

Chest wall volume regulation during exercise in COPD patients with GOLD stages

II to IV

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ABSTRACT

The present study investigated how end-expiratory rib cage and abdominal volume regulation during exercise is related to the degree of dynamic chest wall hyperinflation in patients with different spirometric severity of COPD based on the GOLD classification.

Forty-two COPD patients and eleven healthy age-matched subjects were studied during a ramp-incremental cycling test to the limit of tolerance (W_{peak}). Volume variations of the chest wall [at end-expiration (EEV_{cw}) and end-inspiration] and its compartments [rib cage (V_{rc}) and abdominal (V_{ab})] were computed by Optoelectronic Plethysmography.

At W_{peak} only patients in GOLD stages III and IV exhibited a significant increase in EEV_{cw} (by 454 ± 509 and 562 ± 363 ml, respectively). These patients did not significantly reduce end-expiratory V_{ab}, whereas patients in GOLD stage II resembled healthy subjects in that they significantly reduced end-expiratory V_{ab} (by 287 ± 350 ml). In patients, the greater the increase in EEV_{cw} at W_{peak} , the smaller were the reductions in end-expiratory V_{ab} ($r=0.76$; $p=0.0001$) and the greater was the increase in end-expiratory V_{rc} ($r=0.62$; $p=0.001$).

In COPD patients with different spirometric disease severity, greater degrees of exercise-induced dynamic chest wall hyperinflation are accompanied by lower degrees of end-expiratory abdominal volume displacement and larger increases in end-expiratory rib cage volume.

Key words: Exercise, COPD, Dynamic Hyperinflation, GOLD Stages.

INTRODUCTION

Exercise-induced dynamic hyperinflation refers to the temporary increase in end-expiratory lung volume above the baseline value that takes place not only in patients with moderate and severe COPD [1, 2] but also in patients with mild COPD [3], thereby limiting their exercise tolerance. Therapeutic interventions, such as bronchodilators [4, 5], oxygen supplementation [6, 7] and rehabilitative exercise training [8, 9] improve exercise tolerance by reducing the degree of dynamic hyperinflation. Measurement of operational lung volumes is, therefore, crucial in order to evaluate the effectiveness of these therapeutic interventions. Along this line, opto-electronic plethysmography (OEP) has become a very useful method because it assesses breath-by-breath volume variations of the total chest wall and its compartments (i.e. rib cage and abdominal) during exercise [1, 4, 9, 10].

Two recent studies by ALIVERTI *et al* [4] and GEORGIADOU *et al* [9] investigated the effects of bronchodilators and exercise training, respectively, on the chest wall volume regulation during exercise using the OEP method. They concluded that the changes seen in exercise-induced chest wall hyperinflation after these interventions were almost exclusively attributable to changes of the abdominal and not the rib cage

compartmental volumes. Interestingly, in the study by GEORGIADOU *et al* [9], the training-induced reduction in end-expiratory abdominal volume was significantly correlated with the improvement in exercise tolerance.

In addition, it has been documented that patients who progressively hyperinflate during exercise are not effective in reducing their end-expiratory abdominal volume, whereas those who delay or even avoid to increase end-expiratory chest wall volume with increasing exercise intensity exhibit significant reductions in end-expiratory abdominal volume [1,10]. Furthermore, in the recent study [4] documenting reductions in exercise-induced chest wall hyperinflation after bronchodilator therapy, the essential difference between those patients who improved their exercise tolerance (called improvers) and those who did not (called non-improvers) was in the degree of end-expiratory abdominal volume change; it was suggested a different degree of expiratory muscle recruitment between improvers and non-improvers [4]. Earlier reports on different patterns of expiratory muscle recruitment in patients with COPD were controversial [11, 12]. POTTER *et al* [11] suggested that in some patients, excessive recruitment of expiratory muscles during exercise may lead to dynamic airway compression thus limiting expiratory flow, whereas LEAVER and PRIDE [12] maintained that expiratory transthoracic pressures meet but do not exceed the critical closure pressure during exercise in COPD.

From the above it is apparent that the pattern of end-expiratory dynamic chest wall hyperinflation and its modulation during exercise depends on the regulation of end-expiratory abdominal volume [1, 4, 9, 10]. As previous studies [9-10] have suggested, the likelihood of exhibiting dynamic chest wall hyperinflation during exercise increases with

increasing lung disease severity, manifested by the greater degrees of resting airway obstruction [9, 10] and expiratory flow limitation [2, 3]. We therefore reasoned that in COPD patients with different lung disease severity, greater degrees of exercise-induced dynamic chest wall hyperinflation will be accompanied by lesser reductions in end-expiratory abdominal volume. The purpose of the present study was, therefore, to determine how end-expiratory abdominal volume regulation during exercise is related to the degree of dynamic chest wall hyperinflation in patients with different spirometric severity of COPD based on GOLD classification.

METHODS

Subjects

Forty-two patients (15 women) with clinically stable COPD who participated in the study fulfilled the following entry criteria: (1) post-bronchodilator $FEV_1 < 80\%$ predicted without significant reversibility ($<12\%$ change of the initial FEV_1 value or less than 200 ml), (2) optimal medical therapy according to GOLD [13], and (3) absence of other significant diseases that could contribute to exercise limitation. Twenty two of these patients had also participated in previous studies of our laboratory [1, 9]. Eleven age-matched healthy subjects (3 women) with $FEV_1 > 92\%$ predicted were also studied. Patients signed an informed consent that was approved by the University Ethics Committee.

Study design

COPD patients were classified into GOLD stages II, III and IV using post-bronchodilator spirometric criteria. The classification of severity was as follows: moderate COPD (stage II), $50\% \leq FEV_1 < 80\%$; severe COPD (stage III), $30\% \leq FEV_1 < 50\%$; and very severe COPD (stage IV), $FEV_1 < 30\%$. Patients who had previously participated in studies of our laboratory repeated the present study and were almost evenly distributed across the three GOLD stages (i.e., 7 patients in GOLD stage II, 7 patients in Stage III and 8 patients in GOLD stage IV). Healthy subjects were consecutively recruited from the local community on the basis of their age (i.e.: older than 55 years). Patients and healthy subjects were assessed for pulmonary function and underwent an incremental cycle exercise test to the limit of tolerance.

Pulmonary function assessment

Spirometry, and measurement of lung transfer factor for carbon monoxide (DL_{CO}) (Masterlab; Jaeger, Wurzburg, Germany) and lung volumes by body plethysmography

(Medgraphics Autolink 1085D, Medical Graphics, St' Paul, MN, USA) were performed according to recommended standards [14].

Exercise testing protocols

All subjects performed an incremental test with a ramp increase of load (increments of 5 or 10 watts for COPD and 15 or 20 watts for healthy every minute) to the limit of tolerance (W_{peak}) on an electromagnetically-braked cycle ergometer (Ergoline 800; Sensor Medics, Anaheim, CA, USA). The test consisted of 3 minutes of measurements at rest (R), followed by 3 minutes of unloaded pedalling. Throughout the exercise test subjects were encouraged to maintain a pedalling frequency of 60 revolutions per minute.

During the test flow rate at the mouth and gas exchange variables were recorded breath-by-breath (V_{max} 229; Sensor Medics, Anaheim, CA). Cardiac frequency (f_c) and percentage oxygen saturation ($SpO_2\%$) were determined using the R-R interval from a 12-lead on line electrocardiogram (Marquette Max; Marquette Hellige GmbH, Germany) and a pulse oximeter (Nonin 8600; Nonin Medical, USA), respectively. Subjects wore a nose-clip and breathed through a low dead space mouthpiece. Flow was measured with a hot wire pneumotachograph (V_{max} 229; Sensor Medics, Anaheim, CA; 70 ml dead space) near the mouthpiece, and lung volume changes were obtained by integrating the flow signal. A gas mixture (F_{I,O_2} : 0.26 balanced with Nitrogen) was inspired by all patients from a Douglas bag through a two-way non-rebreathing valve (model 2700, Hans Rudolph; 115 ml dead space) connected to the pneumotachograph. The flow into the Douglas bag was constant and patients breathed the gas mixture at the rate that they demanded. Avoiding desaturation during exercise was a key point of our protocol in order to exclude hypoxia and its variable effects on different patients. In addition, O_2 supplementation was

important in patients with GOLD stages III and IV in order to prevent severe arterial hypoxemia and hence premature cessation of exercise. Accordingly, we decided to supply O₂ to all patients studied to ensure that exercise would not need to be terminated prematurely due to arterial hypoxemia. Healthy subjects breathed room air through the mouthpiece and pneumotachograph. Symptom ratings were monitored every 2-min throughout exercise using the 1-10 Borg scale [15]. The V-slope technique was used to detect the oxygen uptake (V'O₂) at which the anaerobic threshold (AT) occurred [16]. The change in V'O₂ as a function of work rate ($\Delta V'O_2/\Delta WR$) was calculated as an index of aerobic work efficiency [17]. In addition, the oxygen pulse was calculated by dividing the V'O₂ by fc [17].

Chest wall volume and respiratory pressure measurements

Volumes of the total chest wall (V_{cw}) and its compartments, the rib cage (V_{rc}) and the abdomen (V_{ab}) were measured by opto-electronic plethysmography (OEP, BTS, Milan, Italy) as previously described [1, 4, 9, 10]. Throughout the test subjects were asked to maintain an upright posture while seated on the bicycle ergometer with a modified handle bar (similar to the one used by professional cyclists), so that the arms were kept away from the trunk while the hands were grasping the handle in order to make all markers visible. To obtain V_{cw} at total lung capacity (TLC_{cw}) during rest and exercise, subjects were asked to perform inspiratory capacity (IC) manoeuvres as previously described [1, 9,]. Flow limitation at rest and during exercise was determined by inspection of the tidal flow-volume loop in relation to the expiratory boundary of the maximal flow-volume curve as previously described [18]. The inspiratory reserve chest wall volume (IRV_{cw}) was calculated as the difference between the end-inspiratory V_{cw} (EIV_{cw}) and the

TLC_{cw}. IC was also measured by the OEP (IC_{OEP}) as the difference between TLC_{cw} and the end-expiratory volume of the chest wall (EEV_{cw}); the latter value was derived by averaging the EEV_{cw} over a period of 20-s prior to the IC effort [1, 9, 19]. IC_{OEP} values recorded during rest and exercise were compared to the corresponding IC values measured by the spirometer (IC_{SP}). From the breath-by-breath V_{cw} measurements, ventilatory and breathing pattern parameters were determined by calculating the average values during the time that data acquisition was performed by the OEP that was interrupted for 30 s every 2 min in order to allow safe data storage. Comparison of compartmental chest wall volumes and breathing pattern parameters at given ventilation were made over each of the data acquisition periods.

In 12 subjects [9 patients (3 patients of each stage) and 3 healthy subjects] swings in esophageal pressure (Pes), and gastric pressure (Pga) were continuously monitored during exercise. Pes and Pga were assessed by two commercially available thin-walled balloon catheters (Ackrad Laboratories, Inc, Cranford, NJ, USA) coupled to differential pressure transducers (MP-45, ± 250 cm H₂O; Validyne Corp., Northridge, CA, USA). Pressures and flow signals were synchronized to those of the motion analyzer and recorded by the same computer used for optoelectronic plethysmography (OEP system).

Statistical Analysis

Data are presented as mean \pm SD. Group comparisons at baseline characteristics were performed by one-way ANOVA. Two-way analysis of variance (ANOVA) with repeated measures was used to identify statistically significant differences in total and compartmental chest wall volumes across different time points during exercise between the four groups ANOVA was followed by the LSD (least significant difference) test for post-hoc analyses when necessary. For each GOLD stage and for the healthy group,

independent t-tests were applied to assess differences between IC values assessed at the limit of tolerance by the spirometer and the OEP method. Linear regression analyses were performed using the least square method. Qualitative variables were compared by Fisher's exact test. Stepwise multiple regression analysis established the best predictive equations for W_{peak} (dependent variable). Independent variables included resting lung function measurements, and peak exercise gas exchange and breathing pattern measurements and chest wall volume variations. Statistical significance was set at 0.05.

RESULTS

Baseline characteristics

Lung function data for the patients and the healthy subjects are shown in Table 1. Compared to GOLD stage II, COPD patients in GOLD stages III and IV had significantly lower FEV₁, FVC, FEV₁/FVC (%), forced expiratory flow between 25% and 75% of FVC (FEF₂₅₋₇₅), DL_{CO} (% pred) and IC, and significantly higher RV; patients in GOLD stage IV had also higher FRC compared to GOLD stage II. Patients in GOLD stage IV had lower FEV₁, FEV₁/FVC (%) and DL_{CO} (% pred) compared to patients in GOLD stage III. Expiratory flow limitation at rest was observed in 5 patients with GOLD stage II, 10 patients with GOLD stage III and all patients with GOLD stage IV.

Peak physiological responses

Compared to healthy subjects, COPD patients with stages II to IV exhibited an impaired exercise capacity (Table 2) as indicated by the lower W_{peak} (p=0.0001), peak V'O₂ (p=0.0001), and anaerobic threshold (p=0.004). Compared to GOLD stage III and II, patients with GOLD stage IV were characterised by greater impairment in W_{peak} (p=0.001), V'O₂ (p=0.001), oxygen pulse (p=0.004) and anaerobic threshold (p=0.02) that was discernible in all patients in GOLD Stage II, in 10/14 patients in GOLD Stage III and in 8/14 patients in GOLD Stage IV. (Table 2). At the limit of tolerance dyspnoea sensation in patients with GOLD stages III and IV was significantly greater compared to healthy subjects and stage II patients (Table 2). Healthy subjects experienced greater leg discomfort (p=0.011) compared to COPD patients with GOLD stages III and IV. The majority of patients with stages III and IV stopped exercise due to dyspnoea, whereas the

majority of GOLD stage II patients and healthy subjects terminated exercise due to leg discomfort ($p=0.03-0.001$), (Table 2).

In comparison to healthy subjects, COPD patients of all stages demonstrated at peak exercise lower ($p=0.001$) minute ventilation (V'_E), which was due to lower tidal volume (V_T) ($p=0.001$), as breathing frequency (f_b) did not differ ($p=0.677$) among groups (Table 3). Expiratory flow rate (V_T/T_E) was lower in COPD patients compared to healthy subjects; V_T/T_E was lower ($p=0.0001$) only in GOLD stage IV patients relative to GOLD stage II. V_T and inspiratory time (T_I) were significantly lower in GOLD stages III and IV relative to stage GOLD stage II. At the limit of tolerance expiratory flow limitation was present in 4 out of 11 healthy subjects, in 6 patients with GOLD stage II, in 12 patients with GOLD stage III and in all patients with GOLD stage IV.

Operational volumes and respiratory pressures during exercise

During incremental exercise a different pattern in operational chest wall volume regulation was observed between healthy and COPD groups (Fig 1). This difference in the pattern was mainly due to a significant difference ($p=0.0001$) in the end-expiratory and inspiratory reserve volumes from rest across the exercise time points. Accordingly, at the limit of tolerance in healthy subjects mean end-expiratory volume was decreased ($p=0.002$) by 339 ± 619 ml (Table 3; Fig 1, A). At the end of exercise the mean end-expiratory chest wall volume remained unchanged (Table 3; Fig 1, B), in patients with GOLD stage II. However, the response was variable among these patients since 4 of them increased end-expiratory volume by more than 200 ml and 3 by approximately 100 ml, whereas in the remaining 7 end-expiratory volume was either unchanged from rest or decreased by as much as 450 ml. The majority of patients (22 out of 28) in GOLD stage

III (n=10) and IV (n=12) exhibited a progressive increase in end-expiratory chest wall volume by more than 200 ml during exercise. At the limit of tolerance GOLD stage III and IV patients had a significant increase ($p=0.003$) in end-expiratory volume (by 454 ± 509 and 562 ± 363 ml, respectively) the magnitude of which differed significantly ($p=0.001$) from that in GOLD stage II (Table 3; Fig 1, B to D). The difference in end-expiratory volume between patients in GOLD stages III and IV compared to those in GOLD stage II was also reflected in the inspiratory capacity measured both in terms of spirometry and optoelectronic plethysmography (Table 3).

Volume constraints on tidal volume expansion at the limit of tolerance were significantly increased as disease severity classified by spirometry progressed compared to healthy subjects (Table 3; Fig 1). Indeed, IRV_{cw} in GOLD stages III and IV patients (221 ± 273 ml and 167 ± 322 ml, respectively) was significantly lower ($p=0.021$) compared to GOLD stage II patients (530 ± 467 ml) and healthy subjects (573 ± 374 ml) (Table 3; Fig 1, A to D).

The aforementioned differences in the end-expiratory chest wall volumes between groups were mainly attributable to changes in the end-expiratory abdominal volume, which was different ($p=0.003$) among the four groups across the various exercise levels (Fig 2, right panels). Post-hoc analysis showed that GOLD stage III and IV patients (Fig 2, right panels, C and D) differed ($p=0.002$) from GOLD stage II and healthy subjects (Fig 2, right panels, A and B), as the end-expiratory abdominal volume at the limit of tolerance in the former groups (GOLD stage III and IV) did not change from rest, whereas in the latter groups (GOLD stage II and healthy subjects) the end-expiratory abdominal volume was reduced ($p<0.05$) from rest by 287 ± 350 ml and 602 ± 724 ml,

respectively. This reduction in end-expiratory abdominal volume in healthy subjects was greater ($p=0.03$) compared to that in stage II patients. Considering data from COPD patients in all three stages, the changes from rest to the limit of tolerance in end-expiratory abdominal volume were correlated with the changes in end-expiratory chest wall volume ($r=0.76$; $p=0.0001$; SEE: 0.243). When considering data from all patients and healthy controls, the changes from rest to the limit of tolerance in end-expiratory abdominal volume were also correlated with the changes in end-expiratory chest wall volume ($r=0.84$; $p=0.0001$; SEE: 0.277).

Interestingly, only patients exhibited a progressive increase ($p=0.0001$) in end-expiratory rib cage volume (Fig 2, left panels) during exercise. Further statistical analysis revealed a significant interaction ($p=0.0001$) between factors (patient GOLD stage and exercise level) showing that the rate of increase in end-expiratory rib cage volume from rest differed between groups. In fact, during exercise the end-expiratory rib cage volume reached 578 ± 365 ml and 523 ± 311 ml for GOLD stages IV and III (Fig 2, left panels, C and D), respectively. Both were higher ($p=0.045$) than those for GOLD stage II (355 ± 323 ml) and healthy subjects (263 ± 271 ml) (Fig 2, left panels, B and A). End-expiratory rib cage volume at the limit of tolerance in stage II patients was not significantly higher than in healthy controls. In COPD patients of all stages, the changes from rest to the limit of tolerance in end-expiratory rib cage volume were correlated with the changes in end-expiratory chest wall volume ($r=0.62$; $p=0.001$; SEE: 0.330); in COPD patients combined with healthy controls, this correlation also existed ($r=0.44$; $p=0.002$; SEE: 0.483).

The end-inspiratory rib cage volume (Fig 2, *left panels*) was also increased ($p=0.0001$) from rest to peak exercise and was not different ($p=0.880$) among all groups (healthy:

1093±399 ml, GOLD stage II: 838±331 ml, stage III: 1017±406 ml, stage IV: 924±498 ml). Similarly, the end-inspiratory abdominal volume (Fig 2, *right panels*) rose ($p=0.001$) from rest to peak exercise and there was a significant difference ($p<0.05$) among patient groups and healthy controls (healthy: 944±534 ml, GOLD stage II: 753±381 ml, stage III: 814±327 ml, stage IV: 804±394 ml).

Figure 3 shows changes in end-expiratory and end-inspiratory total and compartmental chest wall volumes plotted as function of minute ventilation. For a given level of ventilation during the incremental exercise test, end-expiratory chest wall volume was greater in GOLD stages III and IV than in stage II, and it was also greater in GOLD stage IV than in stage III (Fig 3A). End-expiratory rib-cage volume in stage IV was greater than in stages II and III (Fig 3C). Furthermore, for given ventilation end-expiratory abdominal volume in GOLD stage II was significantly lower than in stage III (Fig 3E).

Figure 4 shows changes in breathing pattern variables plotted as a function of minute ventilation during exercise in patients with GOLD stages II and III. At a given ventilation, stage II patients exhibited significantly higher duty cycle (T_I/T_{TOT}) and mean expiratory flow rate (V_T/T_E).

Figure 5 shows end-expiratory Pga during exercise in a limited number of patients ($n=9$). During exercise, end-expiratory Pga was greater, albeit not significantly, in patients with GOLD stage II compared to patients with GOLD stages III and IV.

Correlates of exercise tolerance in COPD

Because W_{peak} in GOLD stage II patients was limited to the same extent as in GOLD stage III patients, we performed a stepwise multiple regression analysis to identify the variables that had an independent significant contribution to the variance of W_{peak} . The

combination of peak exercise oxygen pulse and leg discomfort explained 35% of the variance of W_{peak} in patients with GOLD stages II and III.

Comparison of OEP with spirometric data

There was a significant difference between IC values assessed by the spirometer and the OEP at the limit of tolerance only in GOLD stage II patients (Table 3). The interclass correlation coefficient between the inspiratory capacity assessed by spirometry and by the OEP method was 0.92 during exercise in patients and healthy subjects. The mean discrepancy between the two methods was 98 ± 76 ml or $4.7 \pm 1.7\%$.

DISCUSSION

The main findings of the study were the following: 1) Despite individual variability, patients in GOLD stages II to IV exhibited dynamic chest wall hyperinflation at the limit of exercise tolerance, and this dynamic hyperinflation increased with increasing lung disease severity. Patients in GOLD stages III and IV exhibited substantial increase in end-expiratory chest wall volume during exercise. These patients did not reduce end-expiratory abdominal volume during exercise, whereas patients in GOLD stage II resembled healthy subjects in that they significantly reduced end-expiratory abdominal volume. 2) In COPD patients of all three stages, the greater the increase in end-expiratory chest wall volume at the limit of tolerance, the smaller was the reduction in end-expiratory abdominal volume and the greater was the increase in end-expiratory rib cage volume. 3) Although GOLD stage II patients attenuated dynamic chest wall hyperinflation compared to GOLD stage III patients, peak exercise workload was limited to the same extent as in GOLD stage III. 4) At the limit of exercise tolerance, both GOLD stages III and IV were severely hyperinflated, but minute ventilation and exercise workload in GOLD stage IV patients were significantly less than in GOLD stage III.

The novel approach of this investigation is the partitioning of volume regulation between the rib cage and the abdominal compartments of the chest wall during exercise in COPD patients with different lung disease severity as classified by spirometry. Accordingly, it is suggested that in the early stages of the disease (GOLD stage II), where resting pulmonary hyperinflation (Table 1) and the incidence of expiratory flow limitation both at rest and exercise are lower compared to stages III and IV, expiratory muscle recruitment forces the end-expiratory abdominal volume to decrease during

exercise, thereby compensating for the small increase in end-expiratory rib cage volume (Fig 2B). In fact, this is the way normal subjects breathe during exercise. [20, 21] This strategy attenuates in most cases the progressive increase in end-expiratory chest wall volume and the occurrence of dynamic chest wall hyperinflation during exercise. Detailed analysis of chest wall volumes and breathing pattern parameters at iso-ventilation during exercise (Figs 3 and 4) confirmed that GOLD stage II patients managed to attenuate the substantial chest wall hyperinflation. The most likely explanation is that, since most of stage II patients did not exhibit expiratory flow limitation during exercise (8 out of 14 patients), expiratory abdominal muscle activity resulted in higher expiratory flow rates compared to stage III (Fig. 4D) and stage IV (Table 3) patients, thereby attenuating the substantial chest wall hyperinflation. Reduced chest wall hyperinflation in stage II yielded significantly greater duty cycle (Fig 4) compared to stage III.

With disease progression (stages III and IV) and the presence of expiratory flow limitation at rest and during exercise, expiratory muscle activation was ineffective in terms of reducing end-expiratory abdominal volume, thereby allowing end-expiratory chest wall volume to rise consequently to the progressive increase in end-expiratory rib cage volume (Fig 2C, D and Fig 3C, E). Measurement of end-expiratory gastric pressure in a fraction of patients (Fig 5) revealed a smaller increase in gastric pressure in stage III and IV compared to stage II patients. Hence, end-expiratory chest wall volume during exercise is modified differently in COPD patients with increasing lung disease severity as classified by spirometry, depending most likely on the degree of expiratory flow limitation and the regulation of both end-expiratory rib cage and abdominal volumes.

This argument is in line with the suggestion [22, 23] that in patients with severe COPD abdominal muscle recruitment is unlikely to have a significant impact on expiratory flow and end-expiratory lung volume and as such in energetic terms it would be advantageous not to use abdominal muscles.

Our original hypothesis was that in patients with different spirometric severity of COPD, greater degrees of exercise-induced dynamic chest wall hyperinflation would be accompanied by lesser reductions in end-expiratory abdominal volume. Our results confirm this hypothesis but also highlight the importance of the rib cage compartmental volume regulation as a contributing factor to dynamic chest wall hyperinflation. The observed progressive increase in end-expiratory rib cage volume during exercise, that was significantly greater in stages III and IV, might be mainly the result of more severe expiratory flow limitation, but also persistent post-inspiratory activity of inspiratory/accessory rib cage muscles, similar to that previously reported during acute bronchoconstriction in asthmatics [24], might contribute.

An additional novelty of the present study is the report of chest wall volume regulation in healthy age-matched subjects and the comparison of the breathing pattern between patients and healthy elderly individuals. Such a comparison revealed that patients with GOLD stage II adopt a similar breathing pattern to that of healthy patients as they both reduce end-expiratory abdominal volume during exercise, whilst exhibiting an increase in end-expiratory rib cage volume. Such an increase in end-expiratory rib cage volume is not observed in young healthy individuals [20]. Aging is known [25] to be associated with decreases in elastic recoil of the lung, chest wall compliance and respiratory muscle performance. Collectively these factors may account for the small end-expiratory rib cage

hyperinflation seen in our healthy elderly. On the other hand, there was a striking difference in the abdominal compartment, in which healthy subjects exhibited significantly greater increases in end-inspiratory volumes compared to COPD. The reason for this could potentially be related with beneficial lengthening of the diaphragm during active expiration [20]. Indeed, the greater reduction in end-expiratory abdominal volume in the healthy subjects compared to COPD patients during exercise (Fig 2, right panels) could likely be associated with increased diaphragm length, greater diaphragmatic power output and descend, and greater expansion of abdominal wall during inspiration [21] resulting in higher end-inspiratory abdominal volume in healthy subjects than in COPD patients. Nevertheless, at the limit of tolerance the inspiratory reserve chest wall volume in stage II patients (530 ml) and in healthy subjects (570 ml) remained higher than the “minimum” inspiratory reserve volume (350 ml) that is commonly taken to represent the inability to further expand tidal volume [2, 5, 7]. As such the main reason for terminating exercise in both groups was leg discomfort.

With further disease progression, manifested by further reduction in FEV₁ (GOLD stage III) and evidently more severe expiratory flow limitation both at rest and during exercise, end-expiratory abdominal volume displacement was minimal during exercise. (Figs 2C, 3E). Consequently, patients exhibited significant end-expiratory dynamic chest wall hyperinflation leading to a significant restriction on tidal volume expansion that was indicated by the minimal inspiratory reserve volume (221ml) at the limit of tolerance [2, 5, 7]. Interestingly, exercise performance was comparable between GOLD stages II and III (Table 2). Thus, the strategy of not reducing end-expiratory abdominal volume during exercise seemed to be effective in GOLD stage III patients. This finding is

in line with that by Aliverti et al [4] who showed that following bronchodilation patients who had better exercise performance were those patients who did not reduce end-expiratory abdominal volume, thus allowing end-expiratory chest wall volume to rise. In the small number of patients it was measured, end-expiratory gastric pressure was greater in patients with GOLD stage II compared to GOLD stage III (Fig 5). Greater activation of abdominal muscles allowed GOLD stage II to dynamically hyperinflate much less than stage III and IV and probably led those patients to stop exercise more from leg discomfort than dyspnoea (Table 2). High expiratory pressures during exercise in patients with COPD [10, 11, 26] and healthy subjects [27-28] can cause adverse circulatory events that ultimately may impair exercise performance. Under this condition high expiratory pressures during exercise in patients with GOLD stage II might have caused adverse circulatory effects that ultimately impaired exercise performance resulting in similar peak exercise tolerance in GOLD stages II and III (Table 2). In the present study the combination of peak exercise oxygen pulse and leg discomfort explained 35% of the variance of exercise tolerance (W_{peak}) in patients with GOLD stages II and III. Patients in GOLD stage II had more frequently leg discomfort and tended to have lower oxygen pulse (expressing the volume of oxygen extracted by the peripheral tissues with each beat - an index of stroke volume) compared to stage III patients. Inadequate oxygen supply to meet the metabolic demands of the limb muscles has been alleged to play a more dominant role in limiting exercise capacity in some patients with COPD than impaired lung function or dynamic hyperinflation [29-31].

Although at the severe end of the disease spectrum (GOLD stage IV) there was only a minimal non-significant worsening of dynamic chest wall hyperinflation compared to

GOLD stage III, exercise tolerance was significantly more impaired compared to that of patients in GOLD stage III. By plotting changes in end-expiratory and end-inspiratory total and compartmental chest wall volumes as a function of minute ventilation (Fig 3), it became evident that for a given level of minute ventilation during the incremental exercise test, end-expiratory chest wall volume in GOLD stage IV patients was greater than in GOLD stage III. At the limit of tolerance, although both GOLD stages were severely hyperinflated, minute ventilation in GOLD stage IV patients was significantly less than minute ventilation in GOLD stage III, thus explaining why exercise tolerance in GOLD stage IV patients was significantly more impaired than in GOLD stage III. In other words, both GOLD stages III and IV were severely hyperinflated at the limit of exercise tolerance and ventilatory limitation should be the main cause to quit exercise (also suggested by that dyspnoea was the most frequent symptom limiting exercise), but this hyperinflation occurred in much lower minute ventilation in GOLD stage IV patients thus resulting in significantly more impaired exercise tolerance in GOLD stage IV than in GOLD stage III patients.

The mean discrepancy ($4.7 \pm 1.7\%$ or 98 ± 76 ml) found in the present study between the IC measured by the spirometer and the OEP method during exercise in all subjects is similar to that previously reported in COPD [1]. With the exception of the IC measurements made at the limit of tolerance in GOLD stage II patients, the assessment of IC by the OEP method was in good agreement with that performed by the spirometer (Table 3). The discrepancy between the two methods of IC measurement found in GOLD stage II may be explained as follows. GOLD stage II patients used and activated their abdominal muscles (see gastric pressure in Figure 5) strongly and more than GOLD

stages III and IV, thus possibly producing substantial greater gas compression and blood shifts from trunk to limbs during expiration than stages III and IV [26]. During the subsequent inspiratory capacity manoeuvre the increase in chest wall volume (measured by OEP) was closely approximated not only by the volume of gas inspired (as that was the case with spirometry) but also by gas decompression and blood shifting [26]. This justifies the finding that IC measured by OEP was 150 ml greater compared to spirometry at the limit of tolerance in GOLD stage II patients. Presumably expiratory muscle activity in GOLD stages III and IV was not high enough to yield a significant difference between the two methods of IC measurement (Table 3). Although the magnitude of change in spirometric IC from rest to the limit of tolerance in stage II patients (280 ml) was within the range previously reported by O'DONNELL *et al* in such patients [32], the discrepancy between the two methods (OEP and spirometry) in IC measurements in GOLD stage II patients emphasizes the difference between dynamic pulmonary and chest wall hyperinflation, as the former reflects exclusively air trapping, whereas the latter manifests air trapping, blood shifting and gas compression. Nevertheless, OEP can provide important complementary information to the spirometric IC method as it allows concomitant assessment of volume variations of the rib cage and abdominal compartments during exercise in patients with COPD.

In conclusion, the present study shows that in COPD patients with different spirometric disease severity, greater degrees of airway obstruction, expiratory flow limitation and exercise-induced dynamic chest wall hyperinflation are accompanied by lower degrees of end-expiratory abdominal volume displacement and larger increases in end-expiratory rib cage volume.

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Table 1. Demographic and lung function characteristics of COPD patients and age-matched healthy subjects

	Healthy (n = 11)	GOLD Stage II (n = 14)	GOLD Stage III (n = 14)	GOLD Stage IV (n = 14)
Age, yr	61 ± 11	67 ± 7	64 ± 8	58 ± 7
Sex, m/f	8/3	8/6	9/5	10/4
Height, cm	161 ± 8	168 ± 8	165 ± 6	169 ± 9
Weight, kg	70 ± 13	77 ± 34	67 ± 8	68 ± 10
BMI, kg/m ²	26.6 ± 3.53	26.0 ± 4.16	24.8 ± 3.15	23.8 ± 2.46
FEV ₁ , L	3.12 ± 0.92	1.61 ± 0.35 *	1.11 ± 0.23 *†	0.71 ± 0.14 *†§
FEV ₁ , %pred	98 ± 13	61 ± 8 *	42 ± 4 *†	24 ± 3 *†§
FVC, L	4.26 ± 0.82	3.17 ± 0.69 *	2.63 ± 0.72 *†	2.61 ± 0.74 *†
FVC, %pred	106 ± 17	93 ± 14	80 ± 17 *†	69 ± 14 *†
FEV ₁ /FVC, %	75 ± 10	51 ± 6 *	44 ± 10 *†	28 ± 5 *†§
FEF _{25-75%} , L/s	2.73 ± 1.52	0.62 ± 0.27 *	0.36 ± 0.13 *†	0.24 ± 0.07 *†
FEF _{25-75%} , %pred	93 ± 51	26 ± 12 *	13 ± 5 *†	8 ± 4 *†
DL _{CO} , %pred	81 ± 38	61 ± 23 *	46 ± 14 *†	32 ± 12 *†§
TLC, L	6.16 ± 0.97	7.46 ± 1.15	6.98 ± 0.86	8.35 ± 1.82 *
TLC, %pred	97 ± 11	119 ± 12	117 ± 12	133 ± 22 *
FRC, L	3.22 ± 0.92	5.11 ± 0.73 *	5.19 ± 0.67 *	6.28 ± 1.14 *†
FRC, %pred	96 ± 12	153 ± 19 *	162 ± 14 *	196 ± 36 *†
RV, L	1.93 ± 0.77	3.88 ± 0.62 *	4.27 ± 0.70 *†	4.92 ± 0.98 *†
RV, %pred	88 ± 31	169 ± 27 *	186 ± 28 *†	244 ± 46 *†
IC, L	2.86 ± 0.91	2.15 ± 0.61 *	2.02 ± 0.38 *†	2.00 ± 0.89 *†
IC, %pred	92 ± 24	80 ± 16 *	65 ± 12 *†	66 ± 20 *†

Data are presented as mean ± SD. BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{25-75%}, mean forced expiratory flow between 25% and 75% of FVC; DL_{CO},

carbon monoxide lung transfer factor; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; IC, inspiratory capacity; * Significant difference ($p < 0.05$) with healthy; † Significant difference from GOLD stage II patients; § Significant difference from GOLD stage III patients.

Table 2. Exercise data at the limit of tolerance in COPD patients and age-matched healthy subjects

	Healthy (n = 11)	GOLD Stage II (n = 14)	GOLD Stage III (n = 14)	GOLD Stage IV (n = 14)
Workrate, W	120 ± 55	53 ± 20 *	55 ± 19 *	34 ± 15 *†§
Workrate, %pred	89 ± 32	50 ± 18 *	45 ± 13 *	26 ± 12 *†§
V'O ₂ , ml·kg ⁻¹ ·min ⁻¹	23.3 ± 7.1	14.3 ± 2.9 *	15.9 ± 2.8 *	11.6 ± 4.8 *†§
V'O ₂ , %pred	96 ± 16	71 ± 11 *	66 ± 19 *	44 ± 15 *†§
ΔV'O ₂ /ΔWR, ml·min ⁻¹ W ⁻¹	11.5 ± 2.3	10.9 ± 4.6	11.6 ± 2.2	12.7 ± 6.9
RER	1.12 ± 0.09	0.95 ± 0.10 *	0.98 ± 0.17 *	0.98 ± 0.13 *
fc, beats·min ⁻¹	140 ± 24	113 ± 19 *	110 ± 17 *	114 ± 12 *
fc, %pred	95 ± 36	76 ± 13 *	71 ± 11 *	71 ± 7 *
O ₂ pulse, ml·beat ⁻¹	12.8 ± 6.6	9.3 ± 2.9 *	9.9 ± 2.8 *	8.0 ± 3.6 *†§
AT, ml·kg ⁻¹ ·min ⁻¹	16.8 ± 6.2	11.0 ± 3.5 *	11.3 ± 2.7 *	9.8 ± 2.6 *†§
SpO ₂ %	96 ± 2	95 ± 2	94 ± 2 *	92 ± 4 †*
Dyspnoea	3 ± 2	4 ± 2 *	6 ± 2 *†	6 ± 1 *†
Leg fatigue	6 ± 2	5 ± 1	3 ± 1 *	3 ± 1 *
Stopped due to fatigue	9	9	3 *†	3 *†
Stopped due to dyspnoea	-	3	10*†	9*†
Stopped due to both fatigue and dyspnoea	2	2	1	2

Data are presented as mean \pm SD. $\dot{V}'O_2$, oxygen uptake; $\Delta\dot{V}'O_2/\Delta WR$, aerobic work efficiency; RER, respiratory exchange ratio; fc, cardiac frequency; O_2 pulse: oxygen pulse; AT, anaerobic threshold; %SpO₂, percentage oxygen saturation. * Significant difference ($p < 0.05$) with healthy; † Significant difference from GOLD stage II patients; § Significant difference from GOLD stage III patients.

Table 3. Ventilatory responses at the limit of tolerance in COPD patients and age-matched healthy subjects

	Healthy (n = 11)	GOLD Stage II (n = 14)	GOLD Stage III (n = 14)	GOLD Stage IV (n = 14)
V'E, L min ⁻¹	68.7 ± 13.8	38.4 ± 8.9 *	36.5 ± 8.4 *	27.6 ± 7.2 *†§
V _T , L	2.37 ± 0.57	1.33 ± 0.34 *	1.21 ± 0.27 *†	1.10 ± 0.32 *†§
fb, breaths min ⁻¹	29 ± 4	30 ± 6	30 ± 6	26 ± 10 *†§
T _I , s	0.95 ± 0.12	0.97 ± 0.27	0.71 ± 0.14 *†	0.81 ± 0.21 *†§
T _E , s	1.21 ± 0.18	1.26 ± 0.30	1.15 ± 0.24	1.61 ± 0.39 *†§
T _I /T _{TOT}	0.44 ± 0.11	0.41 ± 0.15	0.38 ± 0.12 *	0.33 ± 0.14 *
V _T /T _E , L s ⁻¹	2.03 ± 0.58	1.19 ± 0.40 *	1.07 ± 0.31 *	0.89 ± 0.34 *†
IC _{SP} , L	2.87 ± 0.76	1.87 ± 0.48 *#	1.48 ± 0.34 *†	1.37 ± 0.34 *†
ΔIC _{SP} , L	0.01 ± 0.10	- 0.28 ± 0.12 *	- 0.54 ± 0.24 *†	- 0.63 ± 0.35 *†
IC _{OEP} , L	2.85 ± 0.89	2.02 ± 0.63 *	1.48 ± 0.37 *†	1.39 ± 0.37 *†
ΔEIV _{cw} , ml	2036 ± 658	1608 ± 527 *	1740 ± 591 *	1764 ± 609 *
ΔEEV _{cw} , ml	-339 ± 619	85 ± 288 *	454 ± 509 *†	562 ± 363 *†
IRV _{cw} , ml	573 ± 374	530 ± 467	221 ± 273 *†	167 ± 322 *†

Data are presented as mean ± SD. V'E, minute ventilation; V_T, tidal volume; fb, breathing frequency; T_I, inspiratory time; T_E, expiratory time; T_I/T_{TOT}, duty cycle; V_T/T_E, expiratory flow rate; IC_{SP}, inspiratory capacity by spirometry; ΔIC_{SP}, change from rest in spirometric IC; IC_{OEP}, inspiratory capacity assessed by optoelectronic plethysmography; ΔEIV_{cw}, end- inspiratory chest wall volume as a difference from rest; ΔEEV_{cw}, end expiratory chest wall volume as a difference from rest; IRV_{cw}, inspiratory reserve chest

wall volume; * Significant difference ($p < 0.05$) with healthy; † Significant difference from GOLD stage II patients; § Significant difference from GOLD stage III patients ($p < 0.05$). # Significant difference from IC_{OEP}.

FIGURE LEGENDS

Figure 1. Volumes of the total chest wall in healthy subjects (A) and patients with GOLD stage II (B), stage III (C) and stage IV (D) during incremental exercise. Open circles (○) indicate the end-inspiratory chest wall volume and closed circles (●) the end-expiratory chest wall volume changes expressed as differences from the end-expiratory volume at rest (R) (dashed line) at 0, 33, 66 and 100% of the peak work rate. Triangles indicate the chest wall volumes at TLC. Asterisks indicate significant differences in time points compared to healthy subjects and crosses indicate significant differences compared to GOLD stage II patients. Error bars have been omitted for clarity.

Figure 1

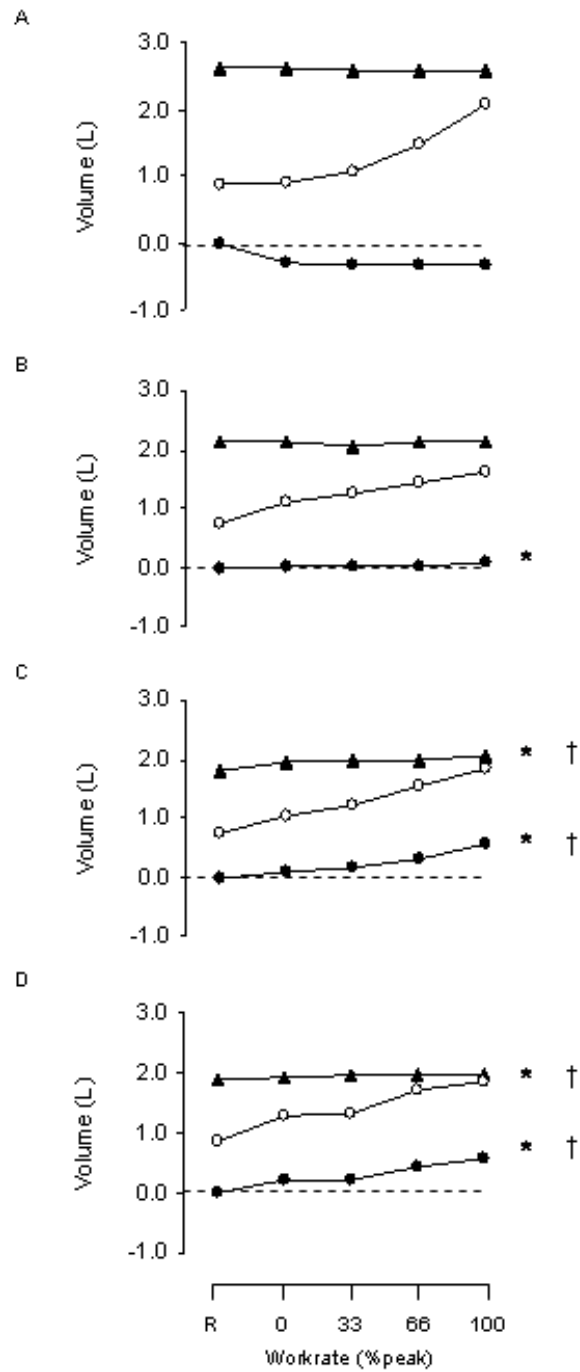


Figure 2. Volumes of the rib cage (left panels) and the abdominal compartments (right panels) in healthy subjects (A) and patients with GOLD stage II (B), stage III (C) and stage IV (D) during incremental exercise. Open circles (O) indicate the end-inspiratory volume and closed circles (●) the end-expiratory

volume changes expressed as differences from the end-expiratory volume at rest (R) (dashed line) at 0, 33, 66 and 100% of the peak work rate. Asterisks indicate significant differences in time points compared to healthy subjects and crosses indicate significant differences compared to GOLD stage II patients. Error bars have been omitted for clarity.

Figure 2

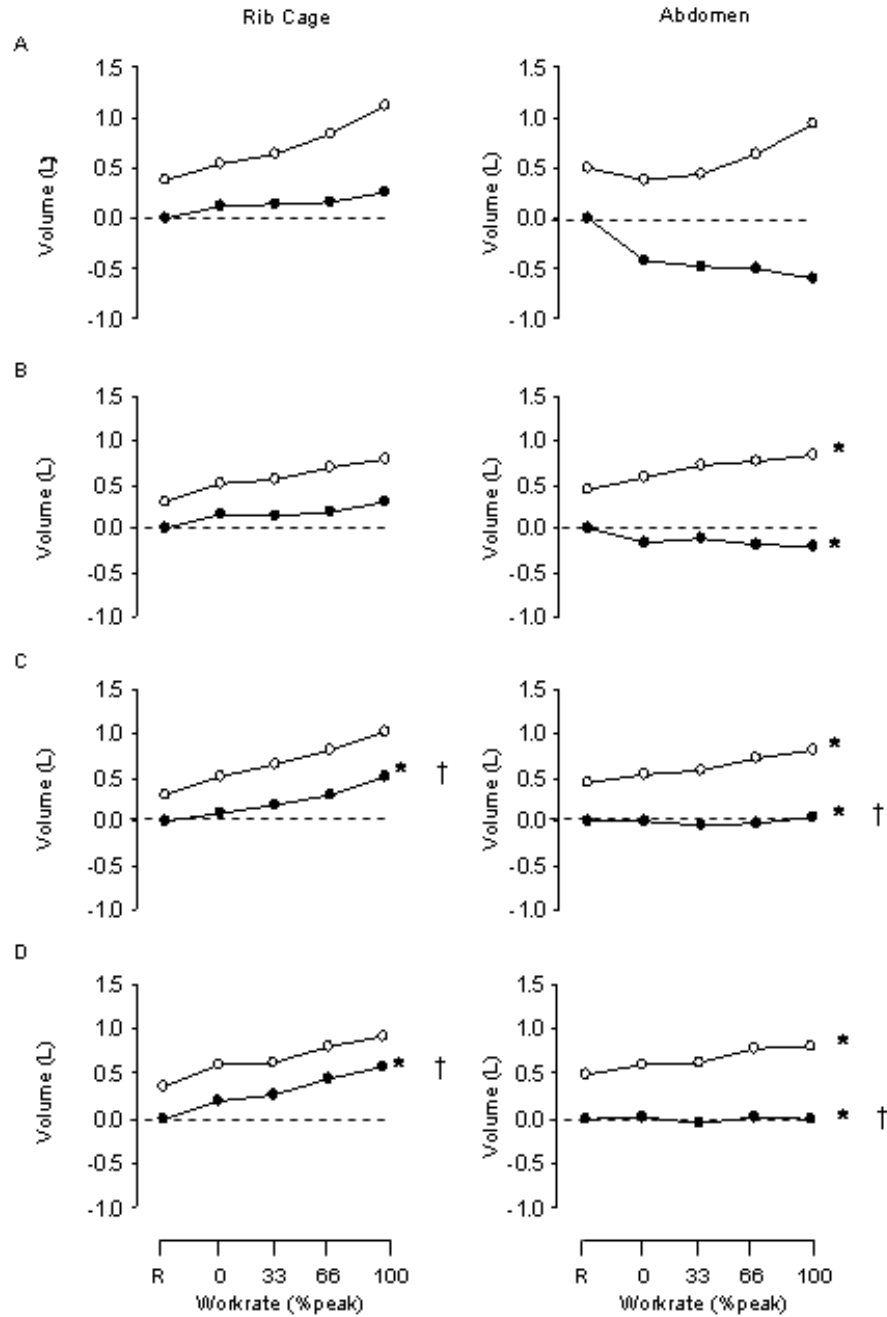


Figure 3. Volumes at end-expiration and inspiration of the total chest wall (A and B), the rib cage compartment (C and D) and the abdomen (E and F) plotted as a function of minute ventilation in patients with GOLD stage II (Δ), stage III (\bullet), and stage IV (\circ). Crosses indicate significant differences compared

to GOLD stage II patients, whereas # indicates significant differences compared to stages II and III. Error bars have been omitted for clarity.

Figure 3

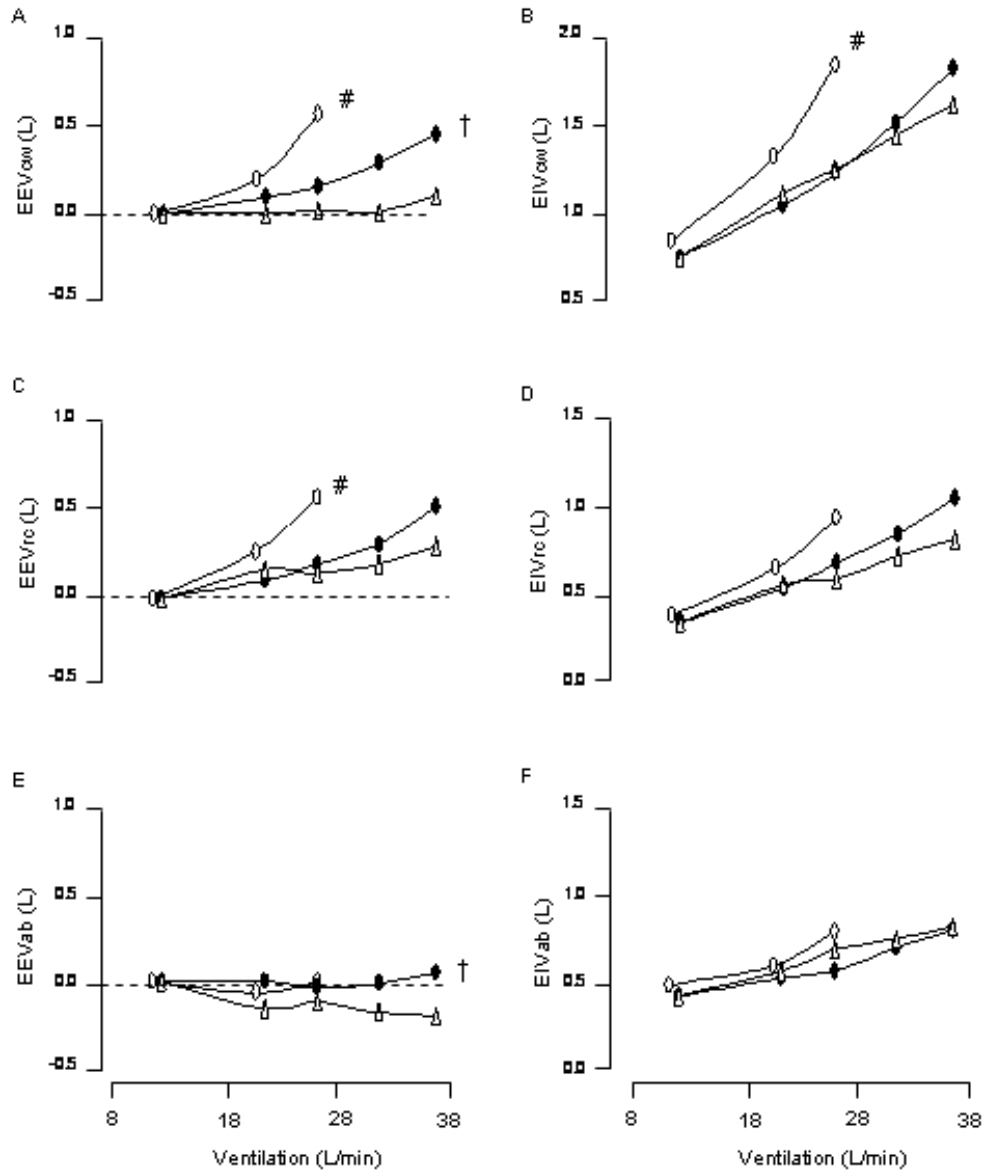


Figure 4. Breathing pattern variables (A: V_T , tidal volume; B: fb, respiratory frequency; C: V_T/T_I , mean inspiratory flow rate; D: V_T/T_E , mean expiratory flow rate; E: T_I/T_{TOT} , duty cycle; F: T_E , expiratory time) plotted as a function of minute ventilation in patients with GOLD stage II (Δ) and stage III (\bullet). Crosses indicate significant differences between GOLD stages II and II, Error bars have been omitted for clarity.

Figure 4

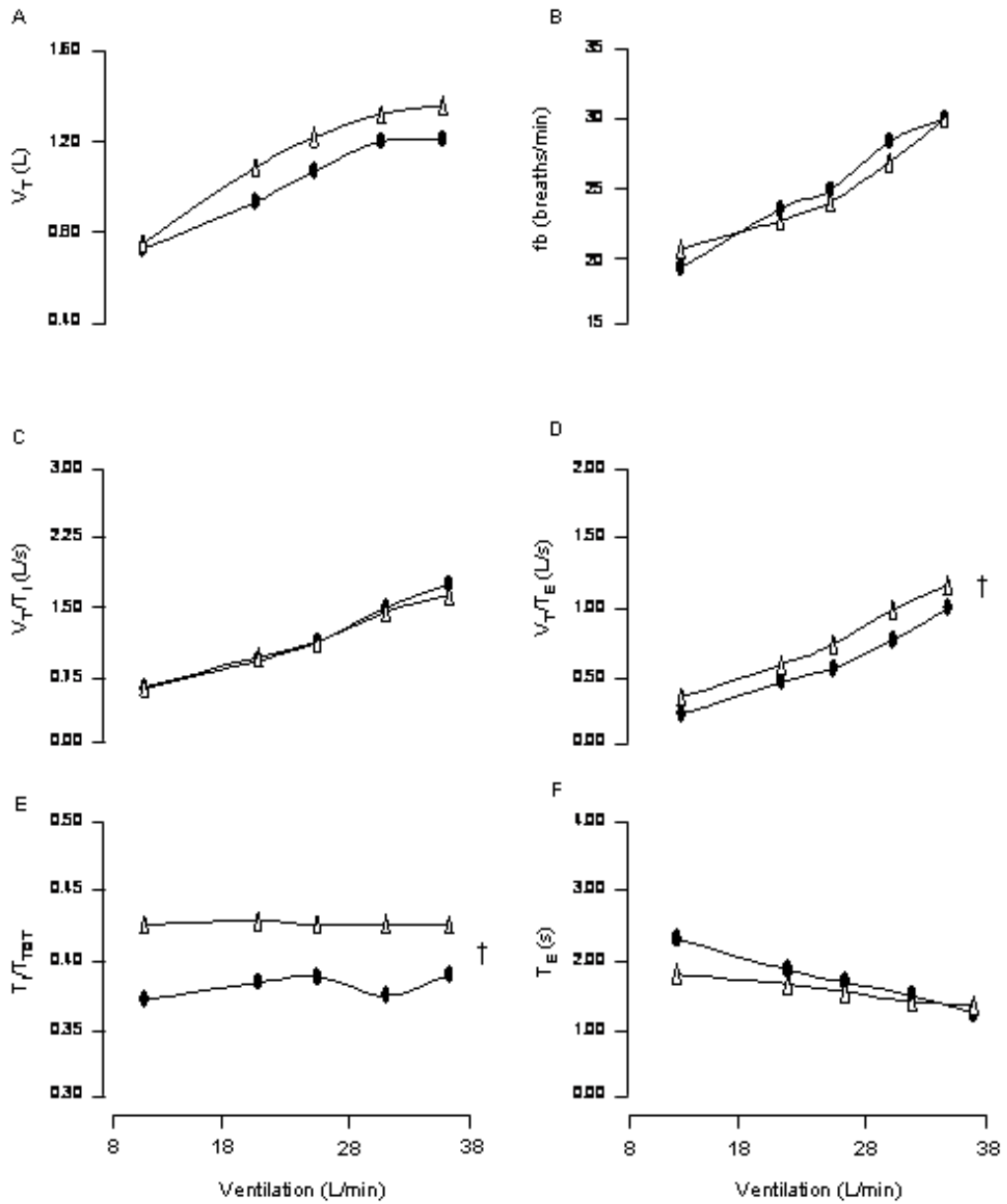


Figure 5. End-expiratory gastric pressure (during unloaded cycling (0 %) and during incremental exercise (at 33, 66 and 100% of the peak work rate) in patients with COPD [GOLD stage II (Δ), stage III (\bullet) and stage IV (\circ)]. Error bars have been omitted for clarity.

Figure 5

