

The voluntary drive to breathe is not decreased in hypercapnic patients with severe COPD

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The voluntary drive to breathe is not decreased in hypercapnic patients with severe COPD. A. Topeli, F. Laghi, M.J. Tobin. ©ERS Journals Ltd 2001.

ABSTRACT: How do the respiratory centres of patients with chronic obstructive pulmonary disease (COPD) and hypercapnia respond to acute increases in inspiratory load? A depressed respiratory motor output has long been postulated, but studies on this issue have yielded inconsistent results, partly due to limitations of investigative techniques. Many of these limitations can be overcome by the twitch interpolation technique, which is capable of accurately quantifying the degree of diaphragmatic activation, termed the voluntary drive to breathe. The hypothesis that patients with COPD and hypercapnia compensate for an acute increase in mechanical load on the inspiratory muscles with a lower voluntary drive to breathe than is the case with normocapnic patients was tested.

Measurements were obtained in 15 patients with COPD, six of whom displayed hypercapnia and nine normocapnia. The maximum degree of diaphragmatic activation, expressed as a voluntary activation index (mean \pm SEM), was higher in hypercapnic than in normocapnic patients (98.7 ± 0.7 versus $94.5 \pm 0.9\%$ ($p = 0.006$)), as was the mean value (94.5 ± 0.7 versus $88.5 \pm 1.9\%$ ($p = 0.01$)). Within-patient values of the index were also less variable in the hypercapnic patients (coefficients of variation, 3.4 ± 0.3 versus $6.1 \pm 0.9\%$, $p = 0.01$). Multiple regression analysis revealed the ratio of dynamic elastance to maximum transdiaphragmatic pressure, an index of inspiratory muscle loading, and pH as the only variables that correlated with maximum voluntary activation index ($r^2 = 0.69$, $p = 0.02$ for each variable).

Contrary to the hypothesis, it was concluded that voluntary activation of the diaphragm was greater and less variable in hypercapnic patients than normocapnic patients with severe chronic obstructive pulmonary disease during an acute increase in inspiratory mechanical load. Whether greater diaphragmatic recruitment during episodes of a severe exacerbation of chronic obstructive pulmonary disease provides a survival advantage for hypercapnic patients with chronic obstructive pulmonary disease remains to be determined.

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The presence of hypercapnia in patients with chronic obstructive pulmonary disease (COPD) augurs an ominous prognosis [1]. Despite extensive research, the mechanism responsible for hypercapnia is not completely understood, limiting the approach to rational therapy. Arterial carbon dioxide tension (P_{a,CO_2}) bears only a weak relationship with the severity of airway obstruction and ventilation/perfusion mismatch [2], suggesting that nonparenchymal factors may be operative. In stable patients with COPD, BEGIN and GRASSINO [3] found that hypercapnic patients had less inspiratory muscle strength and a greater inspiratory load than normocapnic patients. The scatter in load and strength was large, however, and each accounted for less than half of the variance in P_{a,CO_2} . Accordingly, additional factors must contribute to the development of hypercapnia.

A subnormal respiratory motor output has long been postulated as a mechanism for the hypercapnia in patients with COPD. An inability to maintain a

normal respiratory motor response during an exacerbation of COPD could lead to critical hypoventilation, respiratory failure, and death. Unfortunately, investigations have yielded inconsistent results, with reports of increased [4], decreased [5, 6], and equivalent [7, 8] respiratory motor output in hypercapnic and normocapnic patients. These conflicting findings stem, in part, from limitations of techniques used to measure respiratory motor output, such as the diaphragmatic electromyogram and airway occlusion pressure [9]. The twitch interpolation technique [10] overcomes many of these limitations. By recording the increase in transdiaphragmatic pressure (P_{di}) that results when phrenic nerve stimulation is superimposed on a voluntary diaphragmatic contraction, the degree of diaphragmatic activation, also termed the voluntary drive to breathe, can be quantified [10, 11].

Employing this technique in patients with asthma, ALLEN *et al.* [11] found that some patients had a reduced voluntary drive to breathe, which might

predispose to ventilatory failure and fatal asthma. To date, voluntary drive to breathe has not been compared in hypercapnic and normocapnic patients with COPD. The current investigation was conducted to test the hypothesis that patients with COPD and hypercapnia compensate for acute increases in mechanical load on the inspiratory muscles with a lower voluntary drive to breathe than do normocapnic patients.

Methods

Fifteen males with severe COPD were studied (table 1). Six patients had hypercapnia ($P_{a,CO_2} > 47$ mmHg) and nine patients had normocapnia ($P_{a,CO_2} < 43$ mmHg). No patient with an acute exacerbation of their disease within the preceding month was enrolled. The study was approved by the Human Studies Subcommittee of Hines Veterans Administration Hospital, and written informed consent was obtained from all patients.

Airway pressure at 0.1 seconds ($P_{0.1}$) after commencing tidal inspiration against an occlusion was measured using a two-way valve (Hans Rudolph, Kansas City, MO, USA) connected to a pneumotachograph (3700B Hans Rudolph) [12]. End-tidal carbon dioxide tension (P_{ET,CO_2}) was measured at the mouthpiece with a capnometer (Novamatrix, Wallingford, CT, USA). Oesophageal (P_{oes}) and gastric pressures (P_{ga}) were measured using balloon-tipped catheters; P_{di} was obtained by electronic subtraction of P_{oes} from P_{ga} . Airway pressure was measured at the mouthpiece. Transpulmonary pressure was obtained by subtracting P_{oes} from airway

Table 1.—Anthropometric characteristics and pulmonary function data of the normocapnic and hypercapnic patients with chronic obstructive pulmonary disease

	Normocapnic patients	Hypercapnic patients	p-value
Subjects n	9	6	
Age yrs	66.9 ± 3.0	66.5 ± 3.4	0.93
Body mass index kg·m ⁻²	24.7 ± 1.7	29.5 ± 2.5	0.12
FEV ₁ L	0.94 ± 0.06	0.80 ± 0.13	0.39
FVC L	2.46 ± 0.14	2.00 ± 0.27	0.12
FEV ₁ /FVC	37.9 ± 1.4	39.2 ± 3.8	0.72
FRC L	7.12 ± 0.58	6.92 ± 0.45	0.81
RV L	6.39 ± 0.61	6.20 ± 0.40	0.82
TLC L	9.20 ± 0.60	8.28 ± 0.40	0.28
pH	7.41 ± 0.01	7.38 ± 0.01	<0.01
P_{a,CO_2} mmHg	39.9 ± 0.6	52.4 ± 1.6	<0.001
P_{a,O_2} mmHg	69.6 ± 2.0	57.7 ± 4.0	0.01
Arterial bicarbonate content mEq·L ⁻¹	25.6 ± 0.6	31.2 ± 1.1	<0.001
E_{dyn} cmH ₂ O·L ⁻¹	4.37 ± 0.70	9.62 ± 1.66	<0.05
$E_{dyn}/P_{di,max}$ L ⁻¹	25.6 ± 0.6	31.2 ± 1.1	<0.001

Values are expressed as mean ± SEM. FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; P_{a,CO_2} : arterial carbon dioxide tension; P_{a,O_2} : arterial oxygen tension; E_{dyn} : dynamic elastance; $P_{di,max}$: maximal transdiaphragmatic pressure.

pressure. Dynamic lung elastance (E_{dyn}) was calculated as the ratio of change in transpulmonary pressure between instants of zero flow over the change in tidal volume within the same breath [13], and the average value during a 1-min recording of resting breathing was calculated.

Phrenic nerve stimulation

Compound diaphragmatic action potentials were recorded bilaterally with two sets of surface electrodes at the level of the seventh and eighth intercostal spaces and the anterior axillary line. The signals were amplified and band passed filtered (10–1,000 Hz; Gould, Valley View, OH, USA). Bilateral phrenic nerve stimulation was performed using two magnetic stimulators (Magstim 200, Jali, Newton, MA, USA) with two sets of double 40-mm coils (D40-1183.00, Jali, Newton, MA, USA) [14]. The area of optimal stimulation was located by moving the stimulating probe around the posterior border of the sternomastoid muscle at the level of the cricoid cartilage. The area where stimulation elicited the compound diaphragmatic action potentials of greatest amplitude, while the patient rested at end-expiratory lung volume, was marked and subsequent stimulations were performed at this site and at 100% of the stimulators' output (magnetic field of 3.2 Tesla).

Study protocol

Patients came to the laboratory for two visits, 1 to 3 days apart. On the first visit, arterial blood gases and lung volumes were measured. On the second visit, after placement of transducers and while seated with the back supported at a 90° angle, the patient performed 10–15 Mueller manoeuvres, with ≥1 min of rest separating each manoeuvre [11]. The patient was exhorted to maintain the maximal pressure for ~2 s and oscilloscope recordings of P_{oes} provided visual feedback [11]. Maximal transdiaphragmatic pressure ($P_{di,max}$) was measured as the best of the manoeuvres. A single phrenic nerve stimulation was delivered during each Mueller manoeuvre (superimposed- $P_{di,tw}$), and just after completion of the manoeuvres while the patient was relaxing at end-expiratory lung volume (control- $P_{di,tw}$).

After the last stimulation the patient rested for 1 h, and resting breathing was then recorded over 2 min. The patient then underwent a carbon dioxide rebreathing test following standard technique [15]. During resting breathing and carbon dioxide (CO₂) rebreathing, $P_{0.1}$ was recorded every 10–20 s [5]. After a rest period of ≥20 min, CO₂ rebreathing was repeated.

Signal processing and data analysis

Data were recorded and digitized at 2,000 Hz. The amplitude of the superimposed- $P_{di,tw}$ was measured as the increment in P_{di} produced by the stimulation

delivered during the maximal effort, *i.e.* the difference between the maximum displacement in P_{di} secondary to phrenic nerve stimulation and the P_{di} value immediately preceding the stimulation. The amplitude of the control- $P_{di,tw}$ was measured as the difference between the maximum pressure displacement secondary to phrenic nerve stimulation and the P_{di} value immediately preceding stimulation while the patient was relaxing at end-expiratory lung volume. Individual twitch responses were rejected from analysis according to previously described criteria (table 2) [16].

The voluntary activation index of the diaphragm, which reflects the extent of diaphragmatic activation during any given inspiratory effort, was calculated [11] as:

$$\left(1 - \frac{\text{superimposed } P_{di,tw}}{\text{mean control } P_{di,tw}}\right) \times 100 \quad (1)$$

Statistical analysis was performed and unless stated otherwise, data are reported as mean \pm SEM. Paired t-tests were used for data, and linear regression and multiple regression analysis were performed where appropriate; a two-tailed p-value <0.05 was considered statistically significant.

Results

Age, body mass, spirometry and lung volumes were similar in the two groups of patients (table 1). The hypercapnic patients had a lower arterial oxygen tension (P_{a,O_2}) ($p=0.01$) and, as expected, they also had a lower pH ($p<0.01$), and a higher P_{a,CO_2} ($p<0.001$) and arterial bicarbonate content ($p<0.001$).

Respiratory motor output during resting breathing, as reflected by $P_{0.1}$, was similar in the hypercapnic and normocapnic patients (3.0 ± 0.6 and 3.3 ± 0.3 cmH₂O, respectively) ($p=0.65$; fig. 1)). Responsiveness of the respiratory centres to chemical challenge, quantified as the slope of $P_{0.1}$ plotted against P_{ET,CO_2} , did not differ between the hypercapnic and normocapnic patients (0.31 ± 0.12 and 0.54 ± 0.19 cmH₂O \cdot mmHg⁻¹, respectively) ($p=0.40$; fig. 1)). Similarly, when respiratory centre reserve was quantified as the ratio of resting $P_{0.1}$ to $P_{0.1}$ recorded at the end of the CO₂ rebreathing manoeuvre (modified from the study of MONTGOMERY *et al.* [17]), there was no difference between the hypercapnic and normocapnic patients (0.42 ± 0.09 and 0.35 ± 0.05 , respectively) ($p=0.46$)).

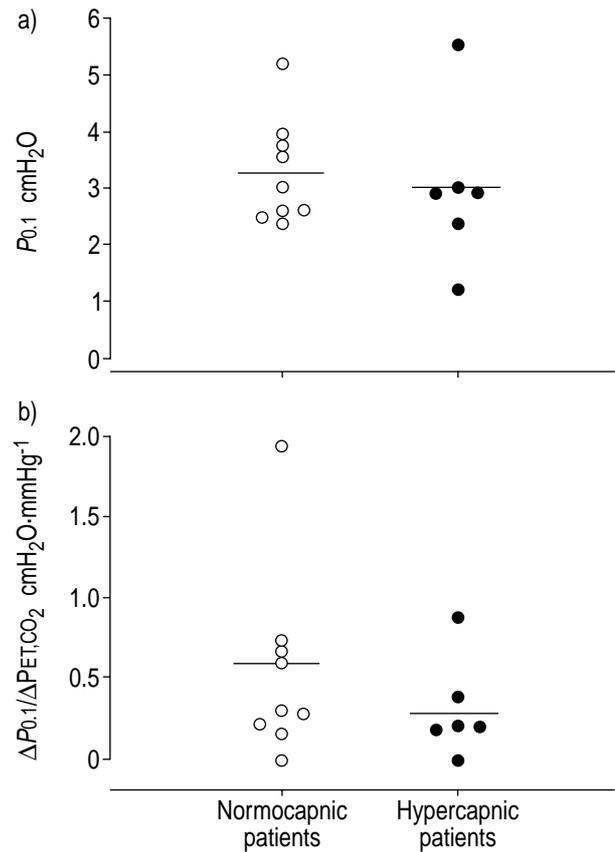


Fig. 1. – a) Resting airway occlusion pressure at 0.1 seconds ($P_{0.1}$) and b) its response to carbon dioxide challenge, assessed by the slope of $P_{0.1}$ plotted against end-tidal carbon dioxide tension ($\Delta P_{0.1}/\Delta P_{ET,CO_2}$) in nine normocapnic patients (\circ) and in six hypercapnic patients (\bullet) with severe chronic obstructive pulmonary disease. Resting values did not differ between the two groups ($p=0.65$ and $p=0.40$, respectively).

Figure 2 shows recordings with the twitch interpolation technique in a representative hypercapnic and normocapnic patient, with the former exhibiting complete diaphragmatic activation and the latter incomplete activation. All but one of the hypercapnic patients achieved a voluntary activation index $>98\%$ during at least one effort, whereas every normocapnic patient had values $<98\%$ (fig. 3). The maximum value of the voluntary activation index was higher in the hypercapnic patients than in the normocapnic patients (98.7 ± 0.7 and $94.5 \pm 0.9\%$, respectively) ($p=0.006$), as was the mean value (94.5 ± 0.7 and $88.5 \pm 1.9\%$, respectively) ($p=0.01$; fig. 3)). Moreover,

Table 2. – Criteria for accepting twitch responses for analysis

For stimulations performed at relaxed functional residual capacity
No change in end-expiratory lung volume from resting functional residual capacity value, as reflected by oesophageal pressure signal, immediately after stimulation
Relaxation of the diaphragm, as signalled by diaphragmatic electromyography activity
For stimulations performed at relaxed functional residual capacity and during the maximal inspiratory manoeuvres
Absence of oesophageal peristalsis at time of twitch stimulation
$<20\%$ variability in amplitude of CDAP of either hemidiaphragm
Absence of electrocardiogram superimposition on CDAP

Adapted from [16]. CDAP: compound diaphragmatic action potential.

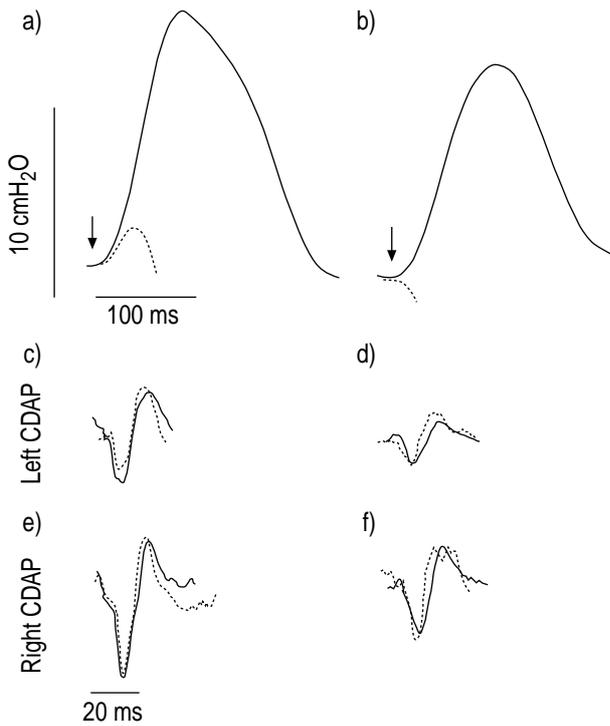


Fig. 2. – a and b) Control twitch diaphragmatic pressure from the twitch protocol ($P_{di,tw}$; —) and superimposed twitch transdiaphragmatic pressure (.....) with (c–f) corresponding compound diaphragmatic action potentials (CDAP) in a representative normocapnic (a, c, e) and hypercapnic patient (b, d, f). Bilateral phrenic nerve stimulation resulted in a detectable superimposed $P_{di,tw}$ in the normocapnic patient, whereas no twitch was elicited in the hypercapnic patient. These recordings indicate complete diaphragmatic activation in the hypercapnic patient and incomplete activation in the normocapnic patient.

within-patient values of the index were less variable in the hypercapnic group than in the normocapnic group (coefficients of variation, 3.4 ± 0.3 and $6.1 \pm 0.9\%$, respectively ($p=0.01$; fig. 3)).

The hypercapnic and normocapnic patients exhibited equivalent diaphragmatic contractility, assessed by $P_{di,max}$ (85.4 ± 20.1 and 98.9 ± 10.3 cmH₂O, respectively ($p=0.52$)) and $P_{di,tw}$ (18.6 ± 3.2 and 20.7 ± 3.0 cmH₂O, respectively ($p=0.66$)). E_{dyn} was higher in hypercapnic than in normocapnic patients (9.62 ± 1.66 and 4.37 ± 0.70 cmH₂O·L⁻¹, respectively ($p=0.02$)). The ratio of E_{dyn} to $P_{di,max}$, an index of inspiratory muscle load, was higher in hypercapnic than in normocapnic patients (0.14 ± 0.03 and 0.05 ± 0.01 ·L⁻¹, respectively ($p=0.03$)); this ratio was correlated with P_{a,CO_2} ($r=0.69$, $p=0.004$) and maximum-voluntary activation index ($r=0.69$, $p=0.004$; fig. 4). Maximum-voluntary activation index was also correlated with P_{a,CO_2} ($r=0.66$, $p=0.007$) and pH ($r=-0.71$, $p=0.003$; fig. 4). When multiple regression analysis was performed using pH, P_{a,CO_2} and $E_{dyn}/P_{di,max}$ as three independent variables and the maximum-voluntary activation index as the dependent variable, pH and $E_{dyn}/P_{di,max}$ were the only factors that correlated with maximum-voluntary activation index (maximum-voluntary activation index = $618.6 + (21.6 \times E_{dyn}/P_{di,max}) - (70.8 \times \text{pH})$ with $p=0.02$ for each variable and $r^2=0.69$ for the model).

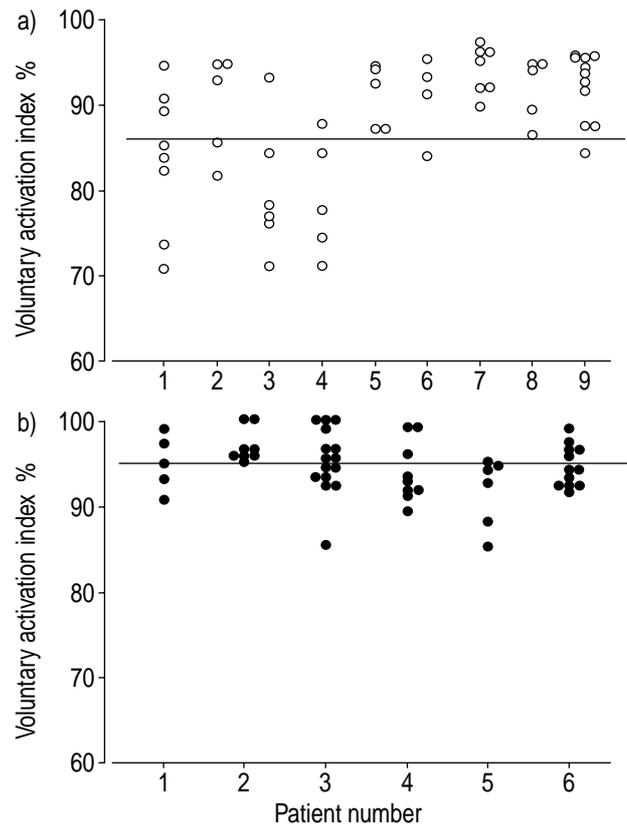


Fig. 3. – Voluntary activation index of the diaphragm during maximal voluntary inspiratory efforts in a) normocapnic and b) hypercapnic patients with severe chronic obstructive pulmonary disease. The mean value of the voluntary activation index, indicated by the horizontal lines, was higher in the hypercapnic patients than in the normocapnic patients ($p=0.01$). The maximum value of the voluntary activation index was higher in the hypercapnic than in the normocapnic patients ($p=0.006$). The within-patient values of the voluntary activation index were less variable in the hypercapnic patients than in the normocapnic patients, with coefficients of variation of 3.4 ± 0.3 versus $6.1 \pm 0.9\%$ ($p=0.01$).

Discussion

Patients with COPD who were hypercapnic achieved almost complete activation of their diaphragm during maximal voluntary efforts, whereas patients with normocapnia displayed lower and more variable activation.

The respiratory motor output response to an acute increase in ventilatory demand, assessed by calculating the ratio of resting $P_{0.1}$ to $P_{0.1}$ recorded at the end of CO₂ rebreathing, was of similar magnitude in the two patient groups, with considerable overlap between the normocapnic and hypercapnic patients. These data suggest that respiratory centre reserve is truly equivalent in hypercapnic and normocapnic patients or that the ratio of resting $P_{0.1}$ to $P_{0.1}$ at the end of a hypercapnic challenge is not sufficiently sensitive for identifying a difference in reserve.

Another similar approach for assessing the response of respiratory motor output to an acute increase in ventilatory demand is to measure the response of $P_{0.1}$ to CO₂ during a rebreathing manoeuvre. Most

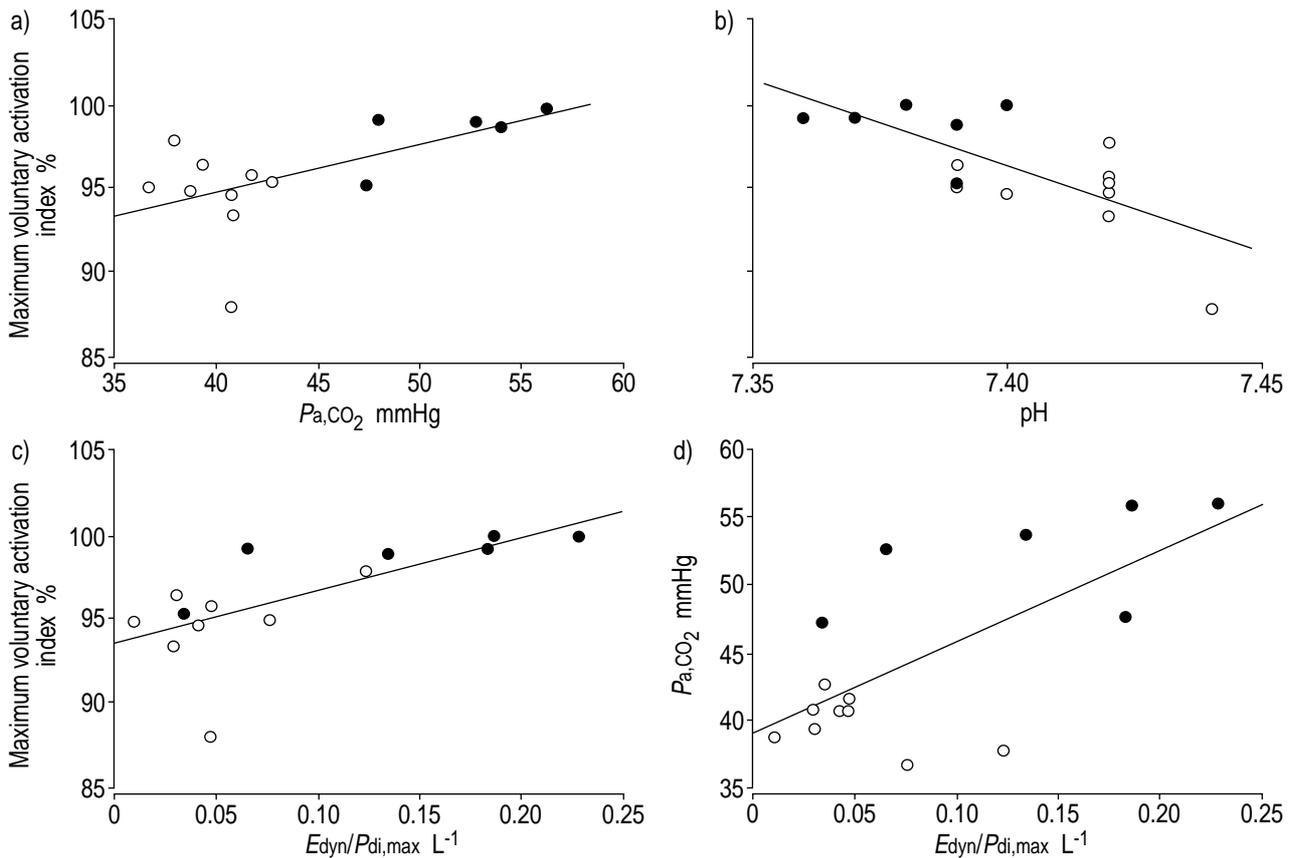


Fig. 4. – The relationships between the maximum value of the voluntary activation index of the diaphragm and a) arterial carbon dioxide tension (P_{a,CO_2}), b) pH and c) the ratio of dynamic lung elastance to maximum transdiaphragmatic pressure ($E_{dyn}/P_{di,max}$), and d) the relationship between $E_{dyn}/P_{di,max}$ and P_{a,CO_2} in 15 patients with severe chronic obstructive pulmonary disease. ○: represent normocapnic patients; ●: represent hypercapnic patients; —: depict the regression lines. The maximum value of the voluntary activation index was correlated with P_{a,CO_2} ($r=0.66$, $p=0.007$), pH ($r=-0.71$, $p=0.003$) and $E_{dyn}/P_{di,max}$ ($r=0.69$, $p=0.004$). $E_{dyn}/P_{di,max}$ was correlated with P_{a,CO_2} ($r=0.69$, $p=0.004$).

investigators have reported that the slope of this response is depressed in hypercapnic patients [6], but some [18], like the present authors (fig. 1), found slopes equivalent to those in normocapnic patients. A serious limitation of this index of respiratory drive is that airway pressure can substantially underestimate intrathoracic pressure in patients with COPD because the time constant of the respiratory system is increased. The problem is aggravated during rebreathing by the progressive rise in lung volume, causing a decrease in inspiratory muscle length, and by positive recoil of the respiratory system at end-expiration [9]. A more fundamental problem is that a patient's slope can cross the normal response line [19]; data points that lie to the left of the intersection imply that drive is supranormal, while points to the right imply blunted drive.

The neural drive to the diaphragm during loading can be assessed using the twitch interpolation technique [10, 11, 20, 21]. In rabbits, FERGUSON [10] found that measurements of the degree of diaphragmatic activation, quantified with the twitch interpolation technique, were closely correlated with recordings of the phrenic nerve electroneurogram ($r^2=0.80-0.96$). The twitch interpolation technique

is extremely sensitive, and when executed carefully, can detect as little as a 1% change in twitch pressure [22]. An additional attraction is that the values of diaphragmatic activation are independent of change in lung volume above functional residual capacity [23]. Accordingly, the measurement diaphragmatic activation, in terms of the voluntary activation index, has several advantages over more commonly used indices of respiratory drive, including $P_{0.1}$ and its response to CO_2 rebreathing.

In 10 healthy subjects, ALLEN *et al.* [11] found that the mean \pm SD value of the voluntary activation index of the diaphragm was $88 \pm 12\%$. The mean value of the index in the present study's normocapnic patients ($88.5 \pm 1.9\%$) was equivalent to that in healthy subjects, but hypercapnic patients had a higher value ($94.5 \pm 0.7\%$). Values during several maximal efforts in the well-motivated individuals of the study of ALLEN *et al.* [11] displayed considerable within-subject scatter (range of values of the index, 40–100%). The within-subject scatter of values was less in the present study's normocapnic patients (range, 71.3–97.9%) than that in the healthy subjects of the study of ALLEN *et al.* [11], and smaller again in the present study's hypercapnic patients (range, 85.4–100%; $p=0.01$).

The smaller scatter in the more severely ill patients (with hypercapnia and an increased mechanical load) is similar to the observed decrease in natural variability of heart rate and breathing pattern in disease states [24, 25].

Several variables modulate the extent of voluntary activation of the diaphragm. Pain arising in muscle or skin can decrease voluntary activation [26], but there is no reason to suspect this factor in the present study's patients. A low lung volume depresses voluntary activation [23], but lung volumes were equivalent in the present patient groups (table 1). Hypoxaemia modulates respiratory drive [9, 27] and, although the hypercapnic patients were more hypoxaemic, no significant correlation was observed between the voluntary activation index and P_{a,O_2} . The voluntary activation index was positively correlated with P_{a,CO_2} and negatively correlated with pH (fig. 4). Likewise, voluntary activation index has been reported to rise with carbon dioxide tension (P_{CO_2}) during inspiratory resistive loading [28]. These observations suggest that chronic respiratory acidosis may enable hypercapnic patients with COPD to generate an increased voluntary activation of the diaphragm.

That both voluntary activation index and P_{a,CO_2} were positively correlated with $E_{dyn}/P_{di,max}$ (fig. 4) suggests that the ability of hypercapnic patients to more fully recruit the diaphragm during acute loading represents an adaptive response to a chronically increased mechanical load. Evidence exists to support the observation that respiratory drive is not impaired in hypercapnic patients. In patients with COPD, the highest diaphragmatic motor discharge frequencies during resting breathing appeared to occur in patients with the highest P_{a,CO_2} levels, although the authors did not set out to determine if the discharge frequencies differed between hypercapnic and normocapnic patients [29]. In healthy subjects sustaining an inspiratory resistive load, MCKENZIE *et al.* [28] noted that the development of hypercapnia was accompanied by an increase in the voluntary activation index of the diaphragm.

It is not clear what advantage, if any, increased voluntary activation of the diaphragm holds for hypercapnic patients with COPD. When faced with an elevated mechanical load, increased muscle activation predisposes to diaphragmatic muscle injury [30]. Downregulation of respiratory motoneuronal output has been postulated as a useful adaptive strategy to avoid structural injury in the face of an elevated load [9, 13], and such disfacilitation has even been termed "central wisdom". Patients with COPD who are incapable of increasing neural drive during a deterioration of their disease, however, are prone to hypoventilation and lethal hypoxaemia. In a recent study of patients with COPD who failed a trial of weaning from mechanical ventilation it was found that patients developed a >40% increase in inspiratory muscle effort as they developed progressive respiratory failure [13]. That is, when faced with an acute increase in mechanical load, patients with COPD do not reduce inspiratory muscle activation, despite the theoretical advantage of doing so. Nevertheless, humans subjects undergoing extreme loading

may find it increasingly difficult to maintain full voluntary activation of their muscles as progressive fatigue develops, *i.e.* they experience central fatigue [21]. Studies in animals [27, 31] also suggest that extreme loading results in depression of drive to the inspiratory muscles.

While it is difficult to separate the contributions of voluntary and involuntary drive to the respiratory motoneurons during external loading, some evidence suggests that the bulbopontine respiratory centres do not fully activate the diaphragm even when the chemical drive to breathe is high [27, 32]. The human motor cortex projects directly and extensively to the diaphragm [33] and is implicated in the production of voluntary inspiratory efforts [34]. Thus, as ALLEN *et al.* [11] have noted, voluntary drive to the diaphragm may be an important defense against the development of hypoventilation during extreme respiratory loading, as can occur with an exacerbation of COPD. If some patients experiencing a severe exacerbation of COPD develop progressive central fatigue, those in whom the voluntary activation index is already low will be at a disadvantage compared with patients having a higher pre-existing voluntary activation index, as the inspiratory pressure swings in the former case might rapidly decrease to levels not sufficient for sustaining alveolar ventilation. This situation is analogous to patients with prior poliomyelitis who exhibited decreased limb muscle endurance during a fatigue protocol compared to healthy subjects, partly due to a greater degree of central fatigue, which, in turn, appears to result from an impairment in voluntary activation of the muscles [35]. In other words, patients with a higher load on their respiratory muscles may have learned how to fully activate their diaphragm on an intermittent basis. This ability to achieve full activation of the diaphragm is likely to provide a survival advantage for the patient with COPD who is faced with an increased mechanical load and worsening gas exchange.

Indirect lines of evidence suggest that the extent of voluntary activation of the diaphragm that patients with COPD can achieve, while clinically stable, could influence their capacity to maintain alveolar ventilation during an exacerbation. Firstly, an increase in P_{a,CO_2} during an exacerbation of COPD has been found to be greater in patients who were normocapnic when clinically stable than in patients who were hypercapnic when clinically stable [36]. This observation suggests that the respiratory controller recruits the inspiratory muscles to a lesser extent in patients who were normocapnic than in those who were hypercapnic (when both were clinically stable). Secondly, hypoxaemia at the time of hospital admission for an exacerbation was less severe in patients who were normocapnic when clinically stable than in patients who were hypercapnic when clinically stable [36]. This observation supports the notion that gas exchange is more severely compromised in patients who are hypercapnic than in those who are normocapnic. Accordingly, when patients with longstanding hypercapnia experience an acute exacerbation of COPD, their only option is to maximally

recruit their inspiratory muscles, or to face life-threatening hypoxaemia. Thirdly, mortality secondary to an exacerbation is not linked to the absolute level of hypercapnia but to the degree of acidosis [37, 38]. These observations suggest that the inability to maintain an adequate alveolar ventilation by almost complete respiratory muscle recruitment may contribute to mortality.

In conclusion, during an acute increase in inspiratory load, patients with chronic obstructive pulmonary disease and hypercapnia were able to activate the diaphragm more fully than patients with the disease and normocapnia. Whether greater diaphragmatic recruitment during severe exacerbations of chronic obstructive pulmonary disease provides a survival advantage remains to be determined.

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