Breathing pattern and carbon dioxide retention in severe chronic obstructive pulmonary disease

Massimo Gorini, Gianni Misuri, Antonio Corrado, Roberto Duranti, Iacopo Iandelli, Eduardo De Paola, Giorgio Scano

Abstract

Background – The factors leading to chronic hypercapnia and rapid shallow breathing in patients with severe chronic obstructive pulmonary disease (COPD) are not completely understood. In this study the interrelations between chronic carbon dioxide retention, breathing pattern, dyspnoea, and the pressure required for breathing relative to inspiratory muscle strength in stable COPD patients with severe airflow obstruction were studied.

Methods – Thirty patients with COPD in a clinically stable condition with forced expiratory volume in one second (FEV1) of <1 litre were studied. In each patient the following parameters were assessed: (1) dyspnoea scale rating, (2) inspiratory muscle strength by measuring minimal pleural pressure (PPLmin), and (3) tidal volume (VT), flow, pleural pressure swing (PPLsw), total lung resistance (RL), dynamic lung elastance (Edyn), and positive end expiratory alveolar pressure (PEEPi) during resting breathing.

Results – Arterial carbon dioxide tension (Paco2) related directly to RL/PPlmin, and Edyn/PPlmin, and inversely to VT and PPlmin. There was no relationship between Paco2 and functional residual capacity (FRC), total lung capacity (TLC), or minute ventilation. PEEPi was similar in eucapnic and hypercapnic patients. Expressing Paco2 as a combined function of VT and PPlmin (stepwise multiple regression analysis) explained 71% of the variance in Paco2. Tidal volume was directly related to inspiratory time (T1), and T1 was inversely related to the pressure required for breathing relative to inspiratory muscle strength (PPLsw, %PPlmin). There was an association between the severity of dyspnoea and both the increase in PPLsw (%PPlmin) and the shortening in T1.

Conclusions – The results indicate that, in stable patients with COPD with severe airflow obstruction, hypercapnia is associated with shallow breathing and inspiratory muscle weakness, and rapid and shallow breathing appears to be linked to both a marked increase in the pressure required for breathing relative to inspiratory muscle strength and to the severity of the breathlessness.

Keywords: chronic obstructive pulmonary disease, hypercapnia, breathing pattern, respiratory muscle weakness, breathlessness.

The mechanisms which lead to chronic hypercapnia in patients with chronic obstructive pulmonary disease (COPD) are not completely understood. Although carbon dioxide retention is dependent on the severity of airflow obstruction, there is considerable variability in the relationship between arterial carbon dioxide tension (Paco2) and forced expiratory volume in one second (FEV1). Other factors such as ventilation-perfusion mismatch, abnormalities in ventilatory control, respiratory muscle weakness, the pattern of breathing, and dynamic pulmonary hyperinflation have been reported to contribute to chronic carbon dioxide retention in patients with COPD. In this connection Bégin and Grassino have recently shown that, in a large group of patients with COPD with a variable degree of airflow obstruction, the probability of developing hypercapnia increases with the severity of the obstruction, obesity, and inspiratory muscle weakness. In that study, however, only half of the variation in Paco2 could be explained, even when Paco2 was expressed as a function of as many as five variables including total lung resistance, dead space, body weight, dynamic lung elastance, and maximal inspiratory mouth pressure. Thus, in the accompanying editorial Rochester hypothesised that other factors must be involved in carbon dioxide retention in patients with COPD and that rapid shallow breathing is likely to be one of these.

Although a more rapid and shallower pattern of breathing has frequently been observed in hypercapnic than in eucapnic patients with COPD, the mechanisms responsible for this breathing strategy have not been clearly defined. Increased activation of vagal afferent nerves consequent to chronic bronchitis and chronic hypoxaemia may contribute to rapid shallow breathing. More recently it has been hypothesised that rapid and shallow breathing in patients with COPD is the consequence of an excessive load imposed on the inspiratory muscles. In these patients a reduction in tidal volume could allow them to reduce the pressure required for breathing relative to inspiratory muscle strength, thus minimising respiratory effort and dyspnoea, and avoiding fatigue. The shallow breathing reduces alveolar ventilation and predisposes to hypercapnia. To our knowledge, however, no previous studies have specifically examined the interrelations between breathing pattern, breathlessness, and relative pressure required.
for breathing in patients with COPD when breathing at rest.

In this study we have analysed the relationship between chronic carbon dioxide retention and the breathing pattern, respiratory muscle load, and the pressure required for breathing relative to inspiratory muscle strength, together with the factors associated with rapid and shallow breathing, in 30 stable COPD patients with severe airflow obstruction.

Methods

Subjects

The study was performed in 30 male outpatients with COPD. Inclusion criteria were severe airflow obstruction (FEV<1 litre) and age <80 years. Exclusion criteria were: (1) left ventricular dysfunction; (2) neuromuscular disorders; (3) neoplasia; (4) thoracic surgery; (5) moderate to severe obesity (body weight >130% of ideal weight17); (6) clinical symptoms suggestive of sleep apnoea syndrome; and (7) functional evidence of restrictive lung disease (total lung capacity <80% of predicted value). All patients gave informed consent to the protocol as approved by the institution's ethics committee. Each patient had been in a clinically stable condition for at least four weeks before the study.

Respiratory symptoms were assessed in each patient by using the standardised questionnaire of the European Community for Coal and Steel. In particular, dyspnoea was graded according to a modified Medical Research Council (MRC) scale ranging from 1 (breathlessness going up one flight of stairs at normal pace) to 4 (breathlessness when dressing or undressing).18

Measurements

All measurements were made while the patients were seated in a comfortable high-back armchair. Spirometric values were measured by the standard technique using a water-sealed spirometer (Godart); functional residual capacity (FRC) was measured by the helium dilution technique. Predicted values for lung function variables are those proposed by the European Community for Coal and Steel. Arterial blood gas tensions were measured with an ABL-3 analyser (Radiometer, Copenhagen, Denmark).

Airflow was measured with a no. 3 Fleisch pneumotachograph and a Validyne pressure transducer (Validyne Corp, Northridge, California, USA) and the flow signal was integrated into the volume. The dead space of the mouthpiece and flow meter was 70 ml and the equipment resistance was 0-92 cm H2O/l/s. From the spirometric results we derived breath-by-breath time and volume components of the respiratory cycle: inspiratory time (Ti), expiratory time (Te), total time of the respiratory cycle (TTOT), and tidal volume (VT). The mean inspiratory flow (VT/Ti), duty cycle (Ti/TTOT), and respiratory frequency (f) were also calculated.

Mouth pressure (PM) was measured through a side port at the mouthpiece using a differential pressure transducer (Validyne, Northridge, California, USA). Oesophageal pressure (POEs) was measured with a conventional balloon catheter system connected to a Validyne differential pressure transducer as previously described. The balloon was positioned in the mid oesophagus and contained 0-4 ml of air. Oesophageal pressure was used as an index of pleural pressure (Ppl). In 15 patients gastric pressure (Pga) was simultaneously measured with a similar balloon catheter system connected to a second differential pressure transducer. This balloon was positioned in the stomach 65-70 cm from balloon tip to nares and contained 2 ml of air. Transpulmonary pressure (Pl) was obtained as the difference between PM and Ppl. All signals were recorded on a multichannel chart recorder.

Total lung resistance (RL) and dynamic lung elastance (Edyn) were measured during rest breathing. Total lung resistance was obtained using the isovolume method. Dynamic lung elastance was determined by dividing the difference in Pl between points of zero flow by VT. To evaluate end expiratory alveolar pressure we used the indirect method recently described by Haluszka and coworkers and Dal Vecchio and colleagues rather than the direct method of airways occlusion. In fact, awake subjects react to airways occlusion in an unpredictable fashion so that no reliable measurement of alveolar pressure can be obtained. We thus looked for the presence of a time lag between the fall in Ppl at the onset of the inspiratory effort and the onset of inspiratory airflow and measured the negative deflection in Ppl that preceded the start of inspiratory flow (fig 1). This negative deflection in Ppl will be referred to here as PEEP for consistency with previous investigations. We also assessed the change in Pga resulting from the contraction of the abdominal muscles during expiration in 15 patients. In agreement with Ninane and colleagues the increase in Pga which occurred during the expiratory phase of the breathing cycle (Pgaeexp) was taken...
Breathing pattern and hypercapnia in COPD

Table 1  Anthropometric characteristics, clinical symptoms, pulmonary function data, and inspiratory muscle strength in 36 patients with COPD and severe airflow obstruction

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%TW = % of ideal weight; PPr.min = minimal inspiratory pressure.

as a reflection of the mechanical effect of abdominal muscle contraction (fig 1).

Inspiratory muscle strength was assessed by measuring minimal (that is, greatest negative) inspiratory pleural pressure (PPr.min) at FRC during both maximal inspiratory efforts against an obstructed mouthpiece and during sniff manoeuvres. The patients were repeatedly encouraged to try as hard as possible and they had a visual feedback of generated pressure. Both PPr.min manoeuvres were repeated until three measurements with less than 5% variability were recorded. The highest PPr.min value obtained was used for analysis.

Protocol
Treatment was withheld for 12 hours before the study and all subjects were tested in the afternoon. Before the experiments each subject was well acquainted with the laboratory and equipment. Lung function tests were performed first and then, after a 40 minute rest period, an arterial blood sample was obtained and changes in volume, flow, Pmm, PPr, and PGA were recorded during three periods of quiet breathing over 30 minutes. Finally, tests of respiratory muscle strength were performed in each patient. It is important to emphasise that patients had not previously been involved in respiratory experiments; furthermore, during the periods of resting breathing each subject was distracted with non-rhythmic music to avoid any acoustic feedback.

Data analysis
Volume and time components of the respiratory cycle, inspiratory PPr swings (PPlsw), RL, ELdyn, PEEPi and PPaO2 were averaged in each patient over 30 consecutive breaths from each run. Unless otherwise specified, data are presented as means (SE). Single and stepwise multiple regression analyses were performed to assess relationships between variables. The proportion of total variance in the dependent variable accounted for by the predictor variable(s) is reported as the square of correlation coefficient ($r^2$), expressed as a percentage. Data comparisons were performed using the Student’s unpaired t test and one-way analysis of variance (ANOVA) when appropriate. A p value of <0.05 was considered statistically significant.

Results
Anthropometric, clinical, pulmonary function data, and PPr.min of patients are shown in table 1. Fourteen patients (nos 1–14) were eucapnic (Paco2 ≤ 6 kPa) and 16 (nos 15–30) were hypocapnic (Paco2 > 6 kPa). The highest PPr.min was obtained by the sniff manoeuvre in 18 patients (nos 2–4, 6–8, 10–14, 16, 18–22, and 28) and by inspiratory effort against an obstructed mouthpiece in 12. Body weight was significantly lower in hypocapnic than in eucapnic patients (90±2 (2.7) and 104±2 (4.6) % of ideal weight, respectively, p=0.01), and six hypocapnic patients and one eucapnic patient had a body weight below 85% of ideal weight. The tracings of volume, flow, PPr, and PGA obtained during quiet, resting breathing in two representative subjects with hypercapnia and eucapnia are shown in fig 1. The breathing was more rapid and shallower, and PPrsw was greater in the hypercapnic patient than in the eucapnic patient. In both patients PEEPi was associated with an increase in gastric pressure during expiration indicating abdominal muscle contraction.
Factors Influencing Carbon Dioxide Retention

The correlation coefficients of P\textsubscript{aco\textsubscript{2}} with different mechanical, inspiratory muscle, and ventilatory parameters are shown in Table 2. P\textsubscript{aco\textsubscript{2}} did not relate to FEV\textsubscript{1}, TLC, or FRC, whereas a weak but significant inverse relationship was found between P\textsubscript{aco\textsubscript{2}} and VC. As shown in Fig 2, there was a significant inverse relationship between P\textsubscript{aco\textsubscript{2}} and P\textsubscript{plmin}. Inspiratory P\textsubscript{plsw} was greater in hypercapnic than in eucapnic patients (14.8 (1-0) and 11.3 (1-2) cm H\textsubscript{2}O, respectively, p<0.05). P\textsubscript{aco\textsubscript{2}} related well to RL/P\textsubscript{plmin} and E\textsubscript{ldyn}/P\textsubscript{plmin}, the higher the P\textsubscript{aco\textsubscript{2}} the greater both the resistive and elastic loads relative to inspiratory muscle strength. Positive end expiratory alveolar pressure was present in all patients but one and was similar in eucapnic and hypercapnic patients (2.8 (0-6) and 3.4 (0-4) cm H\textsubscript{2}O, respectively). In the 15 patients in whom PGA was measured there was a significant relationship between P\textsubscript{EEP\textsubscript{i}} and expiratory rise in gastric pressure (r\textsuperscript{2}=0.66-0.7%), p<0.001, Fig 3.

There was a significant inverse relationship between P\textsubscript{aco\textsubscript{2}} and VT such that P\textsubscript{aco\textsubscript{2}} was highest in patients with the smallest VT (Fig 4).

On the contrary, no significant relationship was found between P\textsubscript{aco\textsubscript{2}} and minute ventilation.

The variables that related significantly to P\textsubscript{aco\textsubscript{2}} were entered into a multiple regression analysis. The regression equation generated by stepwise multiple regression analysis for P\textsubscript{aco\textsubscript{2}} included VT and P\textsubscript{plmin}. These variables accounted for 70.9% of the total variance in P\textsubscript{aco\textsubscript{2}}. The coefficient and F value of both variables in the final equation, and the model r\textsuperscript{2} as each variable is added, are shown in Table 3.
Breathing pattern and hypercapnia in COPD

Figure 5 Relationship between inspiratory time (Ti) and inspiratory pleural pressure swing expressed as a percentage of minimal pleural pressure (Pplsw (%Pplmin)) in 30 patients with severe COPD. The solid line is the regression line and the closed circles are individual data points.

FACTORS INFLUENCING BREATHING PATTERN

Compared with eucapnic patients, hypercapnic patients exhibited a significantly smaller Vt (0.74 (0.02) and 0.52 (0.03) l, respectively, p<0.001), a significantly greater f (15.1 (0.7) and 22.7 (0.9) cycles/min, respectively, p<0.001), and a similar minute ventilation.

Both resistive (RL) and dynamic elastic (Et-dyn) loads for the respiratory muscles were significantly greater in hypercapnic than in eucapnic patients (11.9 (0.7) versus 9.1 (0.8) cm H2O/l/min, p = 0.01; and 11.7 (1.0) versus 6.7 (0.5) cm H2O/l, p<0.001), Vt/Ti being similar in the two groups (0.57 (0.03) and 0.53 (0.02) l/s, respectively).

Tidal volume was directly related to Ti (r² = 55.3%, p<0.001), indicating that shallow breathing in severe COPD patients was mainly accounted for by changes in respiratory timing. As shown in fig 5, there was a significant curvilinear (multiplicative) relationship between Ti and Pplsw (%Pplmin) (r² = 49.6%, p<0.001), such that the shortening in Ti was associated with the increase in the pressure required for breathing relative to inspiratory muscle strength. A weak, direct relationship (r² = 25.3%, p = 0.005) was observed between Ti and Paco₂. However, stepwise multiple regression analysis showed that expressing Ti as a combined function of Pplsw (%Pplmin) and Paco₂ did not significantly increase the explained variance in Ti beyond the contribution of Pplsw (%Pplmin).

Inspiratory time and Pplsw (%Pplmin) in patients grouped according to dyspnoea scale rating are shown in fig 6. There was a significant association between dyspnoea scale rating and both Pplsw (%Pplmin) (p<0.001, ANOVA) and Ti (p<0.005, ANOVA), the patients with severe dyspnoea exhibiting the greatest Pplsw (%Pplmin) and the shortest Ti.

Discussion

The main findings of this study can be summarised as follows: (1) in patients with stable COPD with severe airflow obstruction there is a significant association between hypercapnia and both shallow breathing and inspiratory muscle weakness, and these variables explain more than 70% of the variance in Paco₂; (2) Vt relates well to Ti, and the latter is significantly related to Pplsw (%Pplmin), the shorter the Ti the greater the pressure required for breathing relative to inspiratory muscle strength; (3) there is a significant association between the severity of dyspnoea and both the increase in Pplsw (%Pplmin) and the shortening in Ti.

CRITIQUE OF METHODS

Before discussing these results it is pertinent to consider the limitations of the procedure used in this study. Inspiratory muscle strength was evaluated by measuring PrLmin during voluntary manoeuvres. In this condition the development of PrLmin depends not only on the strength and coordination of inspiratory muscles, but also on the motivation and cooperation of subjects. To minimise this prob-

Figure 6 (A) Mean (SE) inspiratory pleural pressure swing expressed as a percentage of minimal pleural pressure (Pplsw (%Pplmin)) and (B) inspiratory time (Ti) in 30 patients with severe COPD grouped by dyspnoea scale rating.
lem, PPLmin was obtained from different manoeuvres (see Methods) and all patients had a visual feedback of generated pressure as suggested by Laporta and Grassino.77

The breathing pattern was assessed with a noseclip and mouthpiece that may increase VT and decrease respiratory frequency compared with natural breathing.28 In particular, when the breathing pattern in patients with COPD was evaluated from body surface movements using the technique of inductive plethysmography,10,29 VT was found to be somewhat lower than that observed in studies in which only a mouthpiece was used.6,8 In our study the simultaneous measurement of volume, flow and Ppl was necessary to assess the relationships between PaCO2, breathing pattern, and mechanical factors such as RL, Eldyn, and PEEPi during quiet breathing. To minimise the effects of the mouthpiece, however, we used a mouthpiece and flowmeter system with a small dead space; in addition, subjects were well acquainted with the laboratory and equipment before the experiments and each patient was distracted with non-rhythmic music to avoid any acoustic feedback during periods of quiet breathing. Furthermore, our data showing a significant inverse relationship between PaCO2 and VT in patients with severe COPD are in agreement with those obtained by Loveridge and coworkers using inductive plethysmography.10

CARBON DIOXIDE RETENTION IN SEVERE COPD
The present data showing that PaCO2 did not relate significantly to FEV1, and related only weakly to VC are in line with previous studies12 indicating that many patients with COPD with severe airflow obstruction do not develop chronic hypercapnia.

Our results showed that, in stable patients with severe COPD, PaCO2 related directly to both RL/Pplmin and Eldyn/Pplmin, and inversely to both VT and Pplmin. Furthermore, multiple regression analysis showed that expressing PaCO2 as a combined function of VT and Pplmin explained more than 70% of the total variance in PaCO2. These results confirm and extend previous reports5-10,12 in that chronic carbon dioxide retention is primarily associated with shallow breathing and inspiratory muscle weakness in patients with stable COPD with severe airflow obstruction. It is important to stress however that, although correlation is an essential prerequisite to establish a cause and effect relationship, correlation alone does not imply causation. In particular, whether chronic hypercapnia itself may affect inspiratory muscle contractility in patients with severe COPD, as shown for acute respiratory acidosis in normal subjects,10 remains to be established.

Bégin and Grassino12 have recently reported that obesity enhanced the probability of hypercapnia at any level of airflow obstruction and inspiratory muscle weakness in more than 300 patients with COPD with a variable degree of airflow obstruction. In the present study, however, hypercapnic patients had a significantly lower body weight than eucapnic patients; furthermore, in agreement with a previous report,7 we found that body weight had a direct relationship with PPLmin (r2 = 28.8%, p < 0.005) such that underweight was associated with inspiratory muscle weakness. Differences in the selection of patients may partly explain these discrepancies. In fact, in the present study only patients with severe airflow obstruction were included, and obesity – that may be associated with carbon dioxide retention even in the absence of lung disease13 – was an exclusion criterion.

It has recently been shown11,22 that, in most patients with stable COPD breathing at rest, alveolar pressure at end expiration is positive. Assuming that expiration is a passive process and, as a consequence, that alveolar pressure at end expiration is the elastic recoil pressure of the respiratory system, these studies concluded that dynamic pulmonary hyperinflation is frequent in patients with stable COPD.11,22 Furthermore, Haluszka and colleagues have shown that, in patients with stable COPD, PaCO2 was significantly related to PEEPi which suggests that dynamic PEEPi and the expiratory rise in gastric pressure to PEEPi, such that alveolar pressure at end expiration was greater as the expiratory rise in gastric pressure was larger. These data indicate that, in patients with severe COPD, positive alveolar pressure at end expiration is, to a large extent, the consequence of the transmission through the relaxed diaphragm of the rise in abdominal pressure due to abdominal muscle contraction. The present findings therefore confirm that dynamic PEEPi cannot be used to quantify the degree of dynamic pulmonary hyperinflation in many patients with severe COPD.24

BREATHING PATTERN IN SEVERE COPD
Compared with eucapnic COPD patients, those with hypercapnia exhibited more rapid and shallower breathing. Inspiratory PPLslw was greater in hypercapnic than eucapnic patients and, although the elastic and resistive loads were higher in the former than in the latter, VT/TI was similar in the two groups. These data are in agreement with previous reports5-8,12,29 and clearly suggest that shallow breathing in patients with severe COPD is not associated with a reduction in inspiratory neural drive. Furthermore, in our patients VT was related directly to Ti, indicating that a small tidal volume was primarily the consequence of alteration in respiratory timing.

The mechanisms leading to alteration in respiratory timing in patients with COPD have not yet been clearly defined. It has been shown that chronic hypoxaemia may contribute to rapid shallow breathing in these patients.14 The weak but significant relationship between Ti and PaO2 observed in our patients is in line with these observations. However, expression of Ti as a combined function of PPLslw (%Pplmin) and PaO2 did not significantly increase the ex-
Breathing pattern and hypercapnia in COPD

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