Mouth occlusion pressure, CO₂ response and hypercapnia in severe chronic obstructive pulmonary disease

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ABSTRACT: The resting mouth occlusion pressure 0.1 s after onset of inspiration (P0.1) and minute ventilation (V̇E) and their response to CO₂ in patients with chronic obstructive pulmonary disease (COPD) remain controversial.

The ventilatory drive and the factors that predict resting arterial CO₂ tension (Paco2) were studied in 19 eucapnic and 14 hypercapnic severe COPD patients, and 20 controls. The CO₂ response was evaluated by the Read technique. The V̇E and P0.1 as a function of end-tidal CO₂ tension (Pet,CO2) were used to study the ventilatory (∆V̇E/∆Pet,CO2) and P0.1 response (∆P0.1/∆Pet,CO2). In the patients, respiratory muscle function and pleural occlusion pressure 0.1 s after onset of inspiration (Ppl,0.1) were evaluated with simultaneous measurement of pleural (Ppl) and gastric (Pga) pressures.

Hypercapnic patients had lower forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and arterial O₂ tension (PaO₂). Resting P0.1 was higher in patients than in controls, whereas ∆P0.1/∆Paco2 was similar in the three groups. There was no difference in resting P0.1 (3.6±2.0 versus 3.2±2.1 cmH₂O, p=0.2) and Pet,0.1 (1.4±2.3 versus 5.2±3.3 kPa (4.0±1.7 versus 3.9±2.5 cmH₂O, p=0.22) between eucapnic and hypercapnic COPD, whereas ∆V̇E/∆Pet,CO2 was lower in the hypercapnic group (0.29±0.24 versus 0.66±0.5 L·min⁻¹·kPa, p<0.001). By logistic regression only FEV1 and increased diaphragmatic load, and not respiratory drive, predicted resting Paco2.

Irrespective of CO₂ level, baseline central drive (represented by the mouth occlusion and pleural pressures) and CO₂ response are preserved in most patients with severe chronic obstructive pulmonary disease. Effective ventilation is inadequate in the more severely obstructed patients and this results in hypercapnia. Neuroventilatory coupling failure is an attractive explanation for chronic hypercapnia in these patients.

Keywords: Central drive chronic obstructive pulmonary disease hypercapnia mouth occlusion pressure respiratory muscles

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Patients with chronic obstructive pulmonary disease (COPD), may develop hypercapnia as the severity of the disease progresses. Several mechanisms have been proposed to explain CO₂ retention in those patients. In a study of patients with COPD, Begèn and Grassino [1] documented that inspiratory muscle weakness (as expressed by the maximal inspiratory pressure (PImax)) and the degree of airflow obstruction (as expressed by the forced expiratory volume in one second (FEV1)), were the most important determinants of resting arterial carbon dioxide tension (Paco2). They postulated that chronic alveolar hypoventilation was probably the result of a breathing strategy developed to avoid fatigue of weakened muscles, which have to overcome high inspiratory loads [1]. Although appealing, this hypothesis remained unproven since no measurement of central drive was performed in those patients. Recent evidence using needle electrodes inserted into the diaphragm to record motor neuron discharge indicated an increased discharge frequency in eight patients with severe COPD [2]. Interestingly, this was true even of four of the patients who had hypercapnia. The small number of patients did not allow further analysis, but raises questions about adaptive changes in the central controller of patients with COPD. Other factors such as respiratory muscle fatigue, abnormal breathing patterns, and ventilation-perfusion mismatching (ratio of dead space (VD) to tidal volume (VT)) may be contributing to CO₂ retention in those patients. The importance of these mechanisms remains unknown and continues to be a subject of controversy.

The mouth occlusion pressure 0.1 s after onset of inspiration (P0.1) reflects the neuromuscular component of the output of the central respiratory controller in normal subjects and patients with lung disease [3]. Atooe et al. [4] reported decreased ventilatory response to CO₂ in eucapnic and hypercapnic COPD patients, while changes in P0.1 with CO₂ and P0.1 at carbon dioxide tension (PCO₂) 8 kPa (60 torr) were significantly decreased only in the hypercapnic group [4]. In contrast, other authors have shown that resting ventilatory drive as expressed by P0.1 is increased in both eucapnic and hypercapnic patients [5]. To complicate matters, an inherent CO₂ unresponsiveness has been demonstrated in family members of hypercapnic patients [6]. This has given rise to the hypothesis that a poor P0.1 response to CO₂ may be caused by an intrinsically blunted response to hypercapnia which apparently
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Subjects

A total of 33 clinically stable patients with severe COPD consecutively referred for pulmonary rehabilitation and 20 healthy nonsmoking volunteers, participated in this study. There were six females in the eucapnic, four in the hypercapnic, and eight in the control group. The diagnosis of COPD was made according to standard criteria [8] and the definition of severe COPD was based on a value of FEV₁ <35% pred. At the time of entry into the study the patients were receiving stable medical therapy. Fifteen of 19 patients in the eucapnic and 12 of 14 in the hypercapnic group were receiving β-agonists or ipratropium bromide. Eight of 19 and 5 of 14 were on theophylline, respectively. The proportion was 4/19 and 4/14 for oral or inhaled corticosteroid in both groups. Three patients in the normocapnic and five in the hypercapnic group were receiving long-term oxygen therapy. The normal subjects had no history of pulmonary disease or respiratory symptoms and they had a normal physical examination and pulmonary function. The protocol was approved by the local Committee on Human Research and each patient gave informed consent to participate.

For comparison, and based on $P$a,CO₂, the COPD patients were divided into two groups: 1) eucapnic, defined as a $P$a,CO₂ <5.9 kPa (<44 torr) (19 patients), and 2) hypercapnic, with a $P$a,CO₂ >6.0 kPa (>45 torr) (14 patients).

Pulmonary function test and gas exchange

Spirometry was performed with a volume displacement water-sealed spirometer (Warren E. Collins, Braintree, MA, USA), and FEV₁, forced vital capacity (FVC) and FEV₁/FVC were calculated according to the recommendation of the ATS [9]. Functional residual capacity (FRC) was measured in a body plethysmograph (Warren E. Collins) as described by Dubois et al. [10]. Arterial blood samples were taken with the patients at rest and breathing room air. Oxygen was discontinued for at least 30 min in the eight patients on chronic oxygen therapy. The blood samples were analysed for arterial oxygen tension ($P$a,O₂), $P$a,CO₂, and pH with appropriate electrodes (Ciba-Corning, 278 Blood Gas System, Medfield, MA, USA). A metabolic cart (Warren E. Collins) was used to determine resting $V$t, mean partial pressure of expired CO₂ ($P_e$,CO₂) and respiratory frequency ($f$). The ratio of $V$t/$V$r was calculated from the formula:

$$\frac{V_t}{V_r} = \frac{P_a,CO_2 - P_e,CO_2}{P_a,CO_2}.$$  

Mouth occlusion pressure and ventilatory response to CO₂

$P_0.1$, minute ventilation ($V'E$) at rest, and the response to hypercapnia were assessed using the Read rebreathing technique [11]. The subjects were seated comfortably, attached to the mouthpiece with a noseclip in place and breathing room air until the end-tidal $P$CO₂ ($P_{et}$,CO₂) stabilized. They then started rebreathing a mixture of approximately 7% CO₂ and 93% O₂. $V'E$, $P_{et}$,CO₂ and $P_0.1$ were measured with a respiratory pressure module system (Medgraphics RPM system, St. Paul, MN, USA), previously calibrated against an independent pressure system. At randomized intervals, and without the subject's knowledge, the inspiratory side of the rebreathing circuit was occluded for <0.2 s during late expiration with a noiseless and vibration-free pneumatic device. $P_0.1$ was recorded. $V'E$ and $P_0.1$ were plotted against $P_{et}$,CO₂, (∆$V'E$/∆$P_{et}$,CO₂, and $∆P_{0.1}$/∆$P_{et}$,CO₂, respectively) to evaluate the ventilatory and the occlusion pressure response to CO₂.

Evaluation of respiratory muscles function

In the COPD patients gastric ($P_ga$) and pleural ($P_pl$) pressure were continuously monitored using two thin-walled latex balloons (A+E Medical Corp., Farmingdale, NJ, USA) passed transnasally, with one positioned in the stomach and the other in the midoesophagus [12]. Both balloons were secured at the nose. A separate transducer (Validyne Co., Northridge, CA, USA) measured each pressure and the calibrated output was continuously displayed on a strip chart recorder. Mouth pressure was measured using a separate transducer and the calibrated output was displayed on the same recorder. Transdiaphragmatic pressure ($P_{di}$) was calculated as the difference between $P_ga$ and $P_pl$ at end-inspiration. Maximal $P_{di}$ ($P_{di,max}$) was measured at FRC and $P_{max}$ at residual volume (RV), by asking the patients to perform a maximal inspiratory effort against a partially occluded shutter. The patients were asked to expand the chest and abdomen maximally and were coached in the performance of this manoeuvre until three reproducible results were obtained [13]. Maximal expiratory mouth pressure ($P_{Emax}$) was measured at total lung capacity (TLC) by asking the patient to exhale forcefully against a partially occluded airway. The highest value of three determinations was recorded as $P_{Emax}$. To evaluate further the diaphragmatic function, the $P_{di}/P_{di,max}$ ratio and the diaphragmatic tension time index ($T_{di}$) were determined at rest. $P_{di}$ during $V$r was obtained by averaging the peak of five consecutive tidal breaths, and $T_{di}$ was calculated as:

$$T_{di} = P_{di}/P_{di,max} \times t/t_{tot}$$

where $t$ is inspiratory time and $t_{tot}$ is duration of total breathing cycle, and both were measured from the pneumotachographic signal [14, 15].
Mouth occlusion pressure and simultaneous pleural pressure

To validate P₀.₁ pleural occlusion pressure at 0.1 s after onset of inspiration (P₀.₁/₀.₁) obtained at rest and during CO₂ rebreathing was analysed in the patients with COPD. The mean P₀.₁/₀.₁ for all patients was slightly higher than P₀.₁ (5.3±2.7 kPa versus 4.9±2.5 kPa (4±2 versus 3.7±1.9 cmH₂O), p=0.012). There was a significant correlation between P₀.₁ and P₀.₁/₀.₁ (r=0.64, p≤0.0004) in both patient groups. As was seen for P₀.₁, the P₀.₁/₀.₁ was similar between eucapnic and hypercapnic patients (5.4±2.3 versus 5.2±3.3 kPa (4.08±1.7 versus 3.9±2.5 cmH₂O), p=0.22). The value for the slope of ∆P₀.₁/₀.₁/∆Pₑ₉₅CO₂ was higher than that of ∆P₀.₁/₀.₁/∆Pₑ₉₅CO₂ (0.22±0.14 versus 0.28±0.19 cmH₂O·mmHg⁻¹, p=0.0005), but again there was a good correlation between both slopes (r=0.678, p≤0.001). Because normal controls did not undergo respiratory muscle measurements, and therefore had no P₀.₁/₀.₁ determinations, and because there was no difference in the experimental results whether P₀.₁ or P₀.₁/₀.₁ was used, the overall analysis was completed with the use of P₀.₁.

Data analysis

Results are expressed as mean±SD. The differences in spirometry and CO₂ rebreathing data among controls, eucapnic and hypercapnic COPD patients were determined using one-way analysis of variance (ANOVA). Static lung function, blood gases, gas exchange and respiratory muscle (RM) function data in eucapnic and hypercapnic COPD patients were compared using pooled t-tests. In all the COPD patients as a group, Pearson’s test (r) was used to assess the relationship between static lung function, ventilatory drive and RM function with resting Pₑ₉₅CO₂. Stepwise multiple linear regression analysis was used to determine the best predictors of resting Pₑ₉₅CO₂. Statistical significance was accepted at a probability value <0.05.

Results

Pulmonary function and gas exchange

The mean values for the physical characteristics, pulmonary function test and gas-exchange parameters from the controls, eucapnic, and hypercapnic COPD patients are shown in table 1. Controls and patients in both groups were similar in age and weight, but different in height (p<0.05). As expected, vital capacity (FVC) and airway obstruction (FEV₁) were different in the three groups (p<0.001). There was no significant difference in the results of FRC, V₁, fR, and V₁/V₇ between eucapnic and hypercapnic COPD patients (p>0.05). In contrast, hypercapnic patients had lower FVC, FEV₁, and Pₑ₉₅CO₂ (p<0.05).

Mouth occlusion pressure and ventilatory response to CO₂

The resting P₀.₁ and the ventilatory and P₀.₁ response to CO₂ in normals subjects and the two groups of COPD patients are shown in table 2. The resting P₀.₁ was similarly increased in both patient groups compared with controls. As expected, the mean ventilatory response to CO₂ (AV呼吸/ΔPₑ₉₅CO₂), was different between normals and patients (p<0.001 for the hypercapnic group and p<0.01 for the eucapnic group). A similar P₀.₁ response (ΔP₀.₁/₀.₁/ΔPₑ₉₅CO₂) during CO₂ rebreathing was observed for all three groups (p>0.05). No significant difference was found in resting P₀.₁ and P₀.₁/₀.₁ between eucapnic and hypercapnic COPD patients. In contrast, AV呼吸/ΔPₑ₉₅CO₂ was significantly lower in the hypercapnic group (p<0.05).

Respiratory muscle function

As shown in figure 1, a marked reduction in maximal ventilatory pressures (P₁₋max, Pₑ₉₅max, Pₑ₉₅max) was noted in eucapnic and hypercapnic COPD patients. However, no significant difference was found between the two groups. Diaphragmatic load measures (P₀.₁/Pₑ₉₅max and Tdi) were similarly increased in the two groups of patients (fig. 2).

Table 1. – Anthropometric, pulmonary function and gas-exchange data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Eucapnic COPD</th>
<th>Hypercapnic COPD</th>
<th>p-value+</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>19</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age yrs</td>
<td>63±9</td>
<td>62±13</td>
<td>61±6</td>
<td></td>
</tr>
<tr>
<td>Height cm</td>
<td>172±28</td>
<td>170±12</td>
<td>170±12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FVC L</td>
<td>5.5±1.7</td>
<td>5.8±1.6</td>
<td>5.8±1.6</td>
<td></td>
</tr>
<tr>
<td>Weight kg</td>
<td>72±14</td>
<td>74±11</td>
<td>74±20</td>
<td></td>
</tr>
<tr>
<td>Pₑ₉₅CO₂ mmHg</td>
<td>40±3</td>
<td>55±10**</td>
<td>55±10**</td>
<td></td>
</tr>
<tr>
<td>V₁/V₇</td>
<td>0.75±0.18</td>
<td>0.64±0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fR breaths·min⁻¹</td>
<td>20±7</td>
<td>20±4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pₑ₉₅CO₂ mmHg</td>
<td>70±16</td>
<td>56±14***</td>
<td>56±14***</td>
<td></td>
</tr>
</tbody>
</table>
| Data are presented as means±SD. COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; FRC: functional residual capacity; V₁: tidal volume; fR: respiratory frequency; Pₑ₉₅CO₂: arterial oxygen tension; Pₑ₉₅CO₂: arterial carbon dioxide tension; V₁/V₇: ratio of dead space to tidal volume. #: analysis of variance among the three groups. +: p<0.05 versus eucapnic; **+: p<0.01 versus eucapnic 1 mmHg=0.133 kPa.

Table 2. – Control of breathing data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Eucapnic COPD</th>
<th>Hypercapnic COPD</th>
<th>p-value+</th>
</tr>
</thead>
<tbody>
<tr>
<td>P₀.₁ cmH₂O</td>
<td>1.5±0.4*</td>
<td>2.7±1.5</td>
<td>3.2±2.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ΔP₀.₁/₀.₁/ΔPₑ₉₅CO₂ cmH₂O·min⁻¹·torr⁻¹</td>
<td>0.17±0.11</td>
<td>0.21±0.14</td>
<td>0.15±0.13</td>
<td>ns</td>
</tr>
<tr>
<td>AV呼吸/ΔPₑ₉₅CO₂ L·min⁻¹·torr⁻¹</td>
<td>1.76±0.99</td>
<td>0.88±0.72</td>
<td>0.38±0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Data are presented as means±SD. COPD: chronic obstructive pulmonary disease; P₀.₁: mouth occlusion pressure 0.1 s after onset of inspiration; ΔP₀.₁/₀.₁/ΔPₑ₉₅CO₂: slope of occlusion pressure response to hypercapnia; ΔV呼吸/ΔPₑ₉₅CO₂: slope of ventilatory response to hypercapnia. #: analysis of variance among the three groups. p&lt;0.05 versus eucapnic; 1 cmH₂O=1.33 kPa; 1 torr=0.133 kPa.</td>
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</tbody>
</table>
When pulmonary function, gas exchange, ventilatory drive and function measures in all COPD patients as a group were correlated with \( P_{a,CO_2} \) (\( r = -0.64 \)), \( FEV_1 \) (\( r = -0.71 \)), \( \Delta P_{0.1}/\Delta P_{et,CO_2} \) (\( r = -0.42 \)), \( P_{di,max} \) (\( r = -0.38 \)) and \( P_{di}/P_{di,max} \) (\( r = 0.63 \)) and \( T_{di} \) (\( r = 0.62 \)) were found to be significant (\( p < 0.05 \)). The illustrations of the most important correlations are shown in figure 3a and b and figure 4.

Stepwise multiple linear regression analysis determined that the best predictor of \( P_{a,CO_2} \) was the \( FEV_1 \). After this was entered, only \( T_{di} \) (diaphragmatic load index) remained significant. This model explained 59% of the variability in the \( P_{a,CO_2} \). The values and levels of significance of the multiple regression coefficients for \( P_{a,CO_2} \) are given in table 3.

**Discussion**

There are four major findings in this study: 1) compared with control subjects and irrespective of \( CO_2 \) levels, baseline central drive is increased in most patients with severe COPD; 2) the central drive response to \( CO_2 \) stimulation remains intact in the majority of COPD patients with this degree of severity and is similar to that of normal individuals; 3) the hypercapnic patients at a similar central drive have a lower ventilatory response; and 4) the factors that best predict resting \( P_{a,CO_2} \) level in these patients are the degree of airflow obstruction and increased diaphragmatic load, and not a decreased central respiratory drive.

The actual baseline state of the central controller in COPD has remained a controversial subject. These findings indicate that patients with severe COPD have an increased \( P_{0.1} \), irrespective of the level of \( CO_2 \). They also maintain a relatively intact response to further increases in \( CO_2 \). In nine eucapnic and five hypercapnic COPD patients with comparable \( FEV_1 \) to the patients in the present study, ALTOSE *et al.* [4] reported that occlusion pressure at \( PCO_2 \) 8 kPa (60 torr) was significantly greater in eucapnic patients than in normal volunteers, while the hypercapnic group had lower values than both the normals and the eucapnic patients. The occlusion pressure response to \( CO_2 \) (\( \Delta P_{0.1}/\Delta P_{et,CO_2} \)) was normal in the eucapnic patients and subnormal in the hypercapnic group. These authors postulated that chemosensitivity was impaired only in the group...
of patients with hypercapnia [4]. Moreover, an inherent CO₂ unresponsiveness has been reported in family members of hypercapnic patients [5]. Based on these observations some authors have postulated that CO₂ retention in patients with COPD may be due to an intrinsically blunted response to hypercapnia which existed before the development of the lung disease [1, 4, 6]. Alternatively, it is possible that the respiratory centres become “blunted” as CO₂ accumulates and the decreased response is an acquired phenomenon.

The difference between the findings in the study of AUTLESE et al. [4] and the present study are difficult to reconcile on the basis of severity of disease, since both groups of patients were similar. Five hypercapnic patients in the report of AUTLESE et al. [4] may have introduced some small sample bias. This is likely because our findings on 14 hypercapnic patients are in agreement with the findings of SORLI et al. [5]. These authors reported that the CO₂ response was similarly increased in hypercapnic and eucapnic COPD patients. However, using the analysis of the value of doubling ΔPCO₂ (the increase in PCO₂ required to double P0.1) the patients with hypercapnia seemed to have a decreased neuromuscular inspiratory drive in relation to the observed PaCO₂. They suggested that this was consistent with the previously advanced notion that the body adapts to chronic hypercapnia by reducing the sensitivity to CO₂. However, this analysis was not substantiated by any experimental evidence, since ΔP0.1/ΔPeCO₂ was not reported.

In the present study, the occlusion pressure response to CO₂ was not different between normals and the two groups of patients, indicating a preserved response to CO₂. A similar finding to ours was reported by MOURA et al. [16], who documented increased P0.1 in eucapnic and hypercapnic patients compared with controls and observed a normal response to CO₂ in all groups. The larger numbers of patients in the study of MOURA et al. [16] and the present study offer the best explanation to account for the differences from the results of AUTLESE et al. [4]. Likewise, the even higher values of P0.1 reported during failure to wean from mechanical ventilation indicate that the ventilatory centre tends to respond to ventilatory distress in a unimodal direction, increasing its output as ventilatory demands increase [17, 18].

These results indicate that, in terms of P0.1 and ΔP0.1/ΔPeCO₂, the definition of eucapnic patients as “fighters” and hypercapnic patients as “nonfighters” appears to be inappropriate. It seems that in patients with COPD and hypercapnia the neural inspiratory drive is relatively well preserved. This argument is further supported by the results of DETROYER et al. [2] in eight patients with severe COPD. Using needle electrodes inserted in the diaphragm, the authors documented increased neural drive, even in the four patients with increased PaCO₂. The increase in discharge frequency of the diaphragmatic motor units for these patients was in the order of 70–80%. This value is higher than the 20–30% shown to occur in the ribcage muscles under similar conditions. We speculate that patients with severe COPD reach the top values of neuromuscular inspiratory drive and that, after this level is reached, no more increment in the P0.1 can be expected to maintain PaCO₂ within normal limits. This hypothesis is further supported by the lower FVC, FEV₁, and ΔV̇E/ΔPeCO₂ seen in the hypercapnic patients. The best explanation is that the mechanical load cannot be overcome by the increased drive. This results in decreased ventilation and a rise in PaCO₂.

One possible criticism of the present study is the controversial use of P0.1 to measure central drive in patients with COPD. Indeed, P0.1 is influenced by hyperinflation and by resistive and elastic loads. All three factors work to underestimate P0.1 in these patients [19]. In the present study, quite the opposite was observed, that is an increased P0.1 and a normal ΔP0.1/ΔPeCO₂. To validate further the use of P0.1, Ppl,0.1, a more direct measure of central drive, was also determined. The values for Ppl,0.1 were slightly, but significantly higher than those of P0.1, but there was a close correlation between both values and between the slopes of ΔP0.1/ΔPeCO₂ and ΔP0.1/ΔPeCO₂ of the authors documented increased neural drive, even in the four patients with increased PaCO₂. The use of Ppl,0.1 validated the use of P0.1 in our study and substituting P0.1 for Ppl,0.1 would not alter any of the findings reported in this study.

A second point of controversy in which our study sheds some light relates to the factors that are associated with elevated PaCO₂. We found airflow obstruction (FEV₁) and diaphragmatic load (Tdi) were found to be the two most important factors predicting CO₂ level. This is in agreement with the results of BIGN and BRASINNO [1], who reported that inspiratory muscle weakness (as expressed by Pmax) and the degree of airway obstruction (as expressed by FEV₁), were the most important determinants of chronic hypercapnia in patients with clinically stable COPD. However, the interpretation of the results differs. Without measures of central drive in the patients in their study, they postulated that chronic alveolar hypoventilation was probably the result of a breathing strategy to avoid fatigue of weakened muscles, which had to overcome
high inspiratory loads. If that hypothesis were correct, a decreased central drive response to CO$_2$ would be expected. The present findings and those of DeTroyer et al. [2] of increased central drive at rest, and the increased response to CO$_2$ that we observed, argue against that hypothesis. Taken together, these findings indicate that the increased levels of P$_a$CO$_2$ in many patients with severe COPD result from failure of the pump to wash out the produced CO$_2$ even at maximal ventilatory drive, and is not an adaptive phenomenon.

These findings have important clinical implications in that those therapeutic manoeuvres or medications aimed at increasing central drive in patients with severe COPD have no physiological basis and may actually be harmful for the majority of the patients. Conversely, these observations suggest that assistance to the pumping mechanism (mechanical invasive and noninvasive ventilation) through a decrease in diaphragmatic load should result in decreased central drive and perhaps alleviate dyspnoea. It is interesting to note that baseline hypercapnia has been identified as a predictive factor for those patients with COPD who may benefit from noninvasive, intermittent, mechanical ventilation [20]. The improvement observed from mechanical ventilation is associated with decreased dyspnoea and P$_a$CO$_2$. Taken together, it is appealing to speculate that air hunger may be, at least in part, mediated by increased central drive with poor neuro ventilatory coupling. Ventilatory support would reverse this sensation rather quickly, by decreasing diaphragmatic load and improving neuro ventilatory coupling.

In summary, this study has shown that irrespective of CO$_2$ level, baseline central drive is increased in patients with chronic obstructive pulmonary disease compared with control subjects. The occlusion pressure response to CO$_2$ stimulation, whether measured at the mouth or intrathoracically, remains intact in these patients. This suggests that the neural inspiratory drive is relatively well preserved in patients with hypercapnia and that these patients may have reached the upper limit of their drive. The factors that help to predict resting arterial CO$_2$ tension in severe chronic obstructive pulmonary disease are airflow obstruction and increased diaphragmatic load, and not a decreased neuromuscular inspiratory drive. These findings argue against the hypothesis of adaptation to the load and make neuro ventilatory coupling failure a more attractive explanation of chronic hypercapnia in severe chronic obstructive pulmonary disease.

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References