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 (Ppl.min), and (3) tidal volume (VT), flow, pleural pressure swing (Pplsw), total lung resistance (RL), dynamic lung elastance (Edyn), and positive end expiratory alveolar pressure (PEEP) during resting breathing.

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

**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.

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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 (FEV1 < 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-backed 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.19

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/TE), duty cycle (VT/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.20 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 Pga. All signals were recorded on a multichannel chart recorder.

Total lung resistance (RL) and dynamic lung elastance (Edyn) were measured during resting breathing. Total lung resistance was obtained using the isovolume method.22 Dynamic lung elastance was determined by dividing the difference in Pt between points of zero flow by VT. To evaluate end expiratory alveolar pressure we used the indirect method recently described by Haluszka and coworkers19 and Dal Vecchio and colleagues23 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 PEEPi for consistency with previous investigations.11,22,24 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 colleagues25 the increase in PGA which occurred during the expiratory phase of the breathing cycle (PGAexp) was taken

Figure 1 Record of volume (V) (increased upward), flow, pleural pressure (Ppl) and gastric pressure (Pga) during quiet breathing in two representative patients with severe COPD with (A) hypercapnia (patient no. 22 in table 1) and (B) eucapnia (patient no. 1 in table 1). Dynamic positive end expiratory alveolar pressure (Ppl) and the rise in Pga during expiration (2) are illustrated in (A).
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 (P\textsubscript{l}min) at FRC during both maximal inspiratory efforts against an obstructed mouthpiece\textsuperscript{25} and during sniff manoeuvres.\textsuperscript{26} The patients were repeatedly encouraged to try as hard as possible and they had a visual feedback of generated pressure.\textsuperscript{27} Both P\textsubscript{l}min manoeuvres were repeated until three measurements with less than 5\% variability were recorded. The highest P\textsubscript{l}min value obtained was used for analysis.

**Results**

Anthropometric, clinical, pulmonary function data, and P\textsubscript{l}min of patients are shown in Table 1. Fourteen patients (nos 1–14) were eucapnic (P\textsubscript{aco2} ≤ 6 kPa) and 16 (nos 15–30) were hypercapnic (P\textsubscript{aco2} > 6 kPa). The highest P\textsubscript{l}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 hypercapnic than in eucapnic patients (90.1 (2.7) and 104.2 (4.6)\% of ideal weight, respectively, p < 0.01), and six hypercapnic patients and one eucapnic patient had a body weight below 85\% of ideal weight. The tracings of volume, flow, P\textsubscript{et}, and P\textsubscript{g}\textsubscript{a} 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 P\textsubscript{l}sw was greater in the hypercapnic patient than in the eucapnic patient. In both patients PEEPl was associated with an increase in gastric pressure during expiration indicating abdominal muscle contraction.
Table 2  Correlation coefficients of Paco₂ to respiratory function parameters in 30 patients with severe COPD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (% pred)</td>
<td>-0.27</td>
<td>NS</td>
</tr>
<tr>
<td>VC (% pred)</td>
<td>-0.45</td>
<td>0.01</td>
</tr>
<tr>
<td>FRC (% pred)</td>
<td>0.35</td>
<td>NS</td>
</tr>
<tr>
<td>TLC (% pred)</td>
<td>0.29</td>
<td>NS</td>
</tr>
<tr>
<td>Prl.min (cm H₂O)</td>
<td>-0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rₑ (cm H₂O/l/s)</td>
<td>0.38</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Eldyn (cm H₂O/l)</td>
<td>0.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPlsw (cm H₂O)</td>
<td>0.28</td>
<td>NS</td>
</tr>
<tr>
<td>Rₑ/Prl.min (s/l)</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eldyn/Prl.min (l/l)</td>
<td>0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPlsw (% Prl.min)</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vₑ (l)</td>
<td>-0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>f (cycles/min)</td>
<td>0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vₑ (l/min)</td>
<td>-0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in one second; VC = vital capacity; FRC = functional residual capacity; TLC = total lung capacity; Prl.min = minimal pleural pressure; Rₑ = total lung resistance; Eldyn = dynamic lung elastance; PPlsw = pleural pressure swing; Vₑ = tidal volume; f = respiratory frequency; Vₑ = minute ventilation.

FACTORS INFLUENCING CARBON DIOXIDE RETENTION

The correlation coefficients of Paco₂, with different mechanical, inspiratory muscle, and ventilatory parameters are shown in table 2. Paco₂ did not relate to FEV₁, TLC, or FRC, whereas a weak but significant inverse relationship was found between Paco₂ and VC. As shown in fig 2, there was a significant inverse relationship between Paco₂ and Prl.min. Inspiratory PPlsw was greater in hypercapnic than in eucapnic patients (14-8 (1-0) and 11-3 (1-2) cm H₂O, respectively, p<0.05). Paco₂ related well to Rₑ/Prl.min and Eldyn/Prl.min, the higher the Paco₂ 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 H₂O, respectively). In the 15 patients in whom PGA was measured there was a significant relationship between PEEPI and expiratory rise in gastric pressure (r² = 66.7%, p<0.001, fig 3).

There was a significant inverse relationship between Paco₂ and Vₑ such that Paco₂ was highest in patients with the smallest Vₑ (fig 4).

On the contrary, no significant relationship was found between Paco₂ and minute ventilation.

The variables that related significantly to Paco₂ were entered into a multiple regression analysis. The regression equation generated by stepwise multiple regression analysis for Paco₂ included Vₑ and Prl.min. These variables accounted for 70.9% of the total variance in Paco₂. The coefficient and F value of both variables in the final equation, and the model r² as each variable is added, are shown in table 3.

Table 3  Stepwise multiple regression analysis for Paco₂

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Model r² (%)</th>
<th>F</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vₑ</td>
<td>-3.45</td>
<td>60.5</td>
<td>61.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prl.min</td>
<td>-0.02</td>
<td>70.9</td>
<td>11.1</td>
<td>&lt;0.005</td>
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<tr>
<td>Constant</td>
<td>9.93</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

Vₑ = tidal volume; Prl.min = minimal pleural pressure.
Breathing pattern and hypercapnia in COPD

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 (ELdyn) 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 PaO₂. However, stepwise multiple regression analysis showed that expressing Ti as a combined function of PPLSW (%PPlmin) and PaO₂ 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 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-

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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.

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, PrLmin was obtained from different manoeuvres (see Methods) and all patients had a visual feedback of generated pressure as suggested by Laporta and Grassino.7

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.8-9 In our study the simultaneous measurement of volume, flow and PrL 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 studies11-12 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/PrLmin and Eldyn/PrLmin, and inversely to both VT and PrLmin. Furthermore, multiple regression analysis showed that expressing PaCO2 as a combined function of VT and PrLmin 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,13 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,27 we found that body weight had a direct relationship with PrLmin (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 disease27 – was an exclusion criterion.

It has recently been shown11,27 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.11,27 Furthermore, Haluszka and colleagues have shown that, in patients with stable COPD, PaCO2 was significantly related to PEEPi which suggests that dynamic hyperinflation may play a part in chronic carbon dioxide retention.11 In the present study a positive alveolar pressure at end expiration was present in all but one patient and was similar in eucapnic and hypercapnic patients. In agreement with Ninane and coworkers28 we observed that expiration was an active process in many patients, and there was a close relationship between the expiratory rise in gastric pressure and 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 PPLSW 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 reports6-8,12,29 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, expressing Ti as a combined function of PPLSW (%PrLmin) and PaO2 did not significantly increase the ex-
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varied preference in Ti beyond the contribution of PPLSW (%PPlmin). Moreover, it has been reported that respiratory muscle fatigue induced by breathing against an inspiratory resistive load may result in a rapid and shallow breathing.32 However, muscle fatigue is an unlikely explanation for the short Ti and the small VT we observed in hypercapnic patients during resting breathing. In line with previous studies which show that respiratory muscle fatigue can be demonstrated in less than 10% of patients with severe COPD during exacerbations of the disease,33 and in agreement with the study of Bégin and Grassino,34 the present results show that, in patients with severe COPD, PPLSW (%PPlmin) was below 60% (fig 6) — that is, the threshold value associated with inspiratory muscle fatigue in normal subjects.34

Finally, it has recently been hypothesised that, in patients with chronic hypercapnic COPD, a rapid and shallow pattern of breathing is the result of an excessive load on the inspiratory muscles in relation to their maximal strength.315 In this condition, shortening Ti and reducing VT could be a strategy for reducing inspiratory muscle effort and distress and avoiding fatigue.31 In line with the concept that the perception of inspiratory effort and dyspnoea is closely linked to the pressure required for breathing relative to inspiratory muscle strength,36 it has also been suggested that a reduction in Ti involves an integrated response of the respiratory system to the perception of breathlessness. Our data, which show an inverse relationship between Ti and PPLSW (%PPlmin) and a significant association between the severity of dyspnoea and both the increase in PPLSW (%PPlmin) and the shortening in Ti, strongly support the above hypothesis. These findings are also consistent with previous studies which have shown that breathlessness during exercise is significantly related to the PPlsw/MIP and Ti/Ttot ratios both in normal subjects and in patients with cardiorespiratory disorders.36 Although our data are in line with the observation that VT and respiratory timing responses to resistive loading are impaired in patients with COPD with severe inspiratory muscle weakness.36

In conclusion, we have shown that, in patients with stable COPD and severe airflow obstruction, chronic carbon dioxide retention is primarily associated with shallow breathing and inspiratory muscle weakness. It also appears that rapid, shallow breathing is mainly linked to both an excessive increase in the pressure required for breathing relative to inspiratory muscle strength, and to the severity of breathlessness.

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