NA: not applicable. ‖COPD GOLD I, *n* = 10 (7.9%), GOLD 2, *n* = 71 (56.3%), GOLD 3–4, *n* = 45 (35.7%). §using Mann–Whitney U test. Comparison between groups,

Table 2. Peak exercise data in the COPD subjects and normal controls.

	COPD (n = 126)		Control (n = 33)		p value
	mean	SD	Mean	SD	
Borg/V'O$_2$%, no unit	11.7	5.2	6.5	2.5	<.0001
V'O$_2$/kg, mL/min/kg	17.6	5.2	25.9	7.0	<.0001
V'O$_2$% predicted, %	68.7	19.8	91.6	19.3	<.0001
Work rate % predicted, %	75.5	26.1	115.5	23.2	<.0001
V'$_E$, L/min	43.4	12.9	71.4	19.9	<.0001
BR, no unit	0.01	0.30	0.39	0.15	<.0001
B$_f$, breath/min	33.3	6.0	36.4	10.3	<.05
T$_{TOT}$, s	1.86	0.33	1.78	0.51	.29
T$_I$, s	0.78	0.17	0.81	0.20	.45
T$_E$, s	1.10	0.24	0.97	0.34	≤.01
IDC, no unit	0.42	0.06	0.46	0.04	<0.0001
E:I, no unit	1.44	0.37	1.18	0.22	<.001
V$_T$/T$_I$, L/s	1.71	0.49	2.58	0.69	<.0001
V$_T$, L	1.31	0.34	2.01	0.45	<.0001
V$_T$/TLC, no unit	0.22	0.06	0.33	0.05	<.0001
EELV/TLC, no unit	0.63	0.11	0.48	0.09	<.0001
ΔIC, mL	−180.6	344.8	87.7	447.7	<.05
RSBI, breath/L	27.7	11.0	19.3	7.6	<.0001

Abbreviations: Bf: breathing frequency; Borg: Borg score; BR: breathing reserve; Δ: change between at peak exercise and baseline; EELV: end-expiratory lung volume; IC, inspiratory capacity; IDC: inspiratory duty cycle; RSBI: rapid shallow breathing index; TI: inspiratory time; TE: expiratory time; TLC, total lung capacity; TTOT: breathing cycle time; V'E: minute ventilation; V'O2, oxygen uptake; VT, tidal volume. Borg/VO2% indicating Borg measured at peak exercise divided by peak V'O2% predicted; BR indicating I − V'E/MVV; EELV/TLC indicating end-expiratory lung volume at peak exercise and TLC ratio; E:I indicating TE and TI ratio; IDC indicating TI and TTOT ratio; VT/TI indicating mean tidal inspiratory flow; VT/TLC indicating tidal volume at peak exercise and TLC ratio.
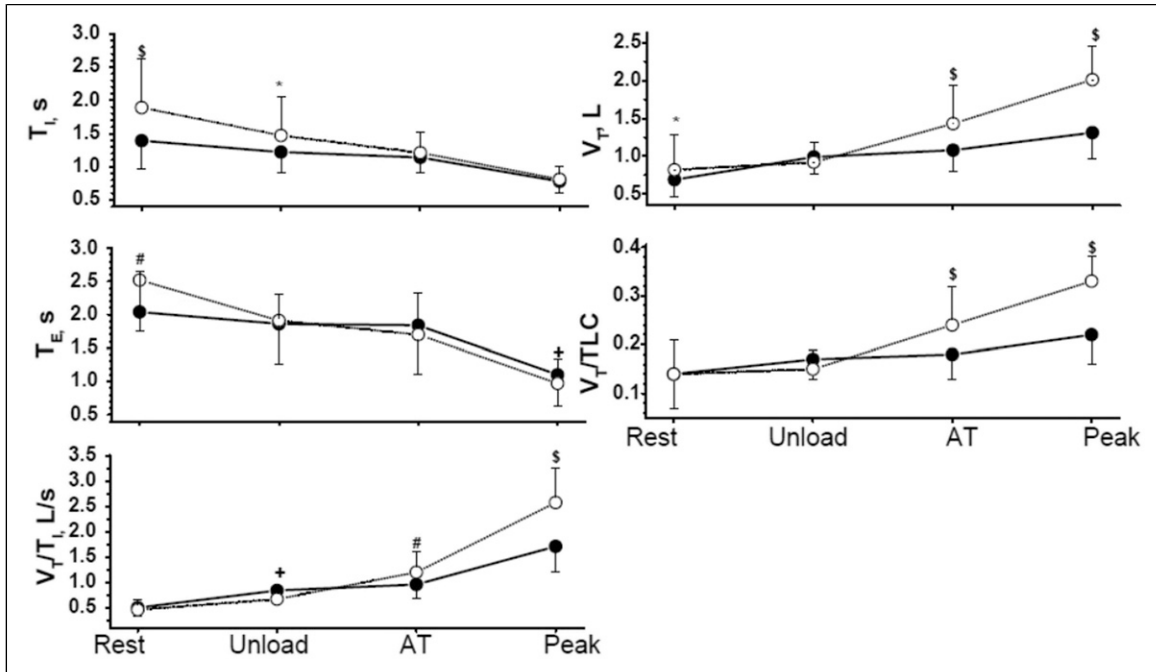
Figure 2. Mean values of expiratory time (T_E), inspiratory time (T_I), tidal volume (V_T), tidal inspiratory flow, V_T and total lung capacity ratio (V_T/TLC), and tidal inspiratory flow (V_T/T_I) in the healthy individuals (open circles) and subjects with chronic obstructive pulmonary disease (solid circles) in response to incremental exercise at rest, unloaded, anaerobic threshold, and peak exercise. The AT was indeterminate in 29 (23%) COPD subjects. Bars indicate standard deviations. No symbol, p = NS,* ≤0.05, + ≤0.01, # ≤0.001, $ ≤0.0001 for group comparison.

Table 3. The effects of resting inspiratory capacity (IC) on lung expandability and tidal inspiratory flow at peak exercise in the subjects with chronic obstructive pulmonary disease.

Group	IC < 80% (n = 69)		IC ≥ 80% (n = 57)		
	mean	SD	mean	SD	p value
EELV/TLC	0.69	0.07	0.54	0.08	<.01
V_T/TLC	0.22	0.05	0.26	0.05	<.01
V_T/T_I, L/s	1.69	0.42	2.06	0.5	<.01

Abbreviations: EELV/TLC, end-expiratory lung volume at peak exercise and total lung capacity ratio; V_T/TLC, tidal volume and TLC ratio; V_T/T_I, tidal volume and inspiratory time ratio indicating mean tidal inspiratory flow.

enlarged even with no change in V_T/T_I. Other studies on tiotropium and salmeterol have reported that improved V_{Tpeak} expansion was attributed to ameliorating DH.[9,12,14] However, improvement in V_T/T_{Ipeak} may also be involved, as B_f was unchanged and hence T_{Ipeak} was also probably unchanged, and thus V_{Tpeak} was increased.[9,12] Another study of patients with severe COPD reported that tiotropium prolonged T_I and did not change V_T at rest, thereby paradoxically reducing V_T/T_I.[26] However, during constant exercise, V_T/T_I was maintained and T_I was expected to be prolonged as B_f was slowed, resulting in an expansion of

V_T.[26] Moreover, changes in ED were correlated with a change in B_f (r = 0.70) but not with a change in IDC (r = 0).[27] As the intensity of exercise increases near heavy exercise (i.e. ≥70% of peak exercise capacity), V_T expansion flattens and critical minimal IRV is reached. However, these effects do not stop exercise immediately, and exercise can continue for a few minutes.[28] This has been reported to result in an "alinear" relationship between minimal IRV and ED. At this moment, increasing B_f shortens T_I and together with a plateaued V_T abruptly increases V_T/T_I. This indicates that an accelerated V_T/T_{Ipeak} at the start of minimal IRV underpins the mechanisms of ED. In other studies on breathing patterns in normal male and female subjects with different ages, V_T/T_I was quite different at different stages of ventilatory stress, however, IDC was not.[29] The standard deviation of IDC was very small (±0.01) in the previous studies of normal subjects and patients with chronic obstructive airway disease.[7,26,29] These results echo the value of V_T/T_I in the mechanisms of ED but not that of IDC (r = 0).[27] In summary, the mechanisms of V_T/T_{Ipeak} were different in the healthy individuals and COPD subjects. V_T/T_{Ipeak} was an exercise effort marker in the healthy individuals, whereas V_T/T_{Ipeak} was a marker of exercise effort, airflow patency, lung expandability, and less dyspnea in the COPD patients. In addition, non-invasive ventilation during exercise had some benefits in the patients with COPD, including

Table 4. Correlation coefficients (r) of inspiratory time (T_{Ipeak}) and expiratory time (T_{Epeak}) in seconds at peak exercise with lung function and exercise dyspnea and effort in subjects with COPD and normal controls.

r	T_{Ipeak}			T_{Epeak}		
	COPD	Control	$\Delta^{\parallel}$	COPD	Control	$\Delta^{\parallel}$
Lung function						
PEFR% pred, %	0.16	−0.04		−0.34†	−0.12	↑
FEV_1/FVC, %	0.14	0.02		−0.29+	−0.23	↑
FEV_1% pred, %	0.16	0.06		−0.42‡	−0.07	↑
Peak exertional dyspnea						
Borg/V'O$_2$%, no unit	−0.07	−0.11		0.25*	−0.26	↑
Peak exercise effort						
V'O$_2$% pred, %	0.02	−0.44+	↓	−0.24*	−0.38*	↓
V'$_E$, L/min	−0.18¶	−0.64‡	↓	−0.57‡	−0.60†	↓
V_T/T_I, L/s	−0.44‡	−0.64‡	↓	−0.28+	−0.42+	↓
B_f, br/min	−0.70‡	−0.93‡	↓	−0.87‡	−0.85‡	
RSBI, br/min/L	−0.50‡	−0.86‡	↓	−0.37‡	−0.77‡	↓
BR, %	0.29+	0.72‡	↓	0.04	0.66‡	↓
V_T, L	0.27+	0.43+	↓	−0.17¶	0.43+	↓

Abbreviations: Bf: breathing frequency; Borg: Borg score; BR: breathing reserve; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; RSBI: rapid shallow breathing index; V'E: minute ventilation; V'O2, oxygen uptake; peak: @ peak exercise; PEFR, peak expiratory flow rate; RBSI: rapid shallow breathing index; VT, tidal volume. % pred: %predicted. r without a symbol alongside indicates that the p value was not significant; || change (Δ) in r compared the normal group to the COPD group; ↓ decrease; ↑ increase; empty: no change; p .05 < ¶ ≤ 0.1, *≤0.05, +≤0.01, †≤0.001, ‡ < 0.0001.

Table 5. Correlation coefficients (r) of mean tidal inspiratory flow at peak exercise (V_T/T_{Ipeak}) with lung function, exertional dyspnea and exercise effort in subjects with COPD and normal controls.

r	V_T/T_{Ipeak}		
	COPD	Control	Change$^{\parallel}$
Lung function			
PEFR% predicted, %	0.46‡	0.30¶	↑
FEV_1/FVC, %	0.33†	−0.06	↑
FEV_1% predicted, %	0.38‡	0.16	↑
D_LCO% predicted, %	0.26+	0.08	↑
Peak exertional dyspnea			
Borg/VO$_2$%, no unit	−0.38†	−0.16	↑
Peak exercise effort			
V'O$_2$% predicted, %	0.43‡	0.56†	↓
V'$_E$, L/min	0.86‡	0.95‡	↓
V_T/T_E, L/s	0.71‡	0.87‡	↓
B_f, breath/min	0.39‡	0.67‡	↓
RSBI, breath/L	−0.39‡	0.28	↑
V_T/TLC, %	0.60‡	0.32¶	↑

Abbreviations: Bf: breathing frequency; DLCO: diffusing capacity of lung for carbon monoxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; peak: @ peak exercise; PEFR, peak expiratory flow rate; RSBI: rapid shallow breathing index; VT, tidal volume; TI, inspiratory time; V'E: minute ventilation; V'O2, oxygen uptake; % pred: %predicted; VT/TE: tidal expiratory flow. ||: change in r compared the normal group to the COPD group. r without a symbol alongside indicates that the p value was not significant, p .05 < ¶ ≤0.1, *≤0.05, +≤0.01, †≤0.001, ‡≤0.0001. VT/TE correlated with VE in the COPD group and the control group, r = 0.97 and 0.98, respectively.

Table 6. Correlation coefficients (r) of tidal volume at peak exercise and total lung capacity ratio (V_{Tpeak}/TLC) — inverse dynamic hyperinflation with the variables of interest in subjects with COPD and normal controls.

r	V_{Tpeak}/TLC		
	COPD	Control	Change$^{\parallel}$
Lung function			
PEFR% predicted, %	0.64‡	0.07	↑
FEV_1% predicted, %	0.61‡	−0.02	↑
TLC% predicted, %	−0.47‡	−0.02	↑
RV/TLC, %	−0.57†	−0.07	↑
D_LCO% predicted, %	0.48‡	−0.23	↑
Peak exertional dyspnea			
Borg/V'O$_2$%, no unit	−0.56‡	−0.04	↑
Peak exercise effort			
V'O$_2$% predicted, %	0.55‡	0.20	↑
V'$_E$, L/min	0.75‡	0.29¶	↑
EELV/TLC, %	−0.79†	−0.23	↑

Abbreviations: DLCO: diffusing capacity of lung for carbon monoxide; EELV: end-expiratory lung volume; FEV1, forced expiratory volume in one second; peak: @ peak exercise; PEFR, peak expiratory flow rate; RV: residual volume; TLC, total lung capacity; V'O2: oxygen uptake; V'E: minute ventilation; r without a symbol alongside indicates that the p value was not significant, p .05 < ¶ ≤ 0.1, *≤ 0.05, +≤ 0.01, †≤ 0.001, ‡≤ 0.0001. ||change of r in the COPD group compared to the controls. ↓: decreased; ↑: increased

unloading work of breathing and overcoming auto-positive end-expiratory pressure.[30] Thus, V_T/T_{Ipeak} may play a role when assessing the effects of bronchodilators[9,12,26] and using non-invasive ventilation.

Volume expansion at peak exercise/TLC has been reported to be an inverse marker of DH, i.e. $EELV_{peak}/TLC$ in patients with COPD (r = −0.83, $p < .0001$),[31] which is consistent with our results (Table 6, r = −0.79, $p < .0001$). However, they were not related in the normal controls because DH did not develop,[31] so that V_{Tpeak}/TLC did not play a role in either EP or ED. However, this marker played a role in the COPD group, which is consistent with previous studies.[1,2,25] Volume expansion at peak exercise/TLC is a beneficial marker for lung expansion, and thus it was moderately to strongly and positively related to FEV_1%, D_LCO%, and V_T/T_{Ipeak} and moderately to strongly and negatively related to TLC%, RV/TLC%, $EELV_{peak}/TLC$ in this study. Volume expansion at peak exercise/TLC is much easier to obtain than EELV/TLC, which requires IC maneuvers for EELV. However, one concern is that TLC may be underestimated in patients with COPD if dilution and washout techniques are used to assess functional residual capacity (FRC).[32] In this study, FRC was measured with body plethysmography, so that TLC would not be underestimated or overestimated when the subjects panted at a rate < 60/min.[32]

Lastly, resting IC < 80% predicted may be a marker of lower lung expandability, tidal inspiratory flow, and higher dynamic hyperinflation (DH) (Table 3).

Study limitations

The number of cases was still small in this study despite being larger than those in previous studies. In addition, female subjects were excluded from this study, and further studies are warranted to investigate any sex-related differences. The inclusion criterion for age was 40–80 years. Because of the wide range of ages, the age of the study group was higher than the controls. In addition, although MIP and MEP were not measured in the normal controls, they may be considered to be normal.[4] The criteria of maximum exercise used in the current study[20] are different from previous reports.[33] We used a BR value of < 30% in the current study, whereas previous reports have used a value < 15%. In addition, we used an respiratory exchange ratio value of ≥ 1.09 compared to ≥ 1.05 in previous reports and a heart rate ≥ 85% compared to 100% in previous reports. However, there is currently no gold standard to define maximal effort.[33]

Conclusion

In addition to the volume effect of DH on tidal volume expandability in the COPD group, the similar T_{Ipeak} in the normal and COPD groups is key to understanding the pathophysiology that tidal inspiratory flow is another mechanism of lung expandability. Although the mechanisms of lung expandability are not clear in healthy individuals (probably exercise effort related), breathing time and flow in relation to exercise effort in healthy individuals may be weakened by impaired lung function. Tidal volume expandability was mildly higher than tidal inspiratory flow in relation to ED and EP in the COPD group.

Authors' contributions

M.L.C. wrote the main manuscript text and prepared figures 1–2. All authors reviewed the manuscript.

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Abbreviations

B_f breathing frequency

BR   Breathing reserve = $1 - V'_E/MVV$

COPD   chronic obstructive pulmonary disease

DH   dynamic hyperinflation

D_LCO diffusing capacity of lung for carbon monoxide

ED   exertional dyspnea

EP   exercise performance

EELV/TLC   end-expiratory lung volume and total lung capacity ratio

FEV_1 forced expired volume in one second

FRC   functional residual capacity;

FVC   forced vital capacity

hs-CRP   high-sensitivity C reactive protein

IC   inspiratory capacity

IDC   inspiratory duty cycle

IE T_I and T_E ratio

IRV   inspiratory reserve volume

MEP   maximal expiratory pressure

MIP   maximal inspiratory pressure

MVV   maximum voluntary ventilation

RSBI   rapid shallow breathing index

RV   residual volume

T_I inspiratory time

T_E expiratory time

TLC   total lung capacity

V'_E minute ventilation

$V'O_2$ oxygen uptake

V_T tidal volume

V_T/T_I mean tidal inspiratory flow

V_T/T_E mean tidal expiratory flow

V_{Tpeak}/TLC tidal volume at peak exercise and TLC ratio