

Dynamics of chest wall volume regulation during constant work rate exercise in patients with chronic obstructive pulmonary disease

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Abstract

This study evaluated the dynamic behavior of total and compartmental chest wall volumes [V_{CW}] = rib cage (V_{RC}) + abdomen (V_{AB})] as measured breath-by-breath by optoelectronic plethysmography during constant-load exercise in patients with stable chronic obstructive pulmonary disease. Thirty males (GOLD stages II-III) underwent a cardiopulmonary exercise test to the limit of tolerance (T_{lim}) at 75% of peak work rate on an electronically braked cycle ergometer. Exercise-induced dynamic hyperinflation was considered to be present when end-expiratory (EE) V_{CW} increased in relation to resting values. There was a noticeable heterogeneity in the patterns of V_{CW} regulation as EEV_{CW} increased non-linearly in 17/30 "hyperinflators" and decreased in 13/30 "non-hyperinflators" ($P < 0.05$). EEV_{AB} decreased slightly in 8 of the "hyperinflators", thereby reducing and slowing the rate of increase in end-inspiratory (EI) V_{CW} ($P < 0.05$). In contrast, decreases in EEV_{CW} in the "non-hyperinflators" were due to the combination of stable EEV_{RC} with marked reductions in EEV_{AB} . These patients showed lower EIV_{CW} and end-exercise dyspnea scores but longer T_{lim} than their counterparts ($P < 0.05$). Dyspnea increased and T_{lim} decreased non-linearly with a faster rate of increase in EIV_{CW} regardless of the presence or absence of dynamic hyperinflation ($P < 0.001$). However, no significant between-group differences were observed in metabolic, pulmonary gas exchange and cardiovascular responses to exercise. Chest wall volumes are continuously regulated during exercise in order to postpone (or even avoid) their migration to higher operating volumes in patients with COPD, a dynamic process that is strongly dependent on the behavior of the abdominal compartment.

Key words: Exertion; Lung mechanics; COPD; Dyspnea; Exercise test

Introduction

Dynamic hyperinflation has a key mechanistic role in breathlessness and exercise intolerance in patients with chronic obstructive pulmonary disease (COPD) (1). Several studies have demonstrated the presence of a critical lung volume at which the elastic work of breathing sharply increases exertional dyspnea, thereby reducing exercise capacity (2-4). These data indicate that downward regulation of the chest wall volume (V_{CW}) is of foremost importance to allow longer exercise durations in these patients.

Evidence in this regard, however, has been mostly gathered from discrete measurements of inspiratory capacity (IC) during exercise to estimate end-tidal volumes (2-4).

Although this approach has provided important physiological insights (as reviewed in Ref. 5), it lacks information concerning the individual behaviors of the V_{CW} compartments [i.e., rib cage (V_{RC}) and abdomen (V_{AB})] (6-11). This is of practical importance since the work of breathing and the respiratory sensations during exercise are strongly influenced by rib cage-abdominal interactions in patients with COPD (6,7,10). In addition, changes in operating lung volumes are estimated from a small number of end-tidal measurements (typically every 2 min) (2-5), thereby precluding a more precise analysis of their time course (kinetics) throughout the exercise bout.

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In this context, optoelectronic plethysmography (OEP) has the advantage of carrying out continuous monitoring of the dynamic behavior of total and regional V_{CW} during exercise (8,9). This method measures breath-by-breath changes in end-inspiratory (EI) and end-expiratory (EE) V_{CW} , V_{RC} and V_{AB} , thereby providing a high-density set of data points, which might be amenable to kinetic analysis. This is likely to provide clinically relevant information, especially during high-intensity, constant work rate exercise test at the limit of tolerance (Tlim), a test format that has been widely used to assess the effects of pharmacological and non-pharmacological interventions in COPD. Assuming, therefore, that any strategy aimed to postpone near-maximum V_{CW} (i.e., a critically reduced inspiratory reserve volume) is likely to be advantageous for these patients (2-5), we tested the following hypotheses: i) dyspnea scores would be higher and Tlim lower in patients with faster kinetics and/or larger increases in EIV_{CW} (and vice versa) and ii) occasional reductions in EEV_{AB} (6,7,10) - conceivably due to the recruitment of expiratory muscles (12-16) - would reduce and slow the increases in V_{CW} thereby being beneficial to breathlessness and exercise tolerance in these patients.

The main objective of this study, therefore, was to assess the magnitude and the time course of changes in total and compartmental chest wall volumes by OEP during high-intensity, constant work rate exercise to Tlim in patients with moderate-to-severe COPD.

Subjects and Methods

Subjects

Thirty males with stable COPD [forced expiratory volume in 1 s (FEV_1) / forced vital capacity <0.7 and post-bronchodilator FEV_1 <60% predicted] presenting a long history of smoking (>20 pack-years) and chronic breathlessness (Medical Research Council scores >2) were enrolled. Main exclusion criteria were: recent exacerbation (within 1 month), long-term oxygen therapy, or arterial oxygen saturation <85% at rest, and treatment with oral corticosteroids and anti-histaminics. The study was approved by the Institutional Medical Ethics Committee (Comitê de Ética em Pesquisa do Hospital São Paulo, São Paulo, SP, Brazil) and all subjects gave written informed consent to participate.

Measurements

Pulmonary function tests. Spirometric tests were performed using a calibrated pneumotachograph (CPF System™, Medical Graphics Corporation - MGC, USA). Residual volume (in L) and total lung capacity (TLC in L) were measured with a constant-volume body plethysmograph (Elite System™, MGC). The single breath transfer factor for carbon monoxide (DL_{CO} in $mL \cdot min^{-1} \cdot mmHg^{-1}$) was measured using the 1085D System™ (MGC). Reference values for these tests were those previously obtained for the adult Brazilian population (17-19).

Exercise tests. Cardiopulmonary exercise tests were performed on an electromagnetically braked cycle ergometer (Corival 400, Lode B.V., The Netherlands) with breath-by-breath variables being measured with a commercially available metabolic cart (CardiO₂ System™, MGC). Subjects initially performed a symptom-limited ramp incremental test (10 W/min) to obtain peak work rate. On a different day, they underwent a Tlim at 70-80% peak work rate, which was preceded by 1 min of unloaded pedaling. During these tests, the following data were recorded as mean of 15 s: oxygen uptake ($\dot{V}O_2$ in L/min), carbon dioxide output ($\dot{V}CO_2$ in L/min), respiratory exchange ratio, minute ventilation ($\dot{V}E$ in L/min), tidal volume (VT in mL), breathing frequency, and inspiratory, expiratory and total respiratory time (in s). At baseline, patients were instructed after 3-4 regular tidal breaths to make maximal IC efforts from end-expiratory lung volume to TLC (2-4). Presence and degree of expiratory flow limitation were estimated by determining the fraction of VT in which tidal flow-volume loops met (or exceeded) the boundaries of the maximal flow-volume curve. Expiratory flow limitation was assumed to be present when at least 50% of the tidal breath satisfied these criteria (5). Oxyhemoglobin saturation was determined by pulse oximetry (in %; Nonin Medical, USA). Subjects were asked to rate their "shortness of breath" and "leg fatigue" at exercise cessation using the 0-10 Borg's category-ratio scale (20).

Chest wall volume measurements. Chest wall kinematics was measured by OEP as previously described (6-10). Briefly, the movement of 89 retro-reflective markers placed front and back over the chest wall from clavicles to pubis was recorded. The markers were positioned on approximately horizontal rows at the following levels: the clavicular line, the manubrio-sternal joint (angle of Louis), the nipples, the xiphoid process, the lower costal margin, the umbilicus, and the anterosuperior iliac crest. Surface landmarks for the vertical columns were: the midlines, both anterior and posterior axillary lines, the midpoint of the interval between the midline and the anterior axillary line, the midpoint of the interval between the midline and the posterior axillary line, and the midaxillary lines. Extra markers were added bilaterally at the midpoint between the xiphoid bone and the most lateral portion of the 10th rib, in the region overlying the lung-apposed ribcage, and in corresponding posterior positions. Each marker was tracked by six video cameras, three in front of the subject and three behind, operating at 60 frames/s and synchronized with co-axial infrared flashing LEDs. Subjects grasped handles positioned laterally to the cycle ergometer in order to lift their arms away from the rib cage so that lateral markers could be visualized. The 3-D coordinates of the markers were calculated with stereo-photogrammetry and linked with a mesh of triangles to create the surface embedding the trunk. The volume of the trunk enclosed by the surface was obtained through a computing algorithm based on the Gauss theorem (OEP System, BTS Bioengineering, Italy) (6-10).

As in most OEP studies involving patients with COPD (6,7,10,21), the chest wall was first modeled as being composed of two compartments - the rib cage and the abdomen ($V_{CW} = V_{RC} + V_{AB}$; see below the description of a *post hoc* analysis). V_{RC} was assumed to begin at the clavicular level and to terminate at the xiphisternum and lower costal margin. V_{AB} was measured down the costal margin to the anterior superior iliac crests. VT measured by OEP was calculated as the difference between end-inspiratory and end-expiratory V_{CW} ($EIV_{CW} - EEV_{CW}$). Inspiratory reserve chest wall volume was calculated as the difference between EIV_{CW} and TLC. All values are reported as “ Δ ” from resting end-expiratory lung volume (in L) and averaged for presentation at selected time points (rest, unload, mid-exercise, and at Tlim).

Data analysis

Before the kinetic analysis of the OEP data, raw EIV and EEV values of V_{CW} , V_{RC} and V_{AB} were individually reviewed for aberrant data points (>20% of the previous breath), with the remaining values being exponentially smoothed and expressed as 10-s moving averages. Considering that: a) a mono-exponential profile was not found in every test; b) higher-order models did not provide an adequate description of the responses in pilot experiments, and c) to minimize the potential effect of different test durations on the kinetics parameters (e.g., half-time), we obtained an index of the dynamics of chest wall compartments by calculating the fraction of end-exercise-resting volumes reached after an “isotime” of 150 s (t_{150} , %), i.e., higher Δ volume at t_{150} indicated faster volume responses.

In a *post hoc* analysis, we also investigated whether a paradoxical (inward) movement of the lower ribcage on inspiration would influence our main findings. This was performed by simultaneously comparing the time courses of changes in pulmonary rib cage (from the clavicular level to the xiphisternum), abdominal rib cage (from the xiphisternum to the lower costal margin), V_{AB} , and V_{CW} . Briefly, three reproducible consecutive breaths (i.e., between-breath variation in EIV_{CW} and EEV_{CW} within 10%) were randomly chosen near t_{150} and Tlim and were used to derive an “average” respiratory cycle. Inspiratory and expiratory phases of the breathing cycles were calculated from the V_{CW} signal. As previously suggested by Aliverti et al. (22), we defined the presence of the paradox when the inspiratory paradox time (the fraction of inspiratory time during which the abdominal rib cage volume decreased) at t_{150} and/or Tlim was larger than 20%.

Statistical analysis

If not otherwise stated, data are reported as means \pm SD in Tables and means \pm SEM for OEP data in Figures. Two-way analysis of variance (ANOVA) with repeated measures was used to identify significant between-group differences in Δ volumes at rest and Tlim. One-way ANOVA was performed to examine statistical differences in other variables at Tlim with appropriate Bonferroni's corrections for multiple comparisons.

Spearman's ρ was used for non-parametric correlation and non-linear regression (power function) was used to express the level of association between selected variables. For all analyses, a statistical significance of 0.05 was used.

Results

Population characteristics

On average, patients had moderate-to-severe airflow obstruction and reductions in DL_{CO} with increased static lung volumes. Twelve patients were classified as GOLD (Global Initiative for Obstructive Lung Disease) stage II (moderate COPD) and the remaining 18 patients as stage III (severe COPD). Responses at peak exercise were typical of COPD patients with such degrees of disease severity (Table 1).

Table 1. Resting and peak exercise characteristics of the sample.

Variables	(N = 30)
Demographic data/antropometry	
Age (years)	66.5 \pm 8.2
Body mass (kg)	68.8 \pm 12.0
Height (cm)	168.4 \pm 8.1
BMI (kg/m ²)	24.1 \pm 3.8
FVC (L)	2.96 \pm 0.72
FVC (% pred)	75.5 \pm 14.9
FEV ₁ (L)	1.27 \pm 0.34
FEV ₁ (% pred)	43.8 \pm 9.5
FEV ₁ /FVC	0.43 \pm 0.08
IC (L)	2.32 \pm 0.53
IC (% pred)	75.1 \pm 15.1
TLC (% pred)	110.5 \pm 12.9
RV (% pred)	180.2 \pm 23.0
DL_{CO} (% pred)	53.3 \pm 18.1
P_aO_2 (mmHg)	72.2 \pm 9.2
SaO_2 (%)	94.4 \pm 3.6
P_aCO_2 (mmHg)	36.2 \pm 4.7
Peak exercise	
Power (W)	70 \pm 14
$\dot{V}O_2$ (mL/min)	1184 \pm 312
$\dot{V}CO_2$ (mL/min)	1205 \pm 355
$\dot{V}E$ (L/min)	46.0 \pm 12.8
$\dot{V}E/MVV$ (%)	0.84 \pm 0.18
HR (bpm)	131 \pm 20

Data are reported as means \pm SD. BMI = body mass index; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 s; IC = inspiratory capacity; TLC = total lung capacity; RV = residual volume; DL_{CO} = lung diffusing capacity for carbon monoxide; P_aO_2 = oxygen partial pressure in arterial blood; SaO_2 = oxyhemoglobin saturation; P_aCO_2 = dioxide partial pressure in arterial blood; $\dot{V}O_2$ = oxygen uptake; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}E$ = minute ventilation; MVV = maximal voluntary ventilation; HR = heart rate.

Patterns of ventilatory kinematics during exercise

There was a noticeable heterogeneity in the patterns of V_{CW} regulation during exercise as EEV_{CW} increased non-linearly in 17/30 “hyperinflators” and decreased in 13/30 “non-hyperinflators” ($P < 0.05$). Amongst the “hyperinflators”, EEV_{AB} decreased slightly, albeit significantly, in 8 patients (group A) but remained stable in the remaining 9 subjects (group B). EEV_{RC} and EIV_{RC} increases were larger and faster in group A compared to group B (Figure 1 for representative patients and Figure 2 for mean data; Table 2). There were significant inverse relationships between the magnitude and the time course of EEV_{AB} and EEV_{RC} in group A ($r = -0.72$ and -0.80 , respectively; $P < 0.05$). There was a trend to a larger end-exercise EIV_{CW} in group A but only its rates of change was significantly faster than in group B (Figures 1 and 2, Table 2). Inspiratory paradox was found in a similar number of patients of both groups (Table 2).

In contrast, the “non-hyperinflators” (group C, $N = 13$) showed marked reductions in EEV_{AB} . This finding, in association with a mild increase in EEV_{RC} , led to a significant reduction of EEV_{CW} . In addition, group C showed the smallest and slowest increases in EIV_{RC} and EIV_{CW} (Figures 1 and 2, Table 2; $P < 0.05$). Inspiratory paradox was less frequently found in these patients compared to the other groups (Table 2).

Between-group comparisons of functional variables at rest

There were no significant between-group differences in resting functional variables or prevalence of GOLD stages (Table 3; $P > 0.05$). Of note, however, 7/8 of patients of group A and 7/9 of group B - but only 5/13 of group C - had

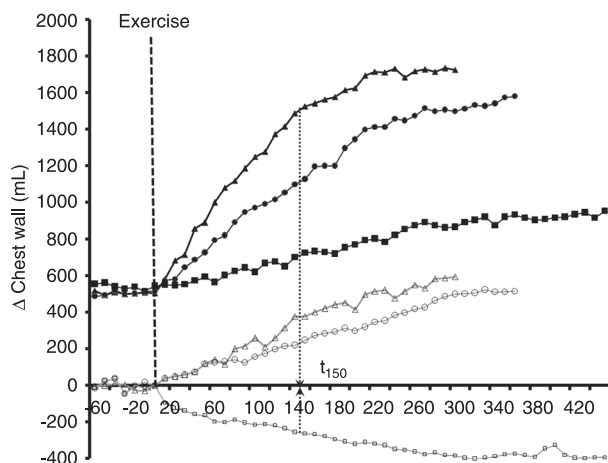


Figure 1. Time course of changes in end-inspiratory (closed symbols) and end-expiratory (open symbols) volumes of the chest wall in patients of groups A (triangles), B (circles) and C (squares). t_{150} is the exercise time elapsed after 150 s. Group A = “hyperinflators” with decreased EEV_{AB} ; group B = “hyperinflators” with stable EEV_{AB} ; group C = “non-hyperinflators”.

resting IC $< 80\%$ predicted, a cut-off value associated with more extensive expiratory flow limitation (EFL) during exercise (23). Resting EFL was also less frequently found in group C (Table 3).

Exercise tolerance and cardiopulmonary responses

The T_{lim} of group C was significantly higher compared to the other groups (Figure 2 and Table 2; $P > 0.05$). There were no significant between-group differences in metabolic, pulmonary gas exchange and cardiovascular responses to exercise (Table 2; $P > 0.05$). Dyspnea scores, however, were larger than leg effort ratings at T_{lim} in group A, whereas the opposite was found in group C (Table 2; $P < 0.05$). Interestingly, dyspnea increased and T_{lim} increased non-linearly as the kinetics of EIV_{CW} was faster in the whole sample (Figure 3; $P < 0.05$).

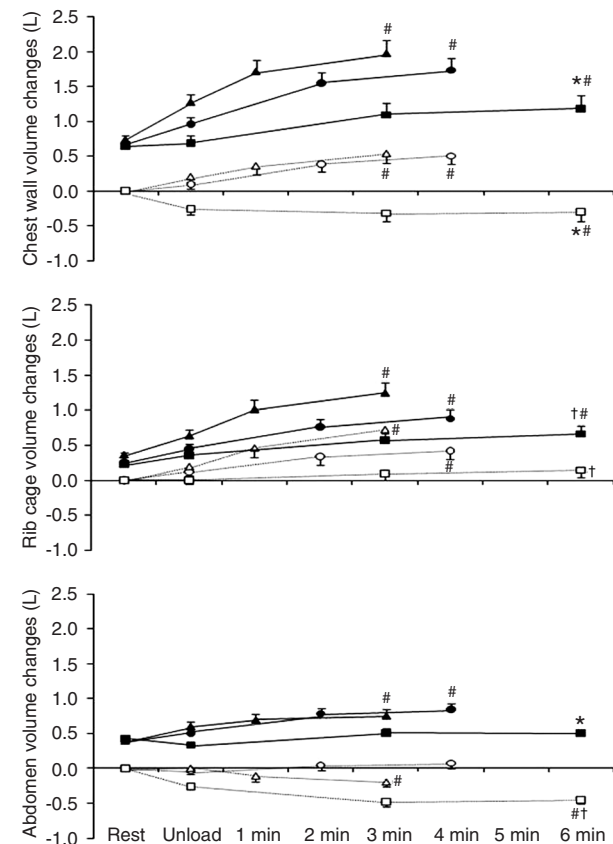


Figure 2. Changes in end-inspiratory (closed symbols) and end-expiratory (open symbols) volumes of the chest wall, rib cage and abdomen as a function of time during constant work rate exercise in patients of groups A (triangles), B (circles) and C (squares). Data are reported as means \pm SEM. Time points represent rest, unload pedaling, mid-exercise, and exercise cessation for each group. $P < 0.05$ (*group C vs groups A and B; †group A vs group B vs group C; #within-group differences from rest (two-way ANOVA with repeated measures). See Figure 1 for explanation of groups.

Table 2. Physiological responses to constant work rate exercise in chronic obstructive pulmonary disease patients showing different patterns of changes in compartmental chest wall volumes measured by optoelectronic plethysmography (OEP).

Variables	Group A (N = 8)	Group B (N = 9)	Group C (N = 13)
Power (W)	61 ± 11	63 ± 21	59 ± 13
Tlim (s)	318 ± 112 ^a	348 ± 94 ^a	462 ± 161 ^b
Metabolic			
$\dot{V}O_2$ (mL/min)	1026 ± 231	1023 ± 234	1002 ± 264
RER	1.02 ± 0.09	1.07 ± 0.10	1.06 ± 0.07
Ventilatory			
$\dot{V}E$ (L/min)	39.1 ± 9.8	40.2 ± 10.5	42.3 ± 14.4
VT (L)	1.22 ± 0.34	1.26 ± 0.27	1.42 ± 0.31
TI/TTOT	0.36 ± 0.03	0.37 ± 0.03	0.33 ± 0.03
VT/TI (L/s)	1.81 ± 0.45	1.82 ± 0.52	2.11 ± 0.63
VT/TE (L/s)	1.02 ± 0.27	1.07 ± 0.27	1.18 ± 0.41
Volume changes			
EIV _{CW}			
Δ (L)	1.24 ± 0.20 ^{*a}	1.06 ± 0.16 ^{*a}	0.53 ± 0.11 ^{*b}
t ₁₅₀ (% Δ)	68 ± 8 ^a	51 ± 10 ^b	36 ± 6 ^c
EEV _{CW}			
Δ (L)	0.53 ± 0.12 ^{*a}	0.50 ± 0.10 ^{*a}	-0.29 ± 0.12 ^{*b}
t ₁₅₀ (% Δ)	76 ± 6 ^a	57 ± 8 ^b	74 ± 10 ^a
EIV _{RC}			
Δ (L)	0.87 ± 0.14 ^{*a}	0.62 ± 0.13 ^{*b}	0.45 ± 0.09 ^{*c}
t ₁₅₀ (% Δ)	64 ± 7 ^a	48 ± 8 ^b	38 ± 7 ^c
EEV _{RC}			
Δ (L)	0.72 ± 0.10 ^{*a}	0.43 ± 0.11 ^{*b}	0.19 ± 0.10 ^c
t ₁₅₀ (% Δ)	79 ± 11 ^a	54 ± 7 ^b	65 ± 11 ^a
EIV _{AB}			
Δ (L)	0.36 ± 0.06 ^{*a}	0.44 ± 0.09 ^{*a}	0.07 ± 0.06 ^b
t ₁₅₀ (% Δ)	77 ± 9	74 ± 10	-
EEV _{AB}			
Δ (L)	-0.29 ± 0.02 ^{*a}	0.07 ± 0.06 ^b	-0.49 ± 0.06 ^{*c}
t ₁₅₀ (% Δ)	76 ± 8	-	73 ± 9
IRV _{CW} (L)	0.37 ± 0.29 ^a	0.45 ± 0.30 ^a	1.17 ± 0.70 ^b
P(+)/P(-)	4/4 ^a	4/5 ^a	2/11 ^b
Cardiovascular			
HR (bpm)	128 ± 18	130 ± 15	132 ± 20
O ₂ pulse (mL·min ⁻¹ ·beat ⁻¹)	8.4 ± 1.9	8.2 ± 1.5	7.5 ± 2.2
Oxygenation			
SpO ₂ (%)	95 (9)	92 (7)	94 (11)
Symptoms			
Dyspnea scores	8 (3) ^a	6 (3) ^b	5 (4) ^b
Leg effort scores	5 (6) ^a	6 (3) ^a	9 (4.5) ^b
Dyspnea-Leg effort scores	3 (4) ^a	0 (2) ^b	-3 (1.5) ^c

Data are reported as means ± SD, means ± SEM (for OEP data) or median (IQR). Group A = "hyperinflators" with decreased EEV_{AB}; group B = "hyperinflators" with stable EEV_{AB}; group C = "non-hyperinflators"; Tlim = limit of tolerance; $\dot{V}O_2$ = oxygen uptake; RER = respiratory exchange ratio; $\dot{V}E$ = minute ventilation; VT = tidal volume; TI, inspiratory time; TTOT = total respiratory time; TE = expiratory time; Δ = exercise-rest; EIV = end-inspiratory volume; EEV = end-expiratory volume; CW = chest wall; RC = rib cage; AB = abdominal; t₁₅₀ = at 150 s; IRV = inspiratory reserve volume; P = inspiratory paradox; HR = heart rate; SpO₂ = oxyhemoglobin saturation by pulse oximetry. *P < 0.05 compared to rest. Significant differences between groups (P < 0.05) are indicated by different superscript letters (a, b, c) (one-way ANOVA).

Discussion

The present study used OEP to determine the extent and to estimate the time course (kinetics) of V_{CW} ($V_{RC} + V_{AB}$) during constant work rate exercise to T_{lim} in patients with moderate-to-severe COPD. Apparently this seems to be the first report showing that, apart from the well-described inverse relationship between the magnitude of increase in EIV_{CW} (i.e., inspiratory reserve volume decrease) (2-4) and exercise tolerance, end-exercise dyspnea worsened and T_{lim} decreased non-linearly as the kinetics of EIV_{CW} became faster in patients who showed (groups A and B) or not (group C) chest wall hyperinflation (Figure 3). Reductions in EEV_{AB} were beneficial for these outcomes since they prevented fast and large increases in V_{RC} from being fully reflected into even-higher V_{CW} in selected "hyperinflators" (group A). In addition, larger decreases in EEV_{AB} were able to deflate the chest wall in the "non-hyperinflators" who showed stable V_{RC} , a finding associated with the highest exercise tolerance (group C). Collectively, therefore, our findings indicate that V_{CW} is continuously regulated during exercise in order to postpone (or even avoid) its migration to higher operating volumes in patients with COPD, a dynamic process that is strongly dependent on the behavior of the abdominal compartment.

Table 3. Resting characteristics of chronic obstructive pulmonary disease (COPD) patients separated by presence or absence of abdominal recruitment and chest wall hyperinflation determined by optoelectronic plethysmography.

Variables	Group A (N = 8)	Group B (N = 9)	Group C (N = 13)
General characteristics			
Age (years)	68.2 ± 8.4	68.2 ± 9.5	64.3 ± 7.1
BMI (kg/m ²)	22.4 ± 4.1	24.0 ± 4.2	25.2 ± 3.0
GOLD stage (II/III)	5/3	3/6	4/9
Spirometric			
FVC (% pred)	83.5 ± 17.1	76.6 ± 13.5	79.8 ± 12.8
FEV ₁ (% pred)	47.1 ± 11.3	45.7 ± 5.8	40.3 ± 9.8
FEV ₁ /FVC (%)	41.6 ± 8.4	44.5 ± 7.6	43.5 ± 9.4
SVC (%)	88.3 ± 15.9	83.0 ± 16.2	76.0 ± 16.6
EFL(+)/EFL(-)	6/2 ^b	7/2 ^b	4/9 ^a
Lung volumes			
IC (% pred)	73.5 ± 9.7	78.3 ± 17.0	73.4 ± 16.7
TLC (%)	111.8 ± 14.8	112.8 ± 17.8	107.8 ± 6.3
IC/TLC	0.30 ± 0.05	0.31 ± 0.03	0.32 ± 0.08
EELV/TLC	0.69 ± 0.05	0.68 ± 0.03	0.67 ± 0.08
RV (% pred)	186.8 ± 32.5	180.3 ± 30	176.5 ± 25.7
RV/TLC	0.52 ± 0.04	0.55 ± 0.04	0.52 ± 0.07
Lung diffusing capacity			
DL _{CO} (% pred)	46.5 ± 11.3	56.7 ± 21.9	54.7 ± 18.8

Data are reported as means ± SD. See Table 2 for explanation of groups. BMI = body mass index; GOLD stages II/III = Global Initiative for Chronic Obstructive Lung Disease in moderate/severe COPD; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 s; SVC = slow vital capacity; EFL = expiratory flow limitation; IC = inspiratory capacity; TLC = total lung capacity; EELV = end-expiratory lung volume; RV = residual volume; DL_{CO} = lung diffusing capacity for carbon monoxide. Significant differences between groups ($P < 0.05$) are indicated by different superscript letters (a, b, c) (one-way ANOVA).

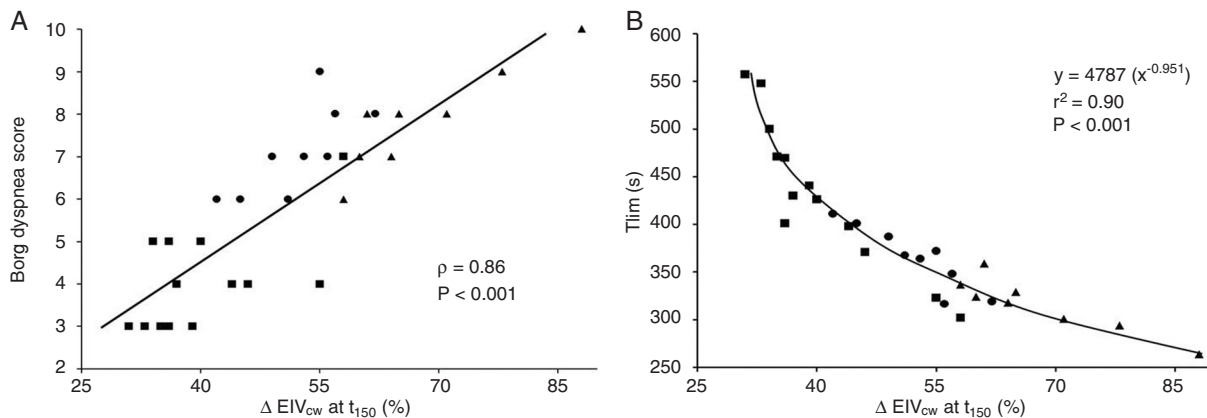


Figure 3. Relationship between end-exercise dyspnea (A) and exercise tolerance limit (T_{lim}) (B) with an index of the kinetics of end-inspiratory volume of the chest wall (EIV_{CW}) in patients of groups A (triangles), B (circles) and C (squares). t_{150} is the exercise time elapsed after 150 s. Spearman's ρ was used for non-parametric correlation in *Panel A* and non-linear regression (power function) in *Panel B*. See Figure 1 for explanation of groups.

The prevailing view is that EFL-induced dynamic hyperinflation is a key etiological mechanism of exertional breathlessness in patients with COPD (5,6). The results of the present study agree with this concept as patients in whom resting EFL was greater (groups A and B) showed larger increases in V_{CW} , which were related to higher dyspnea scores and lower $Tlim$. In contrast, those with less EFL (group C) had smaller increases in V_{CW} , were less prone to exhibit paradoxical (inward) movement of their lower ribcage on inspiration, reported leg effort as the main exercise-limiting symptom, and showed the highest $Tlim$ (Table 2).

OEP has a number of advantages over the traditional IC-based method to estimate the behavior of the operating lung volumes during exercise (2,3). It not only allows breath-by-breath tracking of these volumes but is also not dependent upon patients consistently reaching TLC. Moreover, it is unique as it continuously measures volume changes in the chest wall (V_{CW}) compartments, including those of the abdomen (6-8). Characterization of the dynamics of compartmental V_{CW} by OEP in the present study, therefore, provided incremental information to what was known in the field. Therefore, it became apparent that the time course of changes in V_{CW} differed markedly among individual patients, being non-linearly related to both dyspnea and exercise tolerance (Figure 3). It is interesting to note that previous studies have found that $Tlim$ decreases hyperbolically as a function of the power output (24) despite similar levels of end-exercise dyspnea and lung hyperinflation in patients with moderate-to-severe COPD (22). In the present study, it could be speculated that $Tlim$ decreased curvilinearly as a result of the selected work rates being placed at different points of the individual power-duration curves (24), with the patients reaching their sensory-mechanical "ceilings" at varying rates (25) (Figure 3). In other words, the rate at which these critical constraints were reached was a function of the absolute exercise intensity and the kinetics of V_{CW} . Although this hypothesis needs additional experimental evidence, our data indicate a crucial relevance of the time course at which the mechanical abnormalities develop during constant work rate exercise in patients with COPD.

As also reported in previous OEP studies, we identified two rather opposite patterns of V_{CW} regulation during exercise, i.e., groups A and B ("hyperinflators") vs group C ("non-hyperinflators") (6,7,10,21). However, some of these studies reported that continuous (6) or late exercise (10) decreases in EEV_{AB} were detrimental or not beneficial to maximal incremental exercise capacity in the "non-hyperinflators", respectively. These investigators assumed that the decreases in EEV_{AB} were causally linked to abdominal muscle recruitment, which might have increased the work of breathing and/or reduced the venous return (26,27). Our data suggest that if these deleterious phenomena did occur, they were counterbalanced by the positive effects of lower EEV_{AB} in reducing EIV_{CW} (Figures 1 and 2, Table 2). In addition, the frequency of inspiratory paradox was similar in groups A and B (and lower in group

C), which is not consistent with a dominant role for abdominal recruitment in this deleterious phenomenon. Apart from possible heterogeneities in patients' phenotypes (e.g., degree of emphysema and exercise-induced EFL), this discrepancy might stem from the use of different test paradigms (constant vs incremental exercise), which are associated with dissimilar patterns of ventilatory response. In fact, results of OEP studies with constant work rate exercise tests indicate that exercise tolerance was reduced as abdominal muscle recruitment decreased from GOLD stages I-IV (21); moreover, improved $Tlim$ after pulmonary rehabilitation was associated with larger decrements in EEV_{AB} (28). This issue, however, should be further evaluated by comparing the impact of abdominal muscle recruitment on maximal and submaximal exercise capacity in the same group of COPD patients presenting well-defined "physiological" phenotypes.

The present study has, naturally, some relevant limitations. Lack of gastric and esophageal pressure measurements did not allow measurements of the work of breathing and we acknowledge the descriptive - rather than mechanistic - nature of our investigation. The present authors, like others (6,7,10,21,28), have assumed that changes in EEV_{AB} were linearly related to abdominal muscle recruitment but to date there is no experimental evidence for this assertion. Additional studies are needed to relate the ventilatory kinematic findings to continuous (not only end-exercise) scores of breathlessness. As detailed in the Methods section, we were unable to perform a formal kinetic analysis due to response heterogeneity. However, since there were no differences in baseline volumes and the volumes behaved non-linearly (Figures 1 and 2), the chosen strategy (% Δ volume at t_{150}) is likely to have adequately described their rate of change. Finally, care should be taken to avoid extrapolation of our results to patients with more severe disease since the bulk of the evidence indicates that substantial decrements in EEV_{AB} are uncommon as disease progresses (10,29).

In conclusion, breath-by-breath analysis of ventilatory kinematics by OEP indicated that the extension and, in particular, the rate of increase in chest wall volumes were important determinants of exercise tolerance in patients with moderate-to-severe COPD. Reductions in abdominal volumes were generally beneficial as they blunted and slowed the increases in chest wall volumes in patients showing severe rib cage hyperinflation and deflated the chest wall in those with stable rib cage volumes. These data indicate the appropriateness of pharmacological and non-pharmacological interventions aimed at lessening the extent and slowing the dynamics of increase of chest wall volumes in this patient population.

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