# Mouth occlusion pressure, $CO_2$ response and hypercapnia in severe chronic obstructive pulmonary disease

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*Mouth occlusion pressure, $CO_2$ response and hypercapnia in severe chronic obstructive pulmonary disease. M. Montes de Oca, B.R. Celli. ©ERS Journals Ltd 1998.*

**ABSTRACT: The resting mouth occlusion pressure 0.1 s after onset of inspiration ($P0.1$) and minute ventilation ($V'E$) and their response to $CO_2$ in patients with chronic obstructive pulmonary disease (COPD) remain controversial.**

**The ventilatory drive and the factors that predict resting arterial $CO_2$ tension ($Pa,CO_2$) were studied in 19 eucapnic and 14 hypercapnic severe COPD patients, and 20 controls. The $CO_2$ response was evaluated by the Read technique. The $V'E$, and $P0.1$ as a function of end-tidal $CO_2$ tension ($Pet,CO_2$) was used to study the ventilatory ($\Delta V'E/ \Delta Pet,CO_2$) and $P0.1$ response ($\Delta P0.1/\Delta Pet,CO_2$). 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 $O_2$ tension ($Pa,O_2$). Resting $P0.1$ was higher in patients than in controls, whereas $\Delta P0.1/ \Delta Pet,CO_2$ was similar in the three groups. There was no difference in resting $P0.1$ (3.6±2.0 *versus* 4.3±2.8 kPa (2.7±1.5 *versus* 3.2±2.1 $cmH_2O$), p=0.2) and $Ppl,0.1$ (1.4±2.3 *versus* 5.2±3.3 kPa (4.08±1.7 *versus* 3.9±2.5 $cmH_2O$), p=0.22) between eucapnic and hypercapnic COPD, whereas $\Delta V'E/\Delta Pet,CO_2$ 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 $Pa,CO_2$.**

**Irrespective of $CO_2$ level, baseline central drive (represented by the mouth occlusion and pleural pressures) and $CO_2$ 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.**
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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 $CO_2$ retention in those patients. In a study of patients with COPD, BEGIN and GRASSINO [1] documented that inspiratory muscle weakness (as expressed by the maximal inspiratory pressure ($PI,max$)) 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 ($Pa,CO_2$). 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 con-

troller 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 $CO_2$ 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]. ALTOSE *et al.* [4] reported decreased ventilatory response to $CO_2$ in eucapnic and hypercapnic COPD patients, while changes in $P0.1$ with $CO_2$, and $P0.1$ at carbon dioxide tension ($PCO_2$) 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 $CO_2$ 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 $CO_2$ may be caused by an intrinsically blunted response to hypercapnia which apparently

existed before the development of the lung disease. Based on this indirect evidence, it has been proposed that a low central respiratory drive due to an intrinsically blunted response to hypercapnia may be another contributing factor to the $CO_2$ retention in those patients [1, 7].

A possible reason for the lack of agreement among the studies is that they did not evaluate simultaneously all of the factors associated with chronic hypercapnia. Most of the studies have assessed small groups of patients with a wide and variable range of airway obstruction and the largest study did not evaluate central drive [1].

This study was, therefore, designed to evaluate the ventilatory drive and respiratory muscle function during $CO_2$ rebreathing in 19 eucapnic and 14 hypercapnic patients with severe COPD (forced expiratory volume in one second ($FEV_1$) <35% predicted). The results were compared with those of 20 healthy controls.

## Material and methods

### 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 American Thoracic Society (ATS) criteria [8] and the definition of severe COPD was based on a value of $FEV_1$ <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 ipratroprium 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 $P_{a,CO_2}$, the COPD patients were divided into two groups: 1) eucapnic, defined as a $P_{a,CO_2}$ <5.9 kPa (<44 torr) (19 patients), and 2) hypercapnic, with a $P_{a,CO_2}$ >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 $FEV_1$, forced vital capacity (FVC) and $FEV_1$/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 ($P_{a,O_2}$), $P_{a,CO_2}$, 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 $CO_2$ ($P_{E,CO_2}$) and respiratory frequency ($f_R$). The ratio of $V_D/V_T$ was calculated from the formula:

$$V_D/V_T = P_{a,CO_2} - P_{E,CO_2}/P_{a,CO_2}).$$

### Mouth occlusion pressure and ventilatory response to $CO_2$

$P_{0.1}$, 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 $P_{CO_2}$ ($P_{et,CO_2}$) stabilized. They then started rebreathing a mixture of app-roximately 7% $CO_2$ and 93% $O_2$. $V'_E$, $P_{et,CO_2}$ 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 $P_{et,CO_2}$ ($\Delta V'_E/\Delta P_{et,CO_2}$, and $\Delta P_{0.1}/\Delta P_{et,CO_2}$, respectively) to evaluate the ventilatory and the occlusion pressure response to $CO_2$.

### 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 $P_{I,max}$ 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 ($P_{E,max}$) 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 $P_{E,max}$. To evaluate further the diaphragmatic function, the $P_{di}/P_{di,max}$ ratio and the diaphragmatic tension time index ($T_{tdi}$) were determined at rest. $P_{di}$ during $V_T$ was obtained by averaging the peak of five consecutive tidal breaths, and $T_{tdi}$ was calculated as:

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

where $t_i$ 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 ($P$pl,0.1) obtained at rest and during $CO_2$ rebreathing was analysed in the patients with COPD. The mean $P$pl,0.1 for all patients was slightly higher than $P0.1$ (5.3±2.7 *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 $P$pl,0.1 (r=0.64, p<0.0004) in both patient groups. As was seen for $P0.1$, the $P$pl,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 $\Delta P$pl,0.1/ $\Delta P$et,CO₂ was higher than that of $\Delta P0.1/\Delta P$et,CO₂ (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 $P$pl,0.1 determinations, and because there was no difference in the experimental results whether $P0.1$ or $P$pl,0.1 was used, the overall analysis was completed with the use of $P0.1$.

## Data analysis

Results are expressed as mean±1 SD. The differences in spirometry and $CO_2$ 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 $P$a,CO₂. Stepwise multiple linear regression analysis was used to determine the best predictors of resting $P$a,CO₂. 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, $V$T, $f$R, and $V$D/$V$T between eucapnic and hypercapnic COPD patients (p>0.05). In contrast, hypercapnic patients had lower FVC, FEV1, and $P$a,O₂ (p<0.05).

### Mouth occlusion pressure and ventilatory response to $CO_2$

The resting $P0.1$ and the ventilatory and $P0.1$ response to $CO_2$ in normals subjects and the two groups of COPD patients are shown in table 2. The resting $P0.1$ was simi-

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

| Variable | Control | Eucapnic COPD | Hypercapnic COPD | p-value+ |
|---|---|---|---|---|
| n | 20 | 19 | 14 | |
| Age yrs | 63±9 | 62±13 | 61±6 | NS |
| Height cm | 163±9 | 172±8 | 170±12 | <0.05 |
| Weight kg | 72±14 | 74±11 | 74±20 | NS |
| FVC L | 3.0±0.9 | 2.6±1.1 | 1.7±0.7* | <0.01 |
| FEV1 L | 2.4±0.5 | 0.9±0.3 | 0.6±0.3* | <0.001 |
| FRC L | | 5.5±1.7 | 5.8±1.6 | |
| $V$T L | | 0.75±0.18 | 0.64±0.14 | |
| $f$R breaths·min⁻¹ | | 20±7 | 20±4 | |
| $P$a,O₂ mmHg | | 70±16 | 56±14** | |
| $P$a,CO₂ mmHg | | 40±3 | 55±10** | |
| $V$D/$V$T | | 0.52±0.10 | 0.57±0.07 | |

Data are presented as mean±SD. COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; FRC: functional residual capacity; $V$T: tidal volume; $f$R: respiratory frequency; $P$a,O₂: arterial oxygen tension; $P$a,CO₂: arterial carbon dioxide tension; $V$D/$V$T: ratio of dead space to tidal volume. +: p=analysis of variance among the three groups. *: p<0.05 *versus* eucapnic; **: p<0.01 *versus* eucapnic. 1 mmHg=0.133 kPa.

larly increased in both patient groups compared with controls. As expected, the mean ventilatory response to $CO_2$ ($\Delta V'$E/$\Delta P$et,CO₂), 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 ($\Delta P0.1/\Delta P$et,CO₂) during $CO_2$ rebreathing was observed for all three groups (p>0.05). No significant difference was found in resting $P0.1$ and $P$pl,0.1 between eucapnic and hypercapnic COPD patients. In contrast, $\Delta V'$E/$\Delta P$et,CO₂ 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 ($P$I,max, $P$E,max, $P$di,max) was noted in eucapnic and hypercapnic COPD patients. However, no significant difference was found between the two groups. Diaphragmatic load measures ($P$di/$P$di,max and T$r$di) were similarly increased in the two groups of patients (fig. 2).

Table 2. – Control of breathing data

| Variable | Control | Eucapnic COPD | Hypercapnic COPD | p-value+ |
|---|---|---|---|---|
| $P0.1$ cmH₂O | 1.5±0.4* | 2.7±1.5 | 3.2±2.1 | <0.01 |
| $\Delta P0.1/\Delta P$et,CO₂ cmH₂O·min⁻¹·torr⁻¹ | 0.17±0.11 | 0.21±0.14 | 0.15±0.13 | NS |
| $\Delta V'$E/$\Delta P$et,CO₂ L·min⁻¹·torr⁻¹ | 1.76±0.99 | 0.88±0.72 | 0.38±0.30† | <0.001 |

Data are presented as mean±SD. COPD: chronic obstructive pulmonary disease; $P0.1$: mouth occlusion pressure 0.1 s after onset of inspiration; $\Delta P0.1/\Delta P$et,CO₂: slope of occlusion pressure response to hypercapnia; $\Delta V'$E/$\Delta P$et,CO₂: slope of ventilatory response to hypercapnia. +: p=analysis of variance among the three groups. The value for controls was different from eucapnic and hypercapnic. *: p<0.05 *versus* eucapnic. 1 cmH₂O= 1.33 kPa; 1 torr= 0.133 kPa.
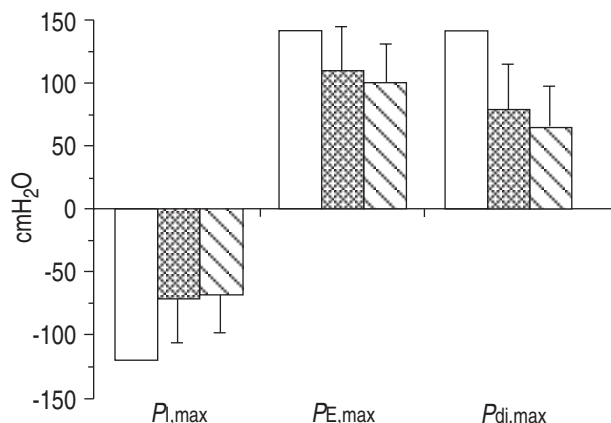
Fig. 1. – Static maximal inspiratory pressures (mean values±SD). $P_{I,max}$: maximal inspiratory pressure; $P_{E,max}$: maximal expiratory pressure; $P_{di,max}$: maximal transdiaphragmatic pressure. The predicted values shown in the figure (=normal) are from the authors' laboratory. There were no significant differences between eucapnic ( ) and hypercapnic ( ) patients. Both groups were lower than normals ( ). 1 $cmH_2O$=1.33 kPa.

*Correlation and multiple linear regression analysis*

When pulmonary function, gas exchange, ventilatory drive and function measures in all COPD patients as a group were correlated with $P_{a,CO_2}$, FVC (r=-0.64), FEV1 (r=-0.71), $\Delta P_{0.1}/\Delta P_{et,CO_2}$ (r=-0.42), $P_{di,max}$ (r=-0.38), $P_{di}/P_{di,max}$ (r=0.63) and $T_{t}di$ (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 FEV1. After this was entered, only $T_{t}di$ (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,
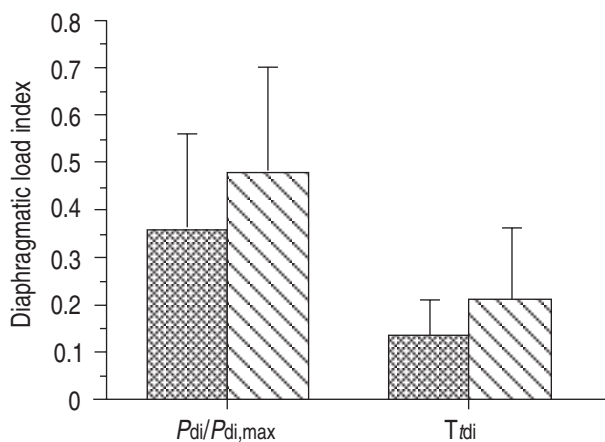


Fig. 2. – Diaphragmatic load indices (mean values±SD). $P_{di}$: transdiaphragmatic pressure; $T_{t}di$: tension time index. There were no differences between eucapnic (▨) and hypercapnic (▧) patients.
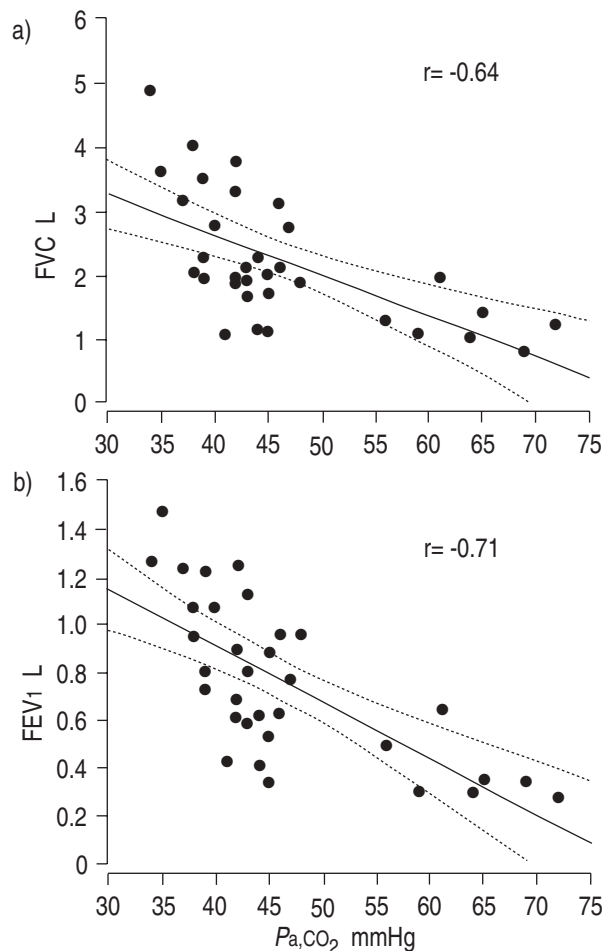


Fig. 3. – Significant correlation between: a) forced vital capacity (FVC); and b) forced expiratory volume in one second (FEV1) with arterial $CO_2$ tension ($P_{a,CO_2}$). ——: regression; ·······: ±95% confidence intervals. 1 mmHg=0.133 kPa.

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 FEV1 to the patients in the present study, ALTOSE *et al.* [4] reported that occlusion pressure at $P_{CO_2}$ 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
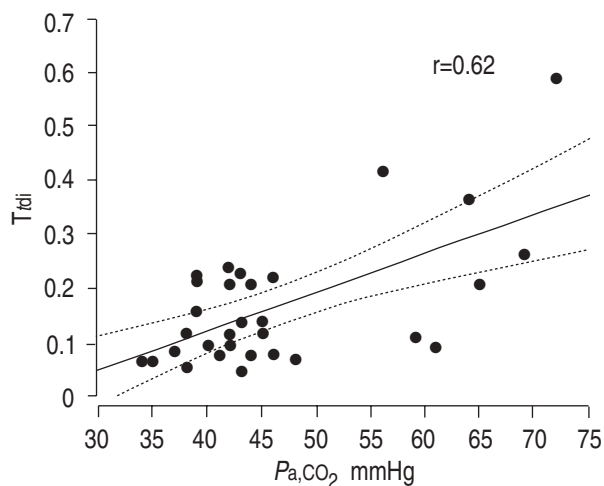
Fig. 4. – Significant correlation between diaphragmatic tension time index ($T_{tdi}$) and arterial $CO_2$ tension ($P_{a,CO_2}$). ———: regression; ........ : ±95% confidence intervals. 1 mmHg=0.133 kPa.

of patients with hypercapnia [4]. Moreover, an inherent $CO_2$ unresponsiveness has been reported in family members of hypercapnic patients [5]. Based on these observations some authors have postulated that $CO_2$ 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 $CO_2$ accumulates and the decreased response is an ac-quired phenomenon.

The difference between the findings in the study of ALTOSE *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 ALTOSE *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 $CO_2$ response was similarly increased in hypercapnic and eucapnic COPD patients. However, using the analysis of the value of doubling $\Delta P_{CO_2}$ (the increase in $P_{CO_2}$ required to double $P_{0.1}$) the patients with hypercapnia seemed to have a decreased neuromuscular inspiratory drive in relation to the observed $P_{a,CO_2}$. They suggested that this was consistent with the previously advanced notion that the body adapts to chronic hypercapnia by reducing the sensitivity to $CO_2$. However, this analysis was not substantiated by any experimental evidence, since $\Delta P_{0.1}/\Delta P_{et,CO_2}$ was not reported.

In the present study, the occlusion pressure response to $CO_2$ was not different between normals and the two groups of patients, indicating a preserved response to $CO_2$. A similar finding to ours was reported by MOURA *et al.* [16],

who documented increased $P_{0.1}$ in eucapnic and hypercapnic patients compared with controls and obs-erved a normal response to $CO_2$ 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 ALTOSE *et al.* [4]. Likewise, the even higher values of $P_{0.1}$ 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 $P_{0.1}$ and $\Delta P_{0.1}/\Delta P_{et,CO_2}$, 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 DE TROYER *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 $P_{a,CO_2}$. 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 $P_{0.1}$ can be expected to maintain $P_{a,CO_2}$ within normal limits. This hypothesis is further supported by the lower FVC, FEV1, and $\Delta V'E/\Delta P_{et,CO_2}$ 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 $P_{a,CO_2}$.

One possible criticism of the present study is the controversial use of $P_{0.1}$ to measure central drive in patients with COPD. Indeed, $P_{0.1}$ is influenced by hyperinflation and by resistive and elastic loads. All three factors work to underestimate $P_{0.1}$ in these patients [19]. In the present study, quite the opposite was observed, that is an increased $P_{0.1}$ and a normal $\Delta P_{0.1}/\Delta P_{et,CO_2}$. To validate further the use of $P_{0.1}$, $P_{pl,0.1}$, a more direct measure of central drive, was also determined. The values for $P_{pl,0.1}$ were slightly, but significantly higher than those of $P_{0.1}$, but there was a close correlation between both values and between the slopes of $\Delta P_{0.1}/\Delta P_{et,CO_2}$ and $\Delta P_{pl,0.1}/\Delta P_{et,CO_2}$. The use of $P_{pl,0.1}$ validated the use of $P_{0.1}$ in our study and substituting $P_{0.1}$ for $P_{pl,0.1}$ 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 $P_{a,CO_2}$. We found airflow obstruction (FEV1) and diaphragmatic load ($T_{tdi}$) were found to be the two most important factors predicting $CO_2$ level. This is in agreement with the results of BEGIN and GRASSINO [1], who reported that inspiratory muscle weakness (as expressed by $P_{I,max}$) 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

Table 3. – Stepwise multiple regression for arterial $CO_2$ tension

| Variable | β | t | p-value |
|---|---|---|---|
| FEV1 | -0.54 | -4.25 | 0.0002 |
| $T_{tdi}$ | 0.38 | 2.9 | 0.006 |

FEV1: forced expiratory volume in one second; $T_{tdi}$: diaphragmatic tension time index.

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 neuroventilatory coupling. Ventilatory support would reverse this sensation rather quickly, by decreasing diaphragmatic load and improving neuroventilatory 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 neuroventilatory coupling failure a more attractive explanation of chronic hypercapnia in severe chronic obstructive pulmonary disease.

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