Airway obstruction, dynamic hyperinflation, and breathing pattern during incremental exercise in COPD patients

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Abstract
Ventilatory capacity is reduced in chronic obstructive pulmonary disease (COPD) patients. Tidal volume ($V_T$) is lower and breathing frequency higher at a given ventilation ($V_E$) compared to healthy subjects. We examined whether airflow limitation and dynamic hyperinflation in COPD patients were related to breathing pattern. An incremental treadmill exercise test was performed in 63 COPD patients (35 men), aged 65 years (48–79 years) with a mean forced expiratory volume in 1 sec (FEV$_1$) of 48% of predicted (SD = 15%). Data were averaged over 20-sec intervals. The relationship between $V_E$ and $V_T$ was described by the quadratic equation $V_T = a + bV_E + cV_E^2$ for each subject. The relationships between the curve parameters $b$ and $c$, and spirometric variables and dynamic hyperinflation measured as the difference in inspiratory capacity from start to end of exercise, were analyzed by multivariate linear regression. The relationship between $V_E$ and $V_T$ could be described by a quadratic model in 59 patients with median $R^2$ of 0.90 (0.40–0.98). The linear coefficient ($b$) was negatively ($P = 0.001$) and the quadratic coefficient ($c$) positively ($P < 0.001$) related to FEV$_1$. Forced vital capacity, gender, height, weight, age, inspiratory reserve volume, and dynamic hyperinflation were not associated with the curve parameters after adjusting for FEV$_1$. We concluded that a quadratic model could satisfactorily describe the relationship between $V_E$ and $V_T$ in most COPD patients. The curve parameters were related to FEV$_1$. With a lower FEV$_1$, maximal $V_T$ was lower and achieved at a lower $V_E$. Dynamic hyperinflation was not related to breathing pattern when adjusting for FEV$_1$.

Introduction
Exertional dyspnea is one of the main factors limiting physical activity in patients with chronic obstructive pulmonary disease (COPD) (O’Donnell and Webb 1993; Maltais et al. 2005; Nici et al. 2006). At a given expired minute ventilation ($V_E$), the tidal volume ($V_T$) is lower and the breathing frequency ($B_f$) higher in patients having COPD compared to healthy subjects (Palange et al. 2007). The maximal ventilatory capacity is reduced (Gallagher 1994), and is closely related to forced expired volume in 1 sec (FEV$_1$) (Clark et al. 1969; Potter et al. 1971).

The mechanism for the ventilatory limitation in COPD is related to expiratory flow limitation and lung hyperinflation. The time constant for the lung, which is the...
product of resistance and compliance, is increased and during progressively higher ventilatory demands, expiration may not be completed before the drive for the next inspiration starts (Hyatt 1983). End-expiratory lung volume increases, and breathing takes place at a higher lung volume where both resistance and compliance are lower. The effect of these changes in lung volume, resistance, and compliance is a shorter time constant allowing complete respiratory cycles, but it is at the cost of a higher work of breathing (Hyatt 1983; O’Donnell and Webb 1993). The $V_t$ is constrained by total lung capacity (TLC) on the inspiratory side. The inspiratory reserve volume (IRV) falls by increasing $V_t$. Expiratory constraints are more complex, influenced by the increased time constant and inspiratory drive (Peters et al. 2006).

The relationship between $V_E$ and $V_T$ during incremental exercise can be described by three phases (Gallagher et al. 1987). In the first phase, there is an almost linear relationship between $V_E$ and $V_T$. In the second phase, the increase in $V_E$ is mainly caused by an increase in $B_I$ and a smaller increase in $V_T$. In the third phase, the increase in $V_E$ is caused by an increase in $B_I$ only, and by the end of this phase there can be a fall in $V_T$ (Gallagher et al. 1987). The relationship between $V_E$ and $V_T$ has previously been described by various methods such as the maximal $V_T$ ($V_{T_{max}}$) or the plateau of $V_T$ and the inflection point (O’Donnell et al. 2006), $V_{T_{max}}$ and $V_T$ at a $V_E$ of 30 L/min (Cotes 1972), $V_T$ at given fractions of peak $V_E$ (Neder et al. 2003), and the slope and intercept of the first part of the response (Hey et al. 1966). However, neither of these methods account for the curvilinearity of the response. In young healthy subjects, the individual relationship between $V_E$ and $V_T$ has been described satisfactorily by a quadratic (Kalsas and Thorsen 2009) and a logarithmic (Naranjo et al. 2005) relationship, but it is not known whether these models are applicable for the general population or patients with lung disease.

The aim of this cross-sectional study was to examine whether a quadratic model could satisfactorily describe the relationship between $V_E$ and $V_T$ during exercise in COPD patients. The hypothesis was that the curve parameters of the quadratic model, which describe the breathing pattern, were related to FEV$_1$, IRV, and dynamic hyperinflation.

**Methods**

**Subjects**

Of the 433 patients included in the Bergen COPD Cohort study (Eagan et al. 2010), 89 patients participated in a pulmonary rehabilitation program during the first 2 years of follow-up in 2006–2008. In 2011–2012, 63 of these patients were available for a cardiopulmonary exercise test on a treadmill. The remaining 26 patients were deceased or disabled.

The included patients had clinically stable COPD in Global Initiative for Chronic Obstructive Lung Disease (GOLD) (Rabe et al. 2007) stages II–IV and age between 48 and 79 years. Thirty-two subjects were in stage II, 23 in stage III, and eight in stage IV. All patients had a smoking history of ≥10 pack-years, a postbronchodilation FEV$_1$ to forced vital capacity (FVC) ratio <0.7 and a postbronchodilator FEV$_1$ <80% of predicted value according to Norwegian reference values (Johannessen et al. 2006). Patients with inflammatory disorders like rheumatoid arthritis, systemic lupus erythematosus or other connective tissue disorders, inflammatory bowel disease, and any active cancer in the last 5 years were not included in the Bergen COPD Cohort study. Exclusion criteria for exercise testing were major cardiovascular disorders, a partial pressure of oxygen in arterial blood less than 8 kPa at rest, or exacerbations that required medical treatment during the last 4 weeks prior to testing. The patients were examined by a physician prior to exercise testing.

**Ethics**

The Western Norway Regional Research Ethics Committee approved the study. Participation in the study was voluntary. Written and oral information was given and written consent was obtained prior to inclusion.

**Spirometry**

Spirometry was conducted on a Viasys Masterscope (Viasys, Hoechberg, Germany) before the exercise test according to the ATS/ERS Standardization of Lung Function Testing (Miller et al. 2005). The FVC and FEV$_1$ were taken as the highest values from at least three satisfactory expiratory maneuvers. The spirometer was calibrated before each test with a 3-L calibration syringe. The body mass index (BMI) was calculated as the body mass divided by the square of height.

**Cardiopulmonary exercise test**

The patients completed an incremental exercise test to their symptom-limited maximum on a treadmill (Woodway, model: PPS 55 med Weiss, Weil am Rhein, Germany). The exercise protocol was a modified Bruce protocol (Bruce 1971; Bruce et al. 1973), and started with rest in the standing position for 2 min. The warm-up phase lasted for 1 min with a walking speed of 1.5 km/h. Blood pressure, electrocardiography (GE Healthcare, Cardio Soft EKG, Freiburg, Germany) and pulse oximetry...
were monitored at rest, continuously during the test and for 3 min into the recovery phase. A tight-fitting oronasal mask was adjusted to each patient and checked for leaks before starting the exercise. The integrated exercise testing system (Care Fusion, V\textsubscript{max} Spectra 229, Hochberg, Germany), was calibrated every morning and immediately before each test. The \( V_t \), \( B_t \) oxygen uptake (\( \text{VO}_2 \)), carbon dioxide production (\( \text{VCO}_2 \)), and heart rate (HR) were measured on a breath by breath basis and averaged over 20-sec intervals. \( V_E \) and \( V_t \) were corrected to the body temperature pressure saturated (BTPS) condition, and \( \text{VO}_2 \) and \( \text{VCO}_2 \) to the standard temperature pressure (STPD) condition.

The patients graded their level of dyspnea and leg discomfort by the Borg CR10 Scale (Borg 1998) before the test started, every second minute during the test, and at peak exercise. In order to measure hyperinflation during exercise, serial measurements of inspiratory capacity (IC) as described by O’Donnell and Webb (1993) were performed. Measurements were taken before the start of exercise, every second minute during exercise and at peak exercise. Patients who had a decrease in IC from rest to peak exercise (\( \Delta \text{IC} \geq 0.4 \text{~L} \)) were characterized as hyperinflators, the rest as nonhyperinflators. We also calculated \( \Delta \text{IC} \) adjusted for resting IC (\( \Delta \text{IC}_{ \text{adj}} \)). A reduction in \( \Delta \text{IC}_{ \text{adj}} \geq 20\% \) was used as cut-off limit for comparison of the subjects (O’Donnell and Laveneziana 2006a). The IRV was calculated as the difference between IC at the end of the test minus the preceding \( V_t \).

Estimated regression coefficients are presented with 95% confidence intervals (CI) and \( p \)-values. The significance level was set at 0.05. The data analyses were performed using IBM SPSS Statistics 21 (SPSS Inc. Chicago, IL).

### Results

Subject characteristics and resting pulmonary function measurements are summarized in Table 1. The patients were airflow limited with a mean \( \text{FEV}_1 \) of 48% of the predicted value (Fig. 1). Thirty-two patients were categorized as hyperinflators with a \( \Delta \text{IC} \geq 0.4 \text{~L} \) and 31 as nonhyperinflators. The same result was demonstrated when using a \( \Delta \text{IC}_{ \text{adj}} \geq 20\% \) as cut-off. The distribution of \( \Delta \text{IC} \) from rest to peak exercise is illustrated in Figure 2. Of the hyperinflators 72% were men, and of the nonhyperinflators 39%. The peak responses to treadmill exercise are presented in Table 2. There were no significant differences in exercise time, \( \text{VO}_2\text{peak} \), \( \text{VCO}_2\text{peak} \), \( V_t\text{peak} \), HR\text{peak}, Borg scores, and desaturation between the hyperinflators and nonhyperinflators. Fifty-three (84%) of the patients stopped exercise due to dyspnea or dyspnea in combination with leg discomfort. Ten (16%) patients stopped due to leg discomfort only. There was approximately 10% difference in ventilation and exercise time between hyperinflators and nonhyperinflators, and the difference was related to anthropometric characteristics and gender. There were more men among the hyperinflators and more women among the nonhyperinflators.

### Statistical analyses

Descriptive statistics were used to characterize the study population (mean, standard deviation [SD], and percent). Independent samples t-tests were used to compare continuous variables and Pearson \( \chi^2 \) tests for categorical variables. The relationship between \( V_E \) and \( V_t \) was described for each individual by the quadratic model

\[
V_t = a + bV_E + cV_E^2
\]

The goodness of fit for the individual patient-specific regression analysis was evaluated by the adjusted coefficient of determination (adjusted \( R^2 \)) and the \( F \)-statistic. For the latter a \( P \)-value <0.05 was required for inclusion of the patient in further analysis. The relationship between the estimated curve parameters in the quadratic model, the intercept (\( a \)), the slope (\( b \)), and the curvature (\( c \)), respectively, and age, gender, height, weight, \( \text{FEV}_1 \), \( \text{FVC} \), IRV, and \( \Delta \text{IC}_{ \text{adj}} \), were analyzed by bivariate and multivariate linear regression analysis. IC at rest was also used in the multivariate analysis, but was not significant and therefore excluded from the final model.

The goodness of fit of the quadratic model was compared with the goodness of fit by a hyperbolic (inverse) model of the form

\[
V_t = a + bV_E^{-1}
\]

Table 1. Characteristics of the study population.

| Variables          | Total (n = 63) | Women (n = 28) | Men (n = 35) | P-value |
|--------------------|---------------|---------------|-------------|---------|
| Age (years)        | 65.7 ± 6.0    | 64.3 ± 6.2    | 66.8 ± 5.6  | 0.089   |
| Pack years         | 37.2 ± 22.1   | 30.3 ± 18.7   | 42.8 ± 23.3 | 0.028   |
| Height (m)         | 1.70 ± 0.1    | 1.63 ± 0.1    | 1.75 ± 0.1  | <0.001  |
| Body mass (kg)     | 76.0 ± 17.4   | 68.1 ± 15.7   | 82.4 ± 16.1 | 0.001   |
| BMI                | 26.2 ± 5.0    | 25.5 ± 5.4    | 26.8 ± 4.7  | 0.330   |
| \( \text{FEV}_1 \) (L) | 1.5 ± 0.6     | 1.2 ± 0.4     | 1.6 ± 0.6   | 0.002   |
| \( \text{FEV}_1 \) (%) | 48.0 ± 14.8   | 48.9 ± 13.0   | 47.3 ± 16.2 | 0.667   |
| \( \text{FVC} \) (L) | 3.1 ± 0.9     | 2.6 ± 0.6     | 3.6 ± 0.8   | <0.001  |
| \( \text{FVC} \) (%) | 82.8 ± 15.3   | 83.9 ± 16.2   | 81.9 ± 14.7 | 0.615   |
| \( \text{FEV}_1/\text{FVC} \) (%) | 46.0 ± 11.1   | 47.0 ± 10.2   | 45.2 ± 12.0 | 0.537   |
| IC (L)             | 2.2 ± 0.8     | 1.8 ± 0.5     | 2.6 ± 0.8   | <0.001  |

Data are presented as mean ± SD. Independent t-test for continuous variables. BMI, body mass index; \( \text{FEV}_1 \), forced expiratory volume in 1 sec; \( \text{FVC} \), forced vital capacity; IC, inspiratory capacity.
In 59 patients, the $P$-value of the $F$-statistic for the quadratic model was <0.05 and the $R^2$ ranged from 0.40 to 0.98 (median of 0.90). Four patients were excluded from further analysis, because in the individual analysis the goodness of fit was not statistically significant. In these patients, the exercise time was short and thereby few data points were available for computing the regression curve. Two of these patients were in GOLD stage III and two in GOLD stage IV. Figure 3 shows a random set of 14 individual responses and the mean response for the 59 patients. The mean of the estimated constant ($a$) was 0.18 (SD = 0.44), the mean linear coefficient ($b$) was 0.076 (SD = 0.035), and the mean quadratic coefficient ($c$) was −0.00102 (SD = 0.00080).

In the multivariate linear regression analyses, the linear coefficient ($b$) was negatively ($P = 0.001$) and the quadratic coefficient ($c$) positively ($P < 0.001$) related to FEV$_1$. Age, gender, height, weight, FVC, IRV, and $\Delta$IC$_{adj}$ were not associated with the curve parameters after adjusting for FEV$_1$ (Table 3).

The $V_{T_{\text{max}}}$ and $V_E$ at $V_{T_{\text{max}}}$ were calculated from the individual quadratic relationships. In adjusted linear regression analyses, both were related to FEV$_1$ ($P < 0.001$), but not to age, gender, height, weight, FVC, and $\Delta$IC.

When using the hyperbolic model, the mean constant was 1.70 (SD = 0.52), and the curvature 14.73 (SD = 8.87). The median $R^2$ was 0.84 (range 0.25–0.95) which was lower than for the quadratic relationship.

**Discussion**

The main findings of this study were: (1) The relationship between $V_T$ and $V_E$ during incremental exercise could be described by a quadratic model in most COPD patients. (2) The linear and quadratic curve parameters were both related to FEV$_1$. With a lower FEV$_1$, maximal $V_T$ was lower and achieved at a lower $V_E$. (3) Dynamic hyperinflation and IRV were not related to the curve parameters.

When using a curvilinear model to describe the relationship between $V_E$ and $V_T$, all observations throughout the incremental exercise test are included in the analysis, and a detailed description of the test from start to end is provided. A limitation with other methods used to describe the relationship between $V_E$ and $V_T$ like the Hey et al. (1966) plot, the $V_{T_{30}}$ and $V_{T_{\text{max}}}$ (Cotes 1972), and $V_T$ at given fractions of peak $V_E$ (Neder et al. 2003), is that all observed data from the exercise test are not included in the analysis. The exercise tests in these studies were done on a cycle ergometer, and in the studies of Cotes (1972) and Hey et al. (1966) the tests were submaximal. Breathing pattern was different with treadmill exercise compared with cycle exercise in a study of young and healthy subjects (Kalsas and Thorsen 2009), but no differences in breathing pattern were observed comparing maximal and submaximal incremental exercise test on a cycle ergometer (Kjelkenes and Thorsen 2010). The $V_{T_{30}}$ require that a ventilation of at least 30 L/min is achieved. In our study, 16 of the COPD patients had a peak ventilation below 30 L/min. We did not use a logarithmic model as described by Naranjo et al. (2005), because it does not account for $V_T$ having a maximal value.

The quadratic model could not be used for all COPD patients in this study. Four patients were excluded from further analysis because the $P$-value of the $F$-statistic in the individual analysis was not significant. The exercise time was short and thereby few data points were available.
for mathematical description of the response in these patients. We considered other mathematical models for all subjects including a hyperbolic model, but with respect to $R^2$, the parabolic was best. For the four excluded subjects, none of these models were applicable. COPD is a progressive disease and in a general COPD population, not all patients will have the functional capacity to complete an incremental exercise test, which is a strenuous maneuver.

Incomplete expiration leads to accumulation of gas in the lung, and a given ventilatory demand can only be sustained when breathing takes place at a lung volume having a time constant that allows complete respiratory cycles. FEV$_1$ is the integrated sum of maximal expiratory flow rates during the first second of a forced exhalation. Maximal expiratory flow rates are determined by airway diameter, compliance of the airway wall, and gas density (Pedersen et al. 1985). COPD is characterized by loss of elastic properties throughout the lung, not specifically located to the airways or the alveolar region (Hogg 2012). In this way, FEV$_1$ is related to both resistance and compliance, and thereby to the time constant, which is the product of the two. A relationship between FEV$_1$ and the curve parameters determining the breathing pattern is therefore not unexpected.

The TLC is expected to remain unaltered during exercise, and therefore dynamic hyperinflation can be described as a reduction in IC from start to end of the exercise test ($\Delta$IC), when end-expiratory lung volume (EELV) increases (Stubbing et al. 1980; Yan et al. 1997; Vogiatzis et al. 2005). In our study, there was no correlation between FEV$_1$ and $\Delta$IC, and as far as we know a relationship between FEV$_1$ and $\Delta$IC has not been demonstrated in other studies. We found no relationship between $\Delta$IC and the curve parameters. The hyperinflators in this study were not different from the nonhyperinflators with respect to FEV$_1$ in percent of predicted, VO$_2$peak, V$_E$peak, and Borg dyspnea score at the end of the test. Desaturation was the same in both groups as well. In young healthy subjects, the individual relationship between V$_E$ and V$_T$ has been described satisfactorily by a quadratic relationship (Kalas and Thorsen 2009), and normal healthy subjects does not hyperinflate during progressive exercise. This may suggest that dynamic hyperinflation is primarily a mechanism for adjusting the time constant of the lung to expiratory flow limitation and is not a determinant of breathing pattern per se.

In healthy subjects, the breathing pattern with respect to V$_T$ and $B_t$ has traditionally been considered a load

| Variables | Total (n = 63) | Hyperinflators (n = 32) | Nonhyperinflators (n = 31) | P-value |
|-----------|---------------|------------------------|---------------------------|---------|
| Gender, male/female (n) | 35/28 | 23/9 | 12/19 |          |
| Exercise time (min) | 6.4 ± 2.2 | 6.6 ± 2.0 | 6.3 ± 2.4 | 0.572 |
| VO$_2$peak (L/min) | 1.36 ± 0.5 | 1.48 ± 0.5 | 1.23 ± 0.5 | 0.065 |
| VCO$_2$peak (L/min) | 1.34 ± 0.67 | 1.43 ± 0.7 | 1.25 ± 0.7 | 0.308 |
| V$_E$peak (L/min) | 47.3 ± 19.6 | 49.3 ± 20.3 | 453 ± 18.9 | 0.419 |
| HR$_{peak}$ (bpm) | 133 ± 19 | 132 ± 18 | 134 ± 20 | 0.711 |
| Dyspnea (Borg Scale) | 8.7 ± 1.6 | 8.8 ± 1.6 | 8.6 ± 1.6 | 0.626 |
| Leg discomfort (Borg Scale) | 5.5 ± 3.0 | 5.4 ± 2.5 | 5.7 ± 3.4 | 0.666 |
| $\Delta$IC(L) | 0.46 ± 0.33 | 0.72 ± 0.25 | 0.20 ± 0.15 | <0.001 |
| SpO$_2$% start | 95.9 ± 2.5 | 95.4 ± 2.7 | 96.5 ± 2.3 | 0.083 |
| SpO$_2$% end | 89.6 ± 5.1 | 89.2 ± 5.5 | 90.0 ± 4.7 | 0.533 |

Data are presented as mean ± SD, unless otherwise stated. VO$_2$, oxygen uptake; VCO$_2$, carbon dioxide production; V$_E$, ventilation, tidal volume; HR, heart rate; $\Delta$IC, inspiratory capacity, IC at the start of the test minus IC at the end of the test; SpO$_2$, oxygen saturation.

Figure 3. A random set of 14 individual responses (thin lines) and the mean response for the 59 patients (bold line).
The constraint for the V1 is lower and achieves at a lower FEV1. Dynamic hyperinflation and IRV are not load compensating mechanisms and could therefore be independent phenomena. The importance of hyperinflation can, however, not be ignored as it is by itself related to dyspnea, respiratory effort, and work of breathing. The constraint for the expansion of V1 on the inspiratory side set by TLC, and how close the patients breathe in relationship to TLC, will also be associated with a higher work of breathing.

The participants in this study had participated in a pulmonary rehabilitation program. The patients recruited could therefore be biased to have higher functional capacity than the common COPD population. The distribution among GOLD stages were 32 patients in stage II, 23 in stage III and eight in stage IV, respectively. There were fewer patients with more serious disease as represented by GOLD stage IV and the most severely ill patients were not able to participate in the study. However, 49% of the patients were in GOLD stages III and IV. We therefore assume that our study population is representative for the common COPD patients met in outpatient clinics or in hospitals.

Table 3. The relationships between the curve parameters and explanatory variables.

| Variable       | Unadjusted B | P-value | Adjusted B | 95% CI          | P-value |
|----------------|--------------|---------|------------|-----------------|---------|
| Curve parameter a |              |         |            |                 |         |
| Age            | -0.003       | 0.761   | 0.009      | -0.013 to 0.030 | 0.423   |
| Gender         | -0.088       | 0.448   | -0.039     | -0.375 to 0.296 | 0.814   |
| Height         | -0.273       | 0.666   | -1.209     | -3.497 to 1.079 | 0.294   |
| Weight         | 0.001        | 0.732   | 9.9 x 10^-5 | -0.008 to 0.009 | 0.981   |
| FEV1           | 0.192        | 0.059   | 0.560      | 0.151 to 0.968  | 0.008   |
| FVC            | 0.005        | 0.938   | -0.184     | -0.477 to 0.110 | 0.215   |
| ΔICadj         | -0.006       | 0.187   | 0.001      | -0.010 to 0.012 | 0.847   |
| IRV            | 0.240        | 0.224   | 0.066      | -0.448 to 0.580 | 0.798   |
| Curve parameter b |              |         |            |                 |         |
| Age            | 36.6 x 10^-5 | 0.632   | -0.001     | -0.002 to 0.001 | 0.439   |
| Gender         | 0.014        | 0.133   | 0.014      | -0.011 to 0.040 | 0.254   |
| Height         | 0.015        | 0.774   | 0.041      | -0.131 to 0.213 | 0.633   |
| Weight         | -2.4 x 10^-5 | 0.927   | 12.3 x 10^-5 | -0.001 to 0.001 | 0.698   |
| FEV1           | -0.020       | 0.016   | -0.053     | -0.083 to -0.022 | 0.001   |
| FVC            | -0.001       | 0.874   | 0.016      | -0.006 to 0.038 | 0.157   |
| ΔICadj         | 0.001        | 0.026   | 20.1 x 10^-5 | -0.001 to 0.001 | 0.622   |
| IRV            | -0.020       | 0.218   | 0.007      | -0.032 to 0.045 | 0.726   |
| Curve parameter c |              |         |            |                 |         |
| Age            | -1.4 x 10^-5 | 0.422   | 1.4 x 10^-5 | -1.8² to 4.7² | 0.389   |
| Gender         | -9.1 x 10^-5 | 0.668   | -38.1 x 10^-5 | -0.001 to 13.5² | 0.144   |
| Height         | 0.002        | 0.193   | -0.001     | -0.004 to 0.003 | 0.663   |
| Weight         | -0.6 x 10^-5 | 0.334   | -0.2 x 10^-5 | -1.5² to 1.1² | 0.810   |
| FEV1           | 0.001        | <0.001  | 0.001      | 0.001 to 0.002  | <0.001  |
| FVC            | 27.0 x 10^-5 | 0.026   | -12.6 x 10^-5 | -0.001 to 32.5² | 0.577   |
| ΔICadj         | -1.8 x 10^-5 | 0.026   | -0.6 x 10^-5 | -2.3² to 1.1² | 0.477   |
| IRV            | 0.001        | 0.013   | -6.6 x 10^-5 | -0.001 to 0.001 | 0.868   |

95% confidence interval (CI) examined by linear regression in multivariate analyses (P < 0.05). FEV1, forced expired volume in 1 sec; FVC, forced vital capacity; ΔIC, inspiratory capacity, IC at the start of the test minus IC at the end of the test; ΔICadj, ΔIC adjusted for resting IC; IRV, inspiratory reserve volume.

1The relationship between V1 and V1 was described by a quadratic model (V1 = a + bV1 + cV1²).
2Values are given multiplied by 10^-5.
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Conflict of Interest

None declared.

References

Borg, G. 1998. P. viii, 104 in Borg’s perceived exertion and pain scales. Human Kinetics, Champaign, IL.
Bruce, R. A. 1971. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. Ann. Clin. Res. 3:323–332.
Bruce, R. A., F. Kusumi, and D. Hosmer. 1973. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am. Heart J. 85:546–562.
Clark, T. J., S. Freedman, E. J. Campbell, and R. R. Winn. 1969. The ventilatory capacity of patients with chronic airways obstruction. Clin. Sci. 36:307–316.
Cotes, J. E. 1972. Response to progressive exercise: a three-index test. Br. J. Dis. Chest 66:169–184.
Eagan, T. M., T. Ueland, P. D. Wagner, J. A. Hardie, T. E. Mollnes, J. K. Damas, et al. 2010. Systemic inflammatory markers in COPD: results from the Bergen COPD Cohort Study. Eur. Respir. J. 35:540–548.
Gallagher, C. G. 1994. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. Clin. Chest Med. 15:305–326.
Gallagher, C. G., E. Brown, and M. Younes. 1987. Breathing pattern during maximal exercise and during submaximal exercise with hypercapnia. J. Appl. Physiol. 63:238–244.
Hey, E. N., B. B. Lloyd, D. J. Cunningham, M. G. Jukes, and D. P. Bolton. 1966. Effects of various respiratory stimuli on the depth and frequency of breathing in man. Respir. Physiol. 1:193–205.
Hogg, J. C. 2012. A pathologist’s view of airway obstruction in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 186(vii–vii).
Hyatt, R. E. 1983. Expiratory flow limitation. J. Appl. Physiol. 55:1–7.
Johannessen, A., S. Lehmann, E. R. Omenaas, G. E. Eide, P. S. Bakke, and A. Gulsvik. 2006. Post-bronchodilator spirometry reference values in adults and implications for disease management. Am. J. Respir. Crit. Care Med. 173:1316–1325.
Kalas, K., and E. Thorsen. 2009. Breathing patterns during progressive incremental cycle and treadmill exercise are different. Clin. Physiol. Funct. Imaging 29:335–338.
Kjelknes, I., and E. Thorsen. 2010. Anticipating maximal or submaximal exercise: no differences in cardiopulmonary responses. Clin. Physiol. Funct. Imaging 30:333–337.
Maltais, F., A. Hamilton, D. Marciniuk, P. Hernandez, F. C. Sciurba, K. Richter, et al. 2005. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. Chest 128:1168–1178.
Miller, M. R., J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, et al. 2005. Standardisation of spirometry. Eur. Respir. J. 26:319–338.
Naranjo, J., R. A. Centeno, D. Galiano, and M. Beaus. 2005. A nomogram for assessment of breathing patterns during treadmill exercise. Br. J. Sports Med. 39:80–83.
Neder, J. A., S. Dal Corso, C. Malaguti, S. Reis, M. B. De Fuccio, H. Schmidt, et al. 2003. The pattern and timing of breathing during incremental exercise: a normative study. Eur. Respir. J. 21:530–538.
Nici, L., C. Donner, E. Wouters, N. Ambrosino, J. Bourbeau, et al. 2006. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am. J. Respir. Crit. Care Med. 173:1390–1413.
O’Donnell, D. E., and P. Laveneziana. 2006a. Physiology and consequences of lung hyperinflation in COPD. Eur. Respir. Rev. 15:61.
O’Donnell, D. E., and P. Laveneziana. 2006b. The clinical importance of dynamic lung hyperinflation in COPD. COPD 3:219–232.
O’Donnell, D. E., and K. A. Webb. 1993. Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. Am. Rev. Respir. Dis. 148:1351–1357.
O’Donnell, D. E., A. L. Hamilton, and K. A. Webb. 2006. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. J. Appl. Physiol. 101:1025–1035.
Otis, A. B., W. O. Fenn, and H. Rahn. 1950. Mechanics of breathing in man. J. Appl. Physiol. 2:592–607.
Palange, P., S. A. Ward, K. H. Carlsen, R. Casaburi, C. G. Gallagher, R. Gosselink, et al. 2007. Recommendations on the use of exercise testing in clinical practice. Eur. Respir. J. 29:185–209.
Pedersen, O. F., S. Lyager, and R. H. Ingram Jr.. 1985. Airway dynamics in transition between peak and maximal expiratory flow. J. Appl. Physiol. 59:1733–1746.
Peters, M. M., K. A. Webb, and D. E. O’Donnell. 2006. Combined physiological effects of bronchodilators and hyperoxia on exertional dyspnoea in normoxic COPD. Thorax 61:559–567.
Poon, C. S. 1987. Ventilatory control in hypercapnia and exercise: optimization hypothesis. J. Appl. Physiol. 62:2447–2459.
Potter, W. A., S. Olafsson, and R. E. Hyatt. 1971. Ventilatory mechanics and expiratory flow limitation during exercise in
patients with obstructive lung disease. J. Clin. Invest. 50:910–919.
Rabe, K. F., S. Hurd, A. Anzueto, P. J. Barnes, S. A. Buist, P. Calverley, et al. 2007. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am. J. Respir. Crit. Care Med. 176:532–555.
Stubbing, D. G., L. D. Pengelly, J. L. Morse, and N. L. Jones. 1980. Pulmonary mechanics during exercise in subjects with chronic airflow obstruction. J. Appl. Physiol. 49:511–515.
Vogiatzis, I., O. Georgiadou, S. Golemati, A. Aliverti, E. Kosmas, E. Kastanakis, et al. 2005. Patterns of dynamic hyperinflation during exercise and recovery in patients with severe chronic obstructive pulmonary disease. Thorax 60:723–729.
Widdicombe, J. G., and J. A. Nadel. 1963. Airway volume, airway resistance, and work and force of breathing: theory. J. Appl. Physiol. 18:863–868.
Yan, S., D. Kaminski, and P. Sliwinski. 1997. Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 156:55–59.