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Carbon dioxide responsiveness in COPD patients with and without chronic hypercapnia

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Carbon dioxide responsiveness in COPD patients with and without chronic hypercapnia. G. Scano, A. Spinelli, R. Duranti, M. Gorini, F. Gigliotti, P. Goti, J. Milic-Emili. ©ERS Journals Ltd 1995.

ABSTRACT: To ascertain whether and to what extent the reduced ventilatory response to a hypercapnic stimulus in chronic obstructive pulmonary disease (COPD) patients depends on a blunted chemoresponsiveness of central origin or to mechanical impairment, we studied two groups of COPD patients without (group A) and with (group B) chronic hypercapnia, but with similar degrees of airway obstruction and hyperinflation.

The study was performed on 17 patients (9 normocapnic and 8 hypercapnic). Six age-matched normal subjects (group C) were also studied as a control. During a CO_2 rebreathing test, ventilation ($\dot{V}_E$), mouth occlusion pressure ($P_{0.1}$), and the electromyographic activity of diaphragm (Edi) were recorded and then plotted against end-tidal carbon dioxide tension (P_{CO_2}).

Inspiratory muscle strength was significantly lower in the hypercapnic group (group B) compared to normocapnic group (A), and in these groups compared to the control group (C). Both patient groups exhibited significantly lower $\Delta\dot{V}_E/\Delta P_{CO_2}$ than the control group. In hypercapnics, $\Delta P_{0.1}/\Delta P_{CO_2}$ was significantly lower than in normocapnics and control group, whilst mouth occlusion pressure as % of maximal inspiratory pressure $\Delta P_{0.1}(\%MIP)/\Delta P_{CO_2}$ did not differ significantly among the three groups. $\Delta Edi/\Delta P_{CO_2}$ increased from C to A. At a P_{CO_2} of 8.65 kPa, $\dot{V}_E$ was similar in the normocapnic and control group, but lower in hypercapnics; Edi was similar in hypercapnic and control group; but greater in normocapnics. $P_{0.1}$(%MIP) did not differ significantly among groups.

Although these data seem to suggest that CO_2 chemoresponsiveness was normal in hypercapnic and increased in normocapnic COPD patients, the lower $\dot{V}_E$ at a P_{CO_2} of 8.65 kPa casts doubts about the adequacy of chemoresponsiveness in the hypercapnic group. In the latter, the reduced $P_{0.1}$ response in face of normal $P_{0.1}$(MIP) and Edi responses to carbon dioxide stimulation could suggest an impairment in inspiratory muscle function. Mechanical impairment and inadequate chemoresponsiveness are both likely to contribute to the low ventilatory response to CO_2 stimulation in chronic hypercapnic COPD patients.

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Since the original study by WHITELAW *et al.* [1], mouth occlusion pressure ($P_{0.1}$) has been found useful in assessing neuromuscular inspiratory drive in patients with chronic obstructive pulmonary disease (COPD) [2–10]. Based on the observation that $P_{0.1}$ was greater in a group of hypercapnic COPD patients than in a group of less hyperinflated normocapnic patients, ŠORLI *et al.* [8] hypothesized that the rate of the rise of phrenic electroneurogram or diaphragmatic electromyogram (Edi), an index of neural inspiratory drive, was greater in the former group. Current methods of electromyogram processing and quantification [11–13] make Edi a useful index of respiratory muscle activation, both in normal subjects and patients with chronic airflow obstruction [9, 11–21]. We have recently applied these methods and, consistent with the hypothesis of ŠORLI *et al*. [8], have shown that COPD patients with hypercapnia have a greater Edi compared to COPD patients with normocapnia [9].

Despite a high $P_{0.1}$ whilst breathing room air, hypercapnic patients with COPD have been reported to have a blunted $P_{0.1}$ responsiveness to exogenous carbon dioxide [3–8]. This pattern is consistent with a previous study by LOURENÇO and MIRANDA [22] showing that the Edi response to carbon dioxide tension (P_{CO_2}) is remarkably low in hypercapnic COPD patients. Contrasting evidence, however, was given in a brief report by GRIBBIN *et al.* [14]. On the other hand, in many relevant papers [8, 10, 14, 22], the study group and the control group were not

accurately matched for age and pulmonary mechanics. This shortcoming needs to be stressed because in assessing the relative importance of factors which affect the respiratory response to exogenous CO_2 stimulation, differentiation of diminished carbon dioxide responsiveness of central origin from that due to mechanical impairment is an important issue of clinical relevance.

Therefore, the present investigation was aimed at evaluating the magnitude of chemoresponsiveness assessed in terms of Edi, $P_{0.1}$ and ventilatory ($\dot{V}_E$) responses to carbon dioxide stimulation in two groups of COPD patients with a similar degree of pulmonary mechanical impairment, one with chronic hypercapnia and the other with normocapnia. We have found that CO_2 responsiveness is high in normocapnics, whilst in hypercapnics, though similar to that of normal control group, it is probably inadequate to sustain $\dot{V}_E$.

Materials and Methods

Subjects

The study was performed on 17 patients with COPD as defined by the criteria of the American Thoracic Society [23]. Eight males and one female (group A), aged 64±4 (SD) yrs, were normocapnic (arterial carbon dioxide tension (Pa_{CO_2}) <5.72 kPa); and eight males (group B) aged 67±4.4 yrs were hypercapnic (Pa_{CO_2} ≥6.25 kPa). All patients complained of exertional dyspnoea. All had roentgenographic findings of pulmonary hyperinflation. At the time of the study, all patients were in a clinically stable state. Each had serial arterial blood gas measurements. Therapy was withheld for 12 h before the study. No patient exhibited a >10% increase in forced expiratory volume in one second (FEV_1) after inhalation of a $ß_2$-agonist bronchodilating agent. Patients with COPD and isolated episodes of CO_2 retention due to acute exacerbation of bronchitis were excluded. We also studied an age-matched control group (C) of 6 normal subjects (3 males and 3 females) in whom lung function was within normal limits, aged 64±10 yrs and height was 166±8 cm. Informed consent was obtained from all subjects before the start of the experiments. All subjects were accustomed to the equipment and experimental procedure.

Measurements

Arterial blood gases and routine spirometry obtained in seated position were assessed as described previously [24]. The normal values for lung volumes are those proposed by European Community for Coal and Steel [25]. Maximal static inspiratory pressure (MIP) at functional residual capacity (FRC), measured against an obstructed mouthpiece with a small leak to minimize oral pressure artifacts, was measured using a differential pressure transducer (Statham SC 1001). The subjects, comfortably seated and wearing a noseclip, performed maximal inspiratory efforts and were instructed to maintain maximal pressures for at least 1 s. The manoeuvres were repeated until three measurements with less than 5% variability were recorded. The highest value obtained was utilized for analysis.

The ventilatory pattern, inspiratory muscle activation, and mouth occlusion pressure were evaluated, with subjects in a comfortable supine position. In the apparatus used, the inspiratory line was separated from the expiratory line by a one-way valve (Hans-Rudolph) connected to a Fleisch No. 3 pneumotachograph. The flow signal was integrated into volume. From the spirogram we derived: inspiratory time (T_I), expiratory time (T_E), total time of the respiratory cycle (Ttot), and tidal volume (V_T). Respiratory frequency (f_R=60/Ttot) and instantaneous ventilation ($\dot{V}_E=V_T \times f_R$) were also calculated. Mouth pressure during CO_2 rebreathing was measured using a pressure transducer (Statham P23ID). Mouth occlusion pressure 0.1 s after the beginning of inspiration ($P_{0.1}$) [1] was recorded as described previously (9, 15–17). Mouth occlusion pressure was expressed both as absolute value (cmH_2O) and as percentage of MIP, in order to normalize $P_{0.1}$ for the individual differences in inspiratory muscle strength [9, 26]. Expired CO_2 (P_{CO_2}) was sampled continuously at the mouth by an infra-red CO_2 meter. The dead space of the equipment was 178 ml and the resistance of the system up to a flow of 4 $l \cdot s^{-1}$ was 0.92 $cmH_2O \cdot l^{-1} \cdot s$.

The electromyographic activity of the diaphragm (Edi) was recorded as described previously [9, 15–17] *via* large surface electrodes from the lower anterolateral rib cage [27].

The muscle action potentials were differentially amplified, filtered between 100 and 1,000 Hz, to remove as much electrocardiographic (ECG) activity as possible, without significantly filtering Edi. The filtered Edi signal and mouth pressure recording were displayed on a single-beam storage oscilloscope (Tektronix 5115). Edi activity was full-wave rectified and integrated over time (time constant 100 ms) using a third-order low-pass filter to provide a measurement of change in average electrical activity as a function of time, referred to as "moving time average" [11–13]. Inspiratory activity was quantified both as peak of activity and as rate of rise of activity. The former was directly measured in arbitrary units (XP), and the latter was obtained by dividing XP by the inspiratory time (XP/T_I).

Because of the variability of the impedance between diaphragm and electrodes, absolute values (mV) are not comparable among different subjects. To overcome this problem and to obtain a reference value, Edi was measured whilst the subject, connected to the pneumotachograph, performed an inspiratory manoeuvre breathing in up to total lung capacity (TLC) [28]. This manoeuvre was repeated at least three times, and in each subject both inspiratory volume and the peak of Edi were closely reproducible (less than 5% variability). The mean level of this Edi activity was taken as a reference; all successive measurements have been expressed as a percentage of the reference value obtained at TLC. Since the EMG activity of inspiratory muscles may include cardiac activity,

we checked cardiac artifacts to manually gate ECG, if necessary, so that it would not contribute substantially to the Edi.

The output of the CO_2 meter, flow signal, integrated flow signal, mouth pressure, and the moving time average were recorded continuously on a multichannel chart recorder. Respiratory cycles, occlusions and Edi were continuously recorded, and the cycles immediately following each occlusion were discarded. Ventilatory parameters and Edi were calculated from the data averaged from the three breaths preceding each occlusion.

Protocol

After a 10 min adaptation period, baseline evaluation began. Successively, the subjects underwent a CO_2 rebreathing test following the procedure recommended by READ [29]. A gas mixture (7% CO_2 and 93% O_2) was inhaled for 3–5 min from a 5–8 *l* bag, the largest bag being reserved for normal subjects. In all cases, the gas volume administered exceeded the subject's vital capacity by 1 *l*. Using these values, the rebreathing bag was kept flaccid. Rebreathing started after 30–45 s, which allowed the subject to equilibrate with the circuit as shown by the plateau on the CO_2 record and minimal P_{CO_2} inspiratory/expiratory swings. Details of the technique have been reported previously [30]. In each normal subject, the rebreathing test was repeated on 2–3 different days, whilst in patients it was duplicated on the same day with an interval of 60 min between each test. The resistance of the circuit used during the CO_2 rebreathing test was such that the mouth pressure during unoccluded breathing was always <2 cmH_2O greater than or less than atmospheric pressure. During CO_2 inhalation, when the open-loop condition was achieved, occlusions were randomly performed every 10–20 s.

In normal subjects and in COPD patients, peak moving average at TLC remained fairly constant from the start to the end of the CO_2 rebreathing run (~5 to 10%). Therefore, it was used to normalize Edi recorded at VT.

Data analysis

For each rebreathing run, changes in $\dot{V}_E$, timing and volume components of breathing pattern, $P_{0.1}$ and Edi were plotted against corresponding P_{CO_2} values [9, 15–17] and subjected to least square linear regression analysis. We made sure that in no case was the response exhibited on one study 20% greater or lower than the response on each of the other studies.

For each normal subject and for each patient mean slope for three or two runs, respectively, was calculated; data were averaged for patients and normal subjects.

Values are mean±SD. Spirometric and arterial blood gas values were compared between normocapnic and hypercapnic patients by means of Mann-Whitney U test for unpaired samples. All other results were compared by Kruskal-Wallis analysis of variance (KWAV) and Mann-Whitney U test when appropriate. A value of $p<0.05$ was considered significant. Bonferroni's adjustment (0.05/n tests) for multiple testing was used.

Results

The anthropometric characteristics and respiratory function data of the patients are summarized in table 1. Age was not significantly different in the three groups; the body weight, expressed as percentage of the ideal weight [31], was 93.3±12%, 95.3±9.5% and 105±7% for groups A, B and C, respectively. The two patient groups also showed similar values of vital capacity (VC), and a similar degree of airway obstruction (FEV_1) and hyperinflation (FRC). MIP differed significantly among the three groups ($p<0.0008$); in groups A and B, MIP was significantly lower ($p<0.05$) compared to the control group (C 91.6±19 cmH_2O), and in group B it was significantly lower than in group A. Arterial oxygen tension (Pa_{O_2}) was significantly lower ($p<0.009$) in group B compared to group A. Arterial pH was similar but arterial bicarbonate (HCO_3^-) content was higher in group B ($p<0.0006$).

As shown in table 2, $\Delta\dot{V}_E/\Delta P_{CO_2}$ was significantly lower in A and B compared to C ($p<0.024$ and $p<0.01$, respectively). $\Delta P_{0.1}/\Delta P_{CO_2}$ was significantly lower in B compared to A ($p<0.02$) and C ($p<0.05$), whilst $\Delta P_{0.1}$ (%MIP)/ΔP_{CO_2} and $\Delta XP/\Delta P_{CO_2}$ did not differ among the three groups (KWAV). In contrast, $\Delta(XP/T_I)/\Delta P_{CO_2}$ increased from C to A ($p<0.028$, KWAV) with a trend to be greater in A than in C ($p<0.063$).

Individual data analysis (table 3 and fig. 1) show that in all patients but one (No. 17) the correlations of both XP and XP/TI with P_{CO_2} were significant. In patient No.

Table 1. – Anthropometric characteristics and pulmonary function data of the patients with COPD with normocapnia (group A) and chronic hypercapnia (group B)

	Group A n=9		Group B n=8		p
Age yrs	64	(4)	67	(4)	NS
Weight %IW	93	(12)	95	(9.5)	NS
VC* %	72	(8.2)	63	(11)	NS
RV* %	185	(34)	203	(27)	NS
FRC* %	157	(22)	166	(20)	NS
TLC %	114	(15)	113	(12)	NS
FEV_1 %	32	(7.9)	27	(8.7)	NS
FEV_1/VC %	34.7	(8.4)	30	(4.8)	NS
MIP cmH_2O	62.9	(15.5)	46	(10)	<0.04
Pa_{O_2} kPa	10.15	(1.23)	8.44	(1.05)	<0.009
Pa_{CO_2} kPa	5.18	(0.42)	6.86	(0.74)	<0.0006
pH	7.40	(0.013)	7.39	(0.027)	NS
HCO_3^- $mEq \cdot l^{-1}$	25.3	(1.3)	30.8	(1.9)	<0.006

Values are presented as mean and SD in parenthesis. VC: vital capacity; RV: residual volume; FRC: functional residual capacity; TLC: total lung capacity; FEV_1: forced expiratory volume in one second; MIP: maximal inspiratory pressure; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; HCO_3: arterial bicarbonate content; NS: nonsignificant; *: percentage of predicted value. Mann-Whitney U-test for unpaired samples was used in all comparisons but Age and MIP, in which Kruskal-Wallis analysis of variance and Mann-Whitney U-Test with Bonferroni's adjustment were used.

Table 2. – Average $\dot{V}_E$, $P_{0.1}$ and Edi response slopes to hypercapnic rebreathing in patients and in normal subjects

Patient group	$\Delta\dot{V}_E/\Delta P_{CO_2}$ $l\cdot min^{-1}$ kPa	$\Delta P_{0.1}/\Delta P_{CO_2}$ cmH_2O/kPa	$\Delta P_{0.1}/\Delta P_{CO_2}$ %MIP/kPa	$\Delta XP/\Delta P_{CO_2}$ %TLC/kPa	$\Delta(XP/TI)/\Delta P_{CO_2}$ (%TLC/s)/kPa
Group A (n=9)	4.17	2.72	4.59	16.55	20.59
	(1.12)	(2.08)	(1.17)	(3.12)	(2.12)
Group B (n=8)	2.67	1.08	2.57	13.54	13.61
	(1.35)	(0.43)	(1.45)	(9.51)	(5.10)
Group C (n=6)	9.17	2.57	2.87	17.39	10.91
	(3.47)	(0.49)	(1.24)	(9.14)	(4.59)
KWAV					
H	13.42	9.05	2.65	0.42	7.10
p	<0.0012	0.01	NS	NS	<0.028
Mann-Whitney test					
p (B *vs* A)	NS	<0.02	NS	NS	NS
p (B *vs* C)	<0.01	<0.05	NS	NS	NS
p (A *vs* C)	<0.024	NS	NS	NS	<0.063

Values are presented as mean(±SD). $\dot{V}_E$: minute ventilation; $P_{0.1}$: mouth occlusion pressure; XP: peak of electromyographic activity of diaphragm; XP/TI: rate of rise of electromyographic activity of diaphragm, obtained by dividing XP by inspiratory time (TI); P_{CO_2}: end-tidal pressure of carbon dioxide; KWAW: Kruskal-Wallis analysis of variance. For further abbreviations see legend to table 1.

17, XP reached a plateau during hypercapnia, indicating that the rise of XP/TI. With increasing P_{CO_2} was due to a decrease in TI with the exception of this patient, the XP/TI response slopes in COPD were similar to or greater than the average ±1SD response slope of this relationship calculated for the control group. In contrast, in six group B patients (Nos 11, 13–17), and in one of group A (No. 9), the $P_{0.1}$ response slopes were lower than the average -1SD resonse slope of this relationship calculated for the control group (table 3 and fig. 2).

Table 4 shows that at P_{CO_2} of 8.65 kPa, $\dot{V}_E$ (p<0.005), TI (P<0.003), XP (p<0.0028) and XP/TI (p<0.0018), but

Table 3. – Individual $P_{0.1}$ and Edi response slopes to hypercapnic rebreathing in the two groups of COPD

Patient No.	$\Delta P_{0.1}/\Delta P_{CO_2}$ cmH_2O/kPa		$\Delta XP/\Delta P_{CO_2}$ %TLC/kPa		$\Delta(XP/TI)/\Delta P_{CO_2}$ (%TLC/s)/kPa	
	s	r	s	r	s	r
Group A						
1	3.684	0.82	7.218	0.78	13.609	0.84
2	3.458	0.99	23.83	0.88	28.947	0.93
3	1.879	0.90	7.894	0.92	14.887	0.94
4	7.744	0.95	32.330	0.71	23.609	0.88
5	1.128	0.86	23.300	0.83	25.563	0.95
6	1.428	0.94	11.128	0.95	19.624	0.98
7	1.729	0.99	23.380	0.91	25.263	0.86
8	2.007	0.94	13.760	0.93	23.533	0.90
9	1.473	0.80	6.075	0.83	10.285	0.84
Group B						
10	1.128	0.73	29.399	0.92	16.466	0.88
11	0.376	0.79	13.609	0.85	11.353	0.73
12	1.804	0.83	24.135	0.91	20.000	0.69
13	0.977	0.37	-1.428	0.94	4.361	0.93
14	1.503	0.92	10.827	0.93	15.338	0.94
15	0.902	0.90	11.128	0.93	14.210	0.85
16	1.053	0.90	12.781	0.91	9.172	0.95
17	0.902	0.84	7.895	-0.18	18.045	0.69

s and r: slopes and correlation coefficients, respectively, of the relationships of $P_{0.1}$, XP and XP/TI with P_{CO_2} during rebreathing. For further abbreviations see legend to tables 1 and 2.

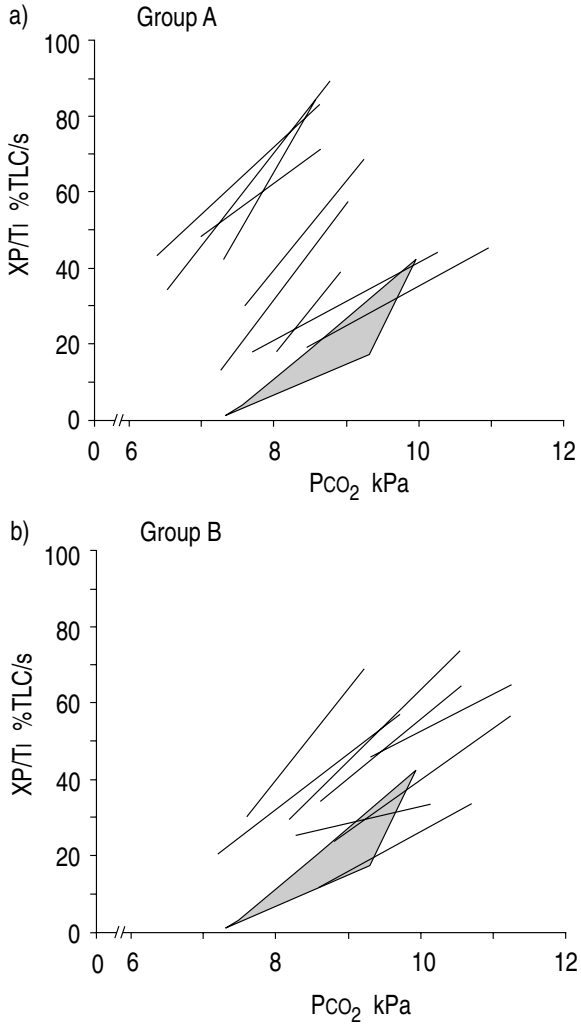

Fig. 1. – Individual plots of electromyographic activity of the diaphragm (Edi) activity (XP/TI) against end-tidal P_{CO_2}. Hatched area depicts normal mean response ±1SD of slope. a) normocapnic (group A) patients. b) hypercapnic (group B) patients. XP: peak of electromyographic activity of diaphragm; XP/TI: rate of rise of electromyographic activity of diaphragm obtained by dividing XP by inspiratory time (TI); TLC: total lung capacity; P_{CO_2}: carbon dioxide tension.

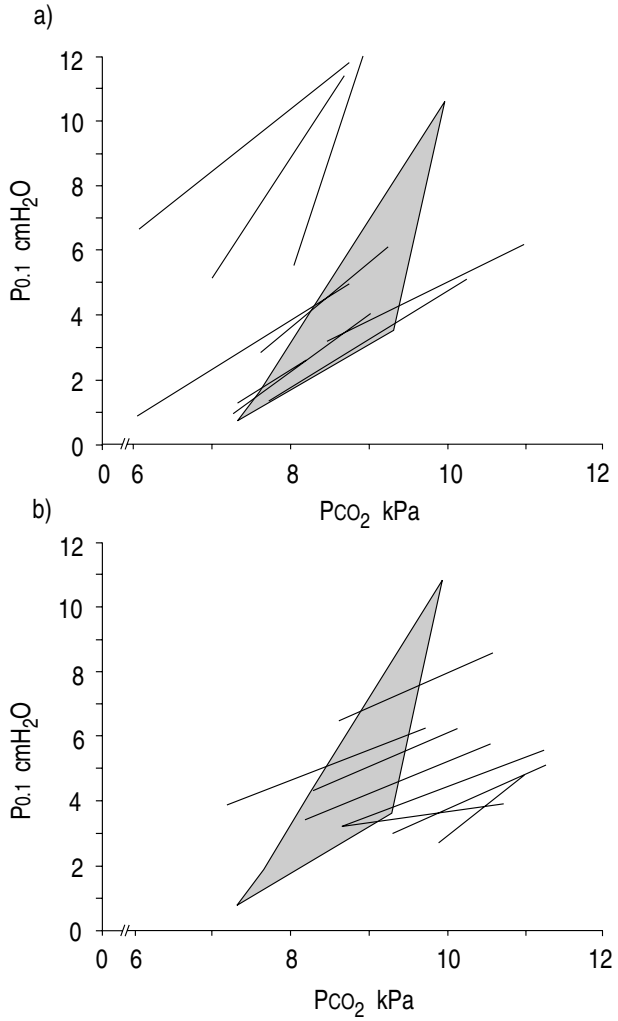

Fig. 2. – Individual plots of P0.1 against end-tidal P_{CO_2}. Hatched area depicts normal mean±1SD of slope. a) normocapnic (group A) patients; b) hypercapnics (group B) patients. P0.1: mouth occlusion pressure; P_{CO_2}: carbon dioxide tension.

Table 4. – Ventilatory and Edi measurements at P_{CO_2} of 8.65 kPa in the three groups studied

Patient group	$\dot{V}_E$	T_I	$P_{0.1}$	XP	XP/T_I
	$l \cdot min^{-1}$	s	%MIP	%TLC	%TLC/s
Group A (n=7)	20.71	1.01	10.89	55.3	56.6
	(2.4)	(0.17)	(5.75)	(16)	(22.2)
Group B (n=6)	13.50	1.16	8.99	35.3	30.01
	(4.15)	(0.27)	(5.05)	(11.4)	(13.7)
Group C (n=6)	25.5	1.74	5.33	25.0	22.6
	(4.4)	(0.66)	(2.86)	(9.90)	(7.70)
KWAV					
H	10.33	11.42	5.03	11.7	12.58
p	<0.005	<0.003	NS	0.0028	0.0018
Mann-Whitney test					
p (B *vs* A)	<0.024	NS	-	NS	NS
p (B *vs* C)	<0.05	NS	-	NS	NS
p (A *vs* C)	NS	<0.005	-	<0.008	<0.005

Values are presented as mean±SD in parenthesis. For abbreviation see legend to tables 1 and 2.

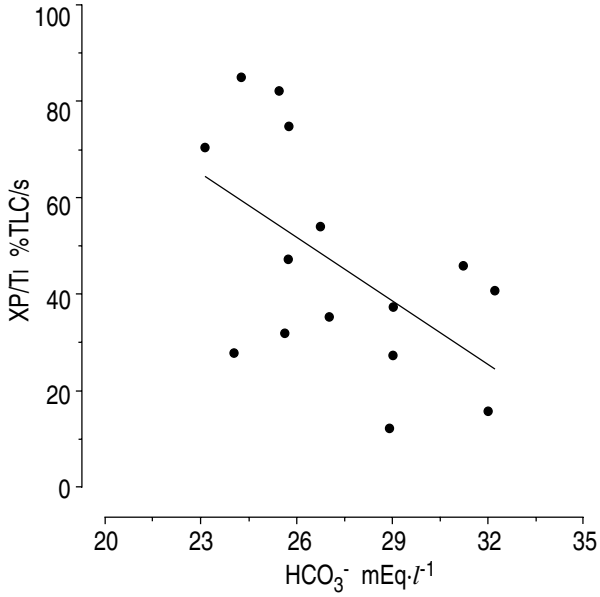

Fig. 3. – The figure depicts the relationship between HCO_3^- and Edi at 8.65 kPa. Individual data points are shown. HCO_3^-: arterial bicarbonate content. For further abbreviations see legend to figure 1.

not $P_{0.1}$(%MIP) differed significantly among the three groups (KWAV). In general, both Edi variables showed a trend to increase from C to A. In particular, XP was greater and T_I lower in A than in C ($p<0.008$ and $p<0.005$, respectively). As a consequence XP/T_I was significantly greater in A than in C ($p<0.005$).

XP/T_I at a P_{CO_2} of 8.65 kPaP_{CO_2} significantly correlated with arterial bicarbonate content obtained during room air breathing ($r=-0.5475$; $p<0.034$) (fig. 3).

Discussion

In this study, we found a high chemoresponsiveness in normocapnic COPD patients, whereas in hypercapnic patients both mechanical impairment and an inadequate chemoresponsiveness were likely to play a role in the low ventilatory response to carbon dioxide stimulation.

In comparing the chemoresponsiveness in two groups of COPD patients we made sure they were accurately matched for age, anthropometric characteristics, and spirometric variables. The last point is mandatory if one wants to establish the relative contribution of pulmonary mechanics in the abnormalities in the control of breathing. The decrease in MIP noticed in COPD patients could depend on a number of factors. MIP is a voluntaly manoeuvre, and factors such as individual motivation and experience with test of respiratory muscle performance could explain, at least in part, the difference in MIP between the patient groups and the control group. However, none of the normal subjects had ever undergone respiratory muscle function tests, and all were unaware of the purposes of the study. Therefore, considering patient's co-operation and familiarity with the techniques, it is likely that the observed decrease in MIP reflects inspiratory muscle weakness.

During the CO_2 rebreathing, consistent with previous studies [2–5, 7], $\Delta V_E/\Delta P_{CO_2}$ was significantly smaller

in groups A and B than in group C. The slope of mouth occlusion pressure response to CO_2 ($\Delta P_{0.1}/\Delta P_{CO_2}$) was smallest in group B, in line with previous studies 3–5, and in general accord with BRADLEY *et al*. [6]. In contrast, the results of GELB *et al*. [2] are different in that they did not observe substantial differences in $\Delta P_{0.1}/\Delta P_{CO_2}$ between normocapnics and hypercapnics, half of whom did not differ from the control subjects. In the present study, we also expressed mouth occlusion pressure as percentage of MIP. Mouth occlusion pressure is an index that reflects both neural drive to, and the resulting force output of, the respiratory muscles [1]. Although $P_{0.1}$ is a reasonable index of neural output to the respiratory muscles in normal subjects, in patients with respiratory muscle weakness (low MIP) $P_{0.1}$ can underestimate the effective neuromuscular respiratory drive [32]. In order to take into account individual differences in inspiratory muscle strength, PETERSON *et al.* [26] expressed $P_{0.1}$ as percentage of MIP. Accordingly, the normalization of $P_{0.1}$ for individual differences in muscle strength allows a more appropriate comparison of chemoresponsiveness between different groups of subjects [9, 26]. In the present study, $\Delta P_{0.1}(\%MIP)/\Delta P_{CO_2}$ and $P_{0.1}(\%MIP)$ at 8.65 kPa did not differ among the three groups.

To our knowledge, only a few studies [14, 15, 21, 22] have dealt with Edi measurement of chemoresponsiveness to carbon dioxide in patients with COPD. In previous papers, we have thoroughly criticized the use of either surface or oesophageal EMG recording to assess respiratory drive in humans [9, 15, 19, 33–36]. Nonetheless, many data in normal and in disease state support the contention that the slope of the moving time average (Edi/T_I) is a reliable measure of the respiratory centre activity [9, 11–21, 33–36]. In the present study, chemoresponsiveness, expressed in terms of Edi response slope ($\Delta XP/T_I/\Delta P_{CO_2}$), increased from C to A ($p<0.028$ KWAV). These findings are somewhat consistent with previous results by GRIBBIN and co-workers [10, 14]. The results obtained in the hypercapnic patients deserve two further commments. Firstly, about 20 yrs ago, in two groups of COPD patients with (group B) and without (group A) hypercapnia, but with more severe mechanical impairment in group B, LOURENÇO and MIRANDA [22] noted that the Edi response to CO_2 was significantly lower in group B relative to a non-age-matched normal control group, whilst in group A it was higher. At variance with the findings of LOURENÇO and MIRANDA [22], in the present study it was found that Edi activity did not differ between the hypercapnic patients and the control group.

We have previously described [9] the methodological differences between the present study and that of LOURENÇO and MIRANDA [22]. We think that the low total integrated Edi activation observed by Lourenço and Miranda in the hypercapnic patients is due, at least in part, to the shorter T_I often exhibited by these patients [6, 8, 9, 17, 37]. With the present method, however, both an increase in peak (XP) activity and a shorter T_I contributed to the progressive increase in Edi (XP/T_I) from C to A (tables 2 and 4). Secondly, adaptive changes are involved in CO_2 responsiveness. These depend on whether or not COPD patients retain CO_2. Hypercapnics show adaptive changes characterized both by a shift of the CO_2 threshold to the right, and a lowering of $P_{0.1}$ to CO_2 response slope (3–5). The methods commonly used in assessing CO_2 responsiveness ($\dot{V}_E$, $P_{0.1}$) do not, however, allow firm conclusions to be drawn on whether the apparent reduction in CO_2 responsiveness in hypercapnic COPD patients is necessarily due to a blunted responsiveness of central origin [7]. With the present EMG method we did not find either a reduction in Edi response slope (with the exeption of patients No. 17) or a consistent rightward shift in Pa_{CO_2} threshold in hypercapnic patients; instead, the Edi response slope was similar to that of normal subjects. Therefore, chemoresponsiveness did not appear to be subnormal in hypercapnic COPD patients. Nonetheless, looking at the data of 8.65 kPa of P_{CO_2} one has also to consider the following: 1) $\dot{V}_E$ was smaller in B than in C, whilst Edi was similar and 2) in contrast, in group A, $\dot{V}_E$ was similar but Edi significantly greater than in C. Based on these findings the question arises of whether Edi was adequate to sustain ventilation in hypercapnic COPD. In other words, we do not exclude the possibility that in some patients an inherent low CO_2 responsiveness was also a contributory factor to hypercapnia.

The amount of Edi activity at P_{CO_2} of 8.65 kPa in COPD patients with or without chronic hypercapnia but similar mechanical abnormalities might depend on two principal factors. Firstly, different buffering capacity. If we assume that in the two groups there was the same difference in HCO_3^- at P_{CO_2} of 8.65 kPa as we noted during room air breathing, this factor is likely to play a role. In fact, for a given level of P_{CO_2} the greater the content of HCO_3^- the lower the hydrogen ion activity and vice versa [38]. The significant relationship we found between Edi and HCO_3^- in patients (fig. 3) seems to be consistent with this hypothesis. Secondly, chronic hypoxaemia. In chronic hypoxaemic-hypercapnic COPD patients and in normoxic-normocapnic COPD patients, hyperoxic condition appeared to result in a similar reduction in the hypoxic drive [8]. If this applies to the conditions of the present study, the neutral respiratory drive (NRD) would be underestimated in both groups. However, as shown in the study by LOURENÇO and MIRANDA [22], the hyperoxic condition imposed by CO_2 rebreathing did not seem capable of modifying the NRD. In fact, during rebreathing with air and oxygen in concentrations adjusted to maintain the resting value of oxygen saturation, values of diaphragmatic response similar to those found with 100% oxygen were observed. In agreement with this, in the paper of BRADLEY *et al*. [6] hypoxic-normocapnic patients had similar $\Delta P_{0.1}/\Delta P_{CO_2}$ response slopes to normoxic-normocapnic patients with similar obstruction and hyperinflation. Therefore, chronic hypoxaemia is not likely to play a major role in the differences observed.

Another point which needs to be discussed concerns the reliability of the mouth occlusion pressure as an index of neuromuscular respiratory drive under the present experimental conditions. Criticism concerns the possibility that: 1) in this condition the relaxation of abdominal muscles may take place only a few milliseconds before inspiration starts, preventing $P_{0.1}$ from reflecting diaphragmatic electromyographic activity [39]; 2)

abnormalities in lung and or chest wall mechanics may change the coupling of neural to muscular events [14, 21, 28], *i.e*. for a given degree of Edi activity the greater the pulmonary volume the lower the inspiratory muscle force; and 3) in COPD patients, inspiratory muscle overloading is likely to occur because of pulmonary hyperinflation and intrinsic positive end expiratory pressure (PEEP). Intrinsic PEEP (PEEPi) imposes an extra burden on the inspiratory muscles [40]. In fact, during inspiration the early part of the pressure that the inspiratory muscles generate (Pmus) is spent counterbalancing PEEPi. In these conditions, the measurement of $P_{0.1}$ would occur over a less advantageous portion of the length tension relationship of the inspiratory muscles.

On the other hand, several lines of evidence indicate that a low mouth pressure response relative to Edi response may be considered as indicative of a low relationship between input and output signals of the system [19, 21, 28, 37, 41]. The observation that, irrespective of a normal $\Delta Edi/\Delta P_{CO_2}$, $\Delta P_{0.1}/\Delta P_{CO_2}$ was lower in group B patients than in either A or C groups seems consistent with the finding of a lower MIP in group B and to indicate a reduced inspiratory muscle ability to generate pressure in the face of a normal chemoresponsiveness. We interpret the similarity of MIP-normalized $P_{0.1}$ response to P_{CO_2} in the three groups (see tables 2 and 4) in this sense.

In conclusion, our data show that CO_2 responsiveness is high in normocapnics, whilst in hypercapnics, though similar to that of the normal control group, it is probably inadequate to sustain ventilation.

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