

Ventilatory and cerebrovascular responses in normocapnic and hypercapnic COPD patients

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ABSTRACT: This study investigated the hypothesis that hypercapnia in some chronic obstructive pulmonary disease (COPD) patients may be related to a high cerebrovascular response to carbon dioxide (CO₂).

The relationship between responses of ventilation and of cerebral blood volume (CBV) to acute changes in carbon dioxide tension in arterial blood (P_{a,CO_2}) was measured in 17 chronic hypercapnic ($P_{a,CO_2} > 6.0$ kPa) and 16 normocapnic ($P_{a,CO_2} \leq 6.0$ kPa) COPD patients, who were matched for degree of airway obstruction (forced expiratory volume in one second 27% predicted). Results were compared with 15 age-matched healthy subjects. CBV was measured using near infrared spectroscopy during normo- and hypercapnia and related to inspired minute ventilation (V'_I) and mouth occlusion pressure ($P_{0.1}$). Hypercapnia (end-tidal pressure of carbon dioxide ($\Delta P_{ET,CO_2}$) > 1 kPa) was induced by giving adequate amounts of CO₂ in the inspired air.

During normocapnia, CBV (mL·100 g⁻¹) was 2.41 ± 0.66 and 2.90 ± 0.60 (mean \pm SD) in the normocapnic and chronic hypercapnic patients, respectively, which was significantly lower compared to healthy subjects (3.53 ± 0.77). All slopes of CO₂ responsiveness ($\Delta CBV/\Delta P_{a,CO_2}$, $\Delta V'_I/\Delta P_{a,CO_2}$, $\Delta P_{0.1}/\Delta P_{a,CO_2}$) were significantly lower in both COPD groups relative to healthy subjects, but were not significantly different between the COPD groups. A poor but positive correlation between ventilatory and cerebrovascular CO₂ responsiveness ($\Delta CBV/\Delta P_{a,CO_2}$ and $\Delta V'_I/\Delta P_{a,CO_2}$) was found in COPD patients and healthy subjects.

The findings do not support the hypothesis of abnormal cerebrovascular responses to carbon dioxide in hypercapnic chronic obstructive pulmonary disease patients.

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Patients with chronic obstructive pulmonary disease (COPD) frequently show a blunted ventilatory response to hypercapnia. This diminished response has been ascribed to either mechanical limitations imposed by the disease process itself ("can't breathe") or to reduced sensitivity of the respiratory centres to the carbon dioxide (CO₂) stimulus ("won't breathe") [1]. Both will result in CO₂ retention and hypercapnia. Furthermore, the carbon dioxide tension in arterial blood (P_{a,CO_2}) values are often used as the input parameter for measuring ventilatory responsiveness. As the central chemoreceptors represent ~80% of the total CO₂ chemosensitivity [2], it might be conceived that the stimulus to these central chemoreceptors, brain interstitial fluid (ISF)-pH, is neither adequately processed, nor adequately reflected by the P_{a,CO_2} value in the hypercapnic COPD patients. The latter may occur when the control of cerebral blood flow (CBF) and cerebral blood volume (CBV) and their responses to changes in P_{a,CO_2} are abnormal.

The importance of CBF as a crucial link in stimulus-response studies of ventilatory control was

first pointed out by the classical study of KETY and SCHMIDT [3]. Since then, CBF was thought to modify the apparent ventilatory responses to changes in P_{a,CO_2} . Variations in blood flow will alter the relationship between P_{a,CO_2} (the stimulus that can be measured) and the CO₂ tension of brain tissue at the central chemoreceptors (the true stimulus). Simultaneous measurements of cerebrovascular and of ventilatory reactivity are therefore important [4].

As reviewed by FEIHL and PERRET [5], both cerebral resistance vessels (arterioles) and capillaries/venules are dilated by hypercapnia. However, a chronic hypercapnia is associated with a blunted cerebrovascular reactivity to acute P_{a,CO_2} variations [6]. As a result, only minor alterations in CBF and CBV can be expected, not able to attenuate the acute hypercapnic stimulus to the central chemoreceptors, and leading to an elevated P_{a,CO_2} in the ISF (true stimulus). Consequently, an elevated ventilatory drive could be expected. However, the opposite, a lowered ventilatory drive is found [7, 8].

According to PONTÉN and SIESJÖ [9] and others [4], a

high CBF (and CBV) washes out tissue CO_2 and lowers P_{a,CO_2} in the ISF, leading to a low chemoreceptor stimulus and a low ventilatory drive. An inverse relationship between cerebrovascular and ventilatory responsiveness to acute hypercapnia in COPD patients was hypothesized. Relatively high vasodilating cerebrovascular responses were hypothesized in hypercapnic patients, leading to a wash-out from CO_2 and a lowered P_{a,CO_2} in the ISF. This would result in a low chemoreceptor stimulus and a low ventilatory drive and sustained systemic hypercapnia. Normocapnic patients, however, may be thought to show a lowered cerebrovascular response and thus an adequate ventilatory drive, leading to systemic normocapnia.

In the present study, cerebrovascular CO_2 responsiveness was expressed as the slope of CBV/CO_2 plot ($\Delta\text{CBV}/\Delta P_{a,\text{CO}_2}$) and ventilatory CO_2 responsiveness was expressed as the slope of inspired minute ventilation ($V'_{\text{I}}/\text{CO}_2$) ($\Delta V'_{\text{I}}/\Delta P_{a,\text{CO}_2}$). CBV was measured using a noninvasive technique of near-infrared spectroscopy (NIRS). Mouth occlusion pressure ($P_{0.1}$) and its response to changes in P_{a,CO_2} ($\Delta P_{0.1}/\Delta P_{a,\text{CO}_2}$) were measured in order to approximate the ventilatory drive independent of airway resistance.

Materials and methods

Subjects

The study was performed on 33 patients with COPD as defined by the American Thoracic Society. Ten males and six females, aged (mean \pm SD) 60 ± 11 yrs, were normocapnic ($P_{a,\text{CO}_2} \leq 6.0$ kPa) and 15 males and two females, aged 63 ± 8 yrs were hypercapnic ($P_{a,\text{CO}_2} > 6.0$ kPa). Patients were excluded if they: 1) had evidence of obstructive sleep disorders or restrictive pulmonary function; 2) had an exacerbation in the 6 weeks before enrollment; 3) had a history of cardiopulmonary, cerebrovascular or other chronic diseases; and 4) took medications other than pulmonary bronchodilating agents, theophyllines and

(systemic) corticosteroids. Three normocapnic and two hypercapnic patients were current smokers, all other patients stopped smoking for >6 months. An age-matched healthy control group (56 ± 10 yrs, six males, 10 females) was also studied. None of them were on medication. A description of the patients is presented in table 1.

At least 2 h prior to the experiments, all participants were asked to abstain from caffeinated drinks and cigarettes, but were allowed to continue their pulmonary medication. All volunteers gave informed consent. The study was approved by the ethical committee of the Department of Pulmonology Dekkerswald, University of Nijmegen.

Measurements

Ventilation measurements. The subjects were in a comfortable, reclining position. They were breathing through a face mask with low-resistance valves for inspiratory and expiratory gas mixture. First, dead space ventilation ($V_{\text{D}}/V_{\text{T}}$) was measured using the Bohr equation. Expiratory air was collected in a Douglas bag for 10 min for measurements of expiratory P_{CO_2} (capnograph N1000, Nellcor Puritan Bennet, MO, USA). Next, the inspiratory port of the mask was connected *via* a Fleisch pneumotachograph (Phipps & Bird, Richmond, VA, USA) to an inspiratory reservoir (fig. 1). The flow signal was integrated into V'_{I} . Air was sampled from the expiratory port of the mask to a capnograph to monitor end-tidal CO_2 ($P_{\text{ET},\text{CO}_2}$, kPa) and respiratory rate (RR, min^{-1}). Changes in inspiratory gas mixture of oxygen (O_2), nitrogen (N_2) and CO_2 were induced by means of a computer-controlled mass flow system (Bronckhorst, Hitec, Veenendaal, the Netherlands). The fraction of inspired O_2 (F_{I,O_2}) was monitored continuously using an oxygen analyser (OM-11, Beckman Inc., CA, USA). Fast changes in the inspiratory gas mixture could be induced; the aimed changes were reached within one breath. Hypercapnia ($\Delta P_{\text{ET},\text{CO}_2} > 1$ kPa) was induced by giving adequate amounts of CO_2 (F_{I,CO_2} 3–5%) in the inspired air.

Table 1. – Characteristics of normocapnic patients, chronic hypercapnic patients and control subjects

Variable	Normocapnic COPD	Hypercapnic COPD	Controls ⁺
Age yr	59.8 ± 10.7	$62.8 \pm 8.4^*$	56 ± 1
BMI $\text{kg}\cdot\text{m}^{-2}$	22.9 ± 2.54	$21.5 \pm 2.4^{**}$	24.2 ± 3.1
FEV1 % pred	$28.8 \pm 9.6^{***}$	$24.3 \pm 7.5^{***}$	88.7 ± 8.8
MIP % pred	87.9 ± 39.9	77.2 ± 29.8	
MEP % pred	69.6 ± 28.7	59.4 ± 25.7	
$V_{\text{D}}/V_{\text{T}}$ %	48 ± 11	53 ± 7	
Ht vol %	41.6 ± 3.6	42.0 ± 3.4	40.8 ± 3.1
P_{a,CO_2} kPa	5.26 ± 0.27	$6.27 \pm 0.45^{***}$	5.14 ± 0.36
P_{a,O_2} kPa	9.05 ± 0.59	$8.31 \pm 0.99^{**}$	
pH	$7.42 \pm 0.02^{***}$	$7.39 \pm 0.02^{**}$	7.45 ± 0.03
HCO_3^- $\text{mEq}\cdot\text{L}^{-1}$	25.2 ± 1.2	$28.0 \pm 1.6^{**}$	25.6 ± 1.8
BE $\text{mEq}\cdot\text{L}^{-1}$	$0.8 \pm 1.2^{***}$	$2.4 \pm 1.3^{**}$	2.1 ± 1.7

Data are presented as mean \pm SD. COPD: chronic obstructive pulmonary disease; BMI: body mass index; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; Ht: haematocrit; BE: base excess; FEV1: forced expiratory volume in one second; V_{D} : dead space volume; V_{T} : tidal volume; P_{a,CO_2} : carbon dioxide tension in arterial blood; P_{a,O_2} : oxygen tension in arterial blood; HCO_3^- : bicarbonate. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$, COPD group compared to control group; ⁺ control group: arterialized capillary blood gas sampling (control group of arterialization capillary blood gas sampling).

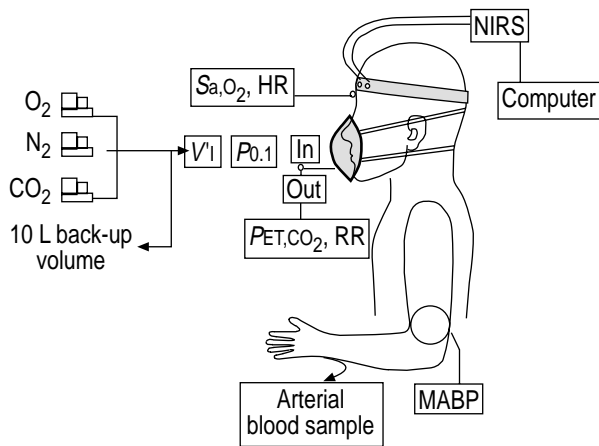


Fig. 1. – Experimental set-up. Flow of oxygen (O_2), nitrogen (N_2), and carbon dioxide (CO_2) are regulated with a mass-flow controller. Arterial oxygen saturation (Sa,O_2) and heart rate (HR) are measured with pulse-oximetry. NIRS: near-infrared spectroscopy; $V'I$: inspired minute ventilation, measured by pneumotachography; $P_{0.1}$: mouth occlusion pressure; MABP: mean arterial blood pressure; P_{ET,CO_2} and RR: end-tidal CO_2 and respiratory rate measured by capnograph. For safety reasons, a back-up volume of 10 L was created. Arterial blood was sampled from the left brachial artery.

Cerebral blood volume measurements. NIRS has been developed to monitor brain oxygenation and dynamics [10]. The theory of NIRS has been described extensively [11]. The technique is based on oxygenation-dependent absorption changes in the blood caused by chromophores, mainly oxy- and deoxyhaemoglobin ($[O_2Hb]$ and $[HHb]$, respectively). Near-infrared light was carried to and from a pulsed continuous-wave NIRS instrument (Oxymon, Depts of Physiology and Instrumentation, University of Nijmegen, the Netherlands) through two fibreoptic bundles (optodes) on the left side of the forehead. One optode emits near-infrared light at three different wavelengths, which penetrates through the skull/brain. The receiving optode is positioned at a distance of 5.5 cm apart from the emitting optode. This distance ensures that most of the extracranial circulation is excluded from the detected signal [12].

Calculation of CBV was described by ELWELL *et al.* [13]. A slight change of saturation ($\sim 5\%$) is necessary to quantify CBV. The change of saturation is related to the difference in concentration of haemoglobin chromophores at two levels of saturation. CBV can be calculated taking the individual haemoglobin concentration into account and a fixed constant. The constant accounts for molecular weight of haemoglobin, cerebral tissue density and the cerebral-to-large vessel haematocrit ratio.

Mouth occlusion pressure measurements. Ventilatory effort during inspiration was determined by $P_{0.1}$ after the start of inspiration. A solenoid valve was positioned in the inspiratory line of the circuit [14]. Closure of the valve during expiration was manually controlled, and the valve automatically opened after the first 100 ms of the occluded inspiration. Five repeated measurements of $P_{0.1}$ were averaged during

each CO_2 condition. $P_{0.1}$ was expressed both as absolute value (cmH_2O) and as percentage of maximal inspiratory pressure (MIP), in order to normalize $P_{0.1}$ for the individual differences in inspiratory muscle strength [15].

Protocol

All patients underwent routine spirometry and blood analysis of haemoglobin, haematocrit and resting arterial blood gases to assign the individual patients into the normocapnic and chronic hypercapnic COPD group. A canula was introduced in the left brachial artery to collect arterial blood samples. Arterial oxygen saturation (Sa,O_2) and heart rate (HR) were monitored with a pulse-oximeter (N200; Nellcor Puritan Bennet, MO, USA), with the sensor attached to the right-frontal forehead (fig. 1).

Hypercapnia was induced by giving adequate amounts of CO_2 in the inspired air. Duplicate measurements of CBV and $P_{0.1}$ during normo- and hypercapnia were performed after a period of 10-min equilibration. Arterial pressure was measured manually during each CO_2 condition. Mean arterial blood pressure (MABP) was calculated as: diastolic pressure + $1/3 \times$ (systolic-diastolic) pressure. All data (except MABP) were linked directly to the NIRS computer for real time display and simultaneous storage with the NIRS data.

Statistics

During the whole experiment, time-averaged values of $V'I$, P_{ET,CO_2} , Sa,O_2 , HR and RR were recorded, expressed as mean \pm SD during each CO_2 challenge. Anthropometric characteristics, pulmonary function, MABP and arterial blood gas values were compared between the three groups by the Mann-Whitney U-test for two independent samples. Within the groups, values during normocapnia were compared to values during hypercapnia using a paired t-test. Between the groups, unpaired t-tests were used to compare outcome variables. For each individual, CBV, $V'I$ and $P_{0.1}$ was plotted against corresponding P_a,CO_2 values and subjected to linear regression analysis. The individual slopes of CBV, $V'I$ and $P_{0.1}$ responses to acute CO_2 changes were calculated using linear regression analysis. Mean slopes of the three groups were compared with an unpaired test. The level of statistical significance was set at $p < 0.05$. All tests should be regarded as explorative due to the multiplicity of tests.

Results

The anthropometric characteristics and respiratory function data of the patients are summarized in table 1. Both COPD groups showed the same degree of airway obstruction (forced expiratory volume in one second (FEV₁)), maximal voluntary ventilation (MVV) and MIP. Acute hypercapnia was attained by

Table 2.—Outcome parameters before (start) and during hypercapnia when taking carbon dioxide responses in normocapnic patients, chronic hypercapnic patients and control subjects

Variable	Normocapnic COPD		Hypercapnic COPD		Controls	
	Start	Hypercapnia	Start	Hypercapnia	Start	Hypercapnia
CBV mL·100 g ⁻¹	2.41 ± 0.66***	3.36 ± 0.75(***)	2.90 ± 0.60[***]	3.76 ± 0.71(***)	3.53 ± 0.77	4.82 ± 1.12
V _I L·min ⁻¹	9.7 ± 2.5**	16.6 ± 4.2(***)	9.0 ± 2.0*	12.5 ± 2.2(***)	7.7 ± 1.4	15.9 ± 8.3(***)
P _{0.1} cmH ₂ O	5.12 ± 2.57	7.14 ± 3.44(***)	5.31 ± 2.89	6.76 ± 3.78(***)		
P _{0.1} MIP %	7.72 ± 4.53	11.42 ± 7.19(*)	8.14 ± 4.38	10.44 ± 5.17(**)		
P _{a,CO₂} kPa	5.26 ± 0.27	6.08 ± 0.24(***)	6.27 ± 0.45**	6.92 ± 0.39(***)	5.14 ± 0.36	5.63 ± 0.29(***)
P _{a,O₂} kPa	9.05 ± 0.59	10.16 ± 1.36(**)	8.31 ± 0.99	8.94 ± 0.81(**)		
MVV % pred	33.1 ± 12.7	55.0 ± 16.7	33.3 ± 10.2	45.6 ± 11.9		
RR min ⁻¹	16 ± 4	19 ± 4(**)	19 ± 5*	19 ± 4	14 ± 3	15 ± 4
V _T mL	640 ± 210	920 ± 225(***)	520 ± 200	710 ± 200(***)	610 ± 200	1130 ± 20(***)
HR min ⁻¹	83 ± 11**	79 ± 19	82 ± 12**	83 ± 12	72 ± 10	71 ± 10
MABP mmHg	106 ± 12***	108 ± 18	111 ± 14***	110 ± 13	85 ± 11	93 ± 12(***)

Data are presented as mean ± SD. CBV: cerebral blood volume; V_I: inspired ventilation; P_{0.1}: mouth occlusion pressure; MIP: maximal inspiratory pressure; MVV: maximal voluntary ventilation; RR: respiratory rate; V_T: tidal volume; HR: heart rate; MABP: mean arterial blood pressure; P_{a,O₂}: oxygen tension in arterial blood; P_{a,CO₂}: carbon dioxide tension in arterial blood; *: p < 0.05; **: p < 0.01; ***: p < 0.001, COPD group compared to control group (normocapnia compared to acutely induced within the group) [normocapnic COPD group compared to hypercapnia COPD group].

means of a $\Delta P_{a,CO_2}$ of 0.83 ± 0.19 , 0.65 ± 0.18 and 0.52 ± 0.27 kPa in the normocapnic, chronic hypercapnic and healthy (control) group, respectively. The degree of (necessary) transient desaturation to measure absolute values of CBV was 6 ± 2 , 7 ± 2 and $8 \pm 2\%$ for the same groups.

Hypercapnia induced significant changes ($p < 0.01$) in all variables except for HR, RR and MABP, within the three groups (table 2). In addition, only normocapnic COPD patients showed a different RR during hypercapnia ($p < 0.01$), compared to the other two groups. MABP was significantly higher in COPD patients compared to healthy subjects ($p < 0.001$), but did not increase further during hypercapnia. In healthy subjects, MABP increased during induction of hypercapnia ($p < 0.001$).

Ventilation and ventilatory responses

Both COPD groups had significantly higher resting values of V_I compared to healthy subjects (table 2). The ventilatory response to CO₂ ($\Delta V_I / \Delta P_{a,CO_2}$) was lower in both COPD groups when compared to the controls, but was only significantly different ($p < 0.01$) in the hypercapnic group compared to controls (table 3). When both COPD groups were compared

and the median rather than the average value of $\Delta V_I / \Delta P_{a,CO_2}$ was taken, a significant, different slope of $\Delta V_I / \Delta P_{a,CO_2}$ between the two COPD groups was found ($p < 0.05$). Average responses (V_I: L·min⁻¹; P_{a,CO₂}: kPa) are displayed in figure 2b.

In contrast to COPD patients, V_I is a good parameter for neuromuscular output of ventilatory drive in healthy subjects. Both absolute values of P_{0.1} (table 2) and its reactivity ($\Delta P_{0.1} / \Delta P_{a,CO_2}$, table 3) were not significantly different between the COPD groups, even after correction for MIP.

Cerebral blood volume and cerebrovascular responses

Twelve out of 192 measurements were rejected and excluded from the CBV calculations because of inadequate measurements. Values of CBV were lower in the normocapnic patients as compared to the hypercapnic patients ($p < 0.01$) (table 2). Both COPD groups showed a significant, lower value of CBV compared to the healthy subjects. The cerebrovascular response to CO₂, $\Delta CBV / \Delta P_{a,CO_2}$, was lower in both COPD groups compared to controls, however, this was only significantly lower ($p < 0.05$) in the hypercapnic group (table 3). Average equations of CBV as a function of P_{a,CO₂} are displayed in figure 2.

Table 3.—Linear regression of cerebral blood volume (CBV), minute ventilation (V_I) and mouth occlusion pressure (P_{0.1}) to hypercapnia in normocapnic patients, chronic hypercapnic patients and control subjects

Variables	Normocapnic COPD			Hypercapnic COPD			Controls		
	Slope	y-intercept	r	Slope	y-intercept	r	Slope	y-intercept	r
CBV P _{a,CO₂} mL·100 g ⁻¹ ·kPa ⁻¹	1.59 ± 0.91	-5.18 ± 5.27	0.9	1.23 ± 0.67*	-5.16 ± 3.56	0.77	2.10 ± 1.35	-7.02 ± 7.1	0.66
V _I P _{a,CO₂} L·min ⁻¹ ·kPa ⁻¹	8.2 ± 4.9*	-33.4 ± 26.2*	0.96	5.5 ± 4.4***	-26.7 ± 34.3**	0.93	13.9 ± 7.1	-62.9 ± 36.8	0.85
P _{0.1} P _{a,CO₂} cmH ₂ O·kPa ⁻¹	2.65 ± 1.84	-8.67 ± 9.3	0.81	2.83 ± 1.50	-12.38 ± 9.18	0.80			

Data are presented as mean ± SD. P_{a,CO₂}: carbon dioxide tension in arterial blood; COPD: chronic obstructive pulmonary disease. *: p < 0.05; **: p < 0.01; ***: p < 0.001, COPD-group compared to control group. y-intercept: CBV, V_I and P_{0.1} value at a P_{a,CO₂} of 0 kPa.

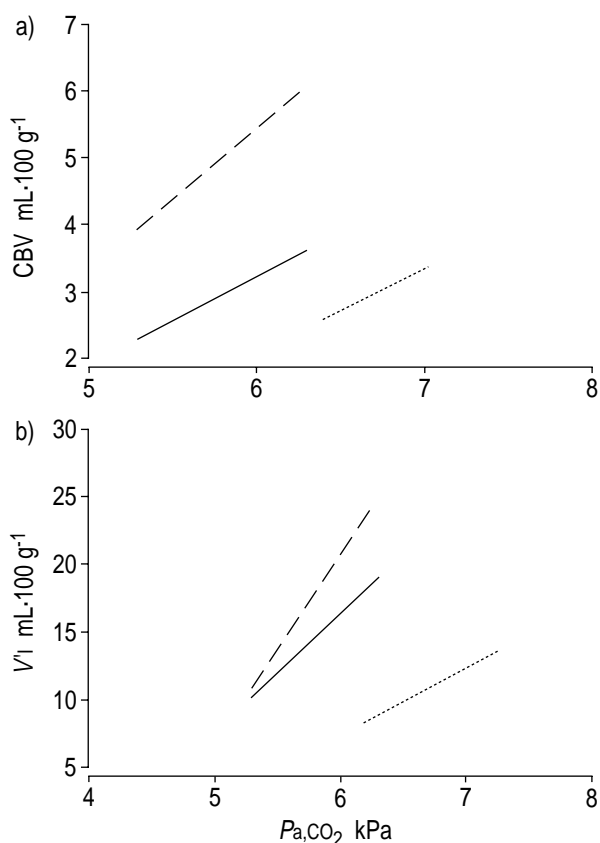


Fig. 2. – Ventilatory and cerebrovascular responses to carbon dioxide. Regression equations were obtained for data from each individual subject and averaged for the group. All values of a) cerebral blood volume (CBV) and b) inspired minute ventilation ($\dot{V}I$) were indexed to similar carbon dioxide tension in arterial blood (P_{a,CO_2}) values to show average group results. - - -: controls; —: normocapnic chronic obstructive pulmonary disease; ····: hypercapnic chronic obstructive pulmonary disease.

Correlation between the different outcome parameters

A poor correlation was seen in the control group between the individual CBV and $\dot{V}I$ responses to acute hypercapnia ($\Delta CBV/\Delta P_{a,CO_2}$ and $\Delta \dot{V}I/\Delta P_{a,CO_2}$). A low, but significant correlation was found for all COPD patients (fig. 3). When the COPD group was subdivided, the normocapnic patients tended to show a steeper slope ($\Delta \dot{V}I/\Delta P_{a,CO_2}/\Delta CBV/\Delta P_{a,CO_2}$) as compared to the hypercapnic patients (fig. 4). However, the latter correlations were poor and not significant. In addition, when $\dot{V}I$ was related to MVV% and $\dot{V}I$ (MVV%)/ $\Delta P_{a,CO_2}$ was correlated to $\Delta CBV/\Delta P_{a,CO_2}$ (not displayed), correlations remained poor. Nevertheless, the slope of these correlations was positive, showing that high cerebrovascular responses were accompanied by high ventilatory responses to CO_2 .

Correlations between the individual CBV and $P_{0.1}$ slopes ($\Delta CBV/\Delta P_{a,CO_2}$ and $\Delta P_{0.1}/\Delta P_{a,CO_2}$) were poor and not significant in both COPD groups ($r=0.28$ and 0.04 in the normocapnic and hypercapnic COPD group, respectively). In order to evaluate CBV with respect to parasympathetic tone, CBV and HR were

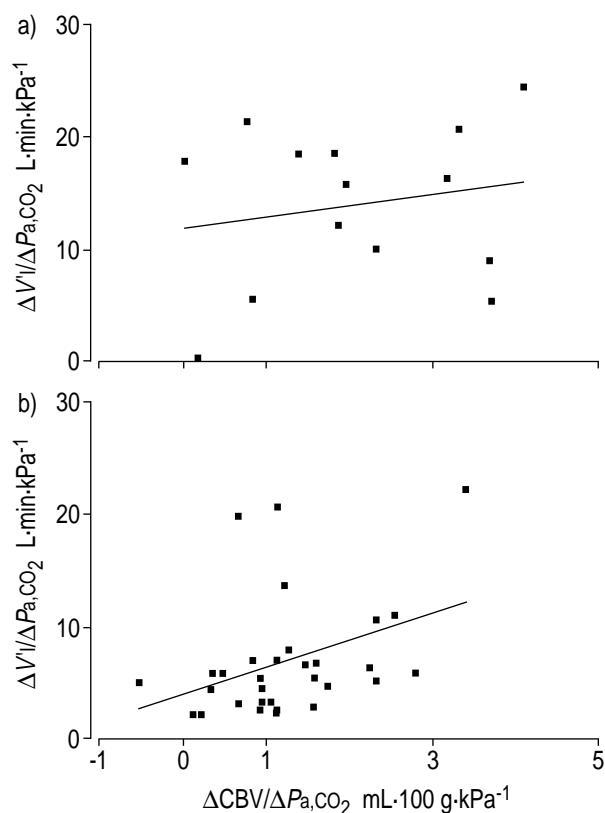


Fig. 3. – Correlation between ventilatory and cerebrovascular carbon dioxide (CO_2)-responsiveness in healthy subjects (control) and chronic obstructive pulmonary disease (COPD) patients. The relationship between a) the individual ventilatory/ CO_2 tension in arterial blood ($\Delta \dot{V}I/\Delta P_{a,CO_2}$) and cerebrovascular ($\Delta CBV/\Delta P_{a,CO_2}$) CO_2 -responsiveness in healthy subjects and b) in normo- and hypercapnic COPD patients. The regression equation, describing the inter-individual relationship between a) $\dot{V}I/\Delta P_{a,CO_2}$ and $\Delta CBV/\Delta P_{a,CO_2}$ is $\Delta \dot{V}I/\Delta P_{a,CO_2} = 0.99 \times \Delta CBV/\Delta P_{a,CO_2} + 11.80$ ($r=0.2$; $p=0.5$) and b) $\Delta \dot{V}I/\Delta P_{a,CO_2} = 2.36 \times \Delta CBV/\Delta P_{a,CO_2} + 3.99$ ($r=0.38$; $p<0.05$). $\dot{V}I$: inspired minute ventilation ($L \cdot \text{min}^{-1}$); CBV: cerebral blood volume ($\text{mL} \cdot 100 \text{ g}^{-1}$).

correlated. There was no correlation between absolute values of CBV and HR in normocapnic ($r=0.1$) and hypercapnic COPD patients ($r=0.2$) and controls ($r<0.1$).

Discussion

Cerebrovascular responses were studied and correlated with ventilatory reactivity in healthy subjects and both normo- and hypercapnic COPD patients. Acute hypercapnia gave rise to significant changes of CBV and ventilatory ($\dot{V}I$ and $P_{0.1}$) outcome parameters in all investigated subjects. Healthy subjects showed the highest CBV- and $\dot{V}I$ -responsiveness, whereas hypercapnic COPD patients showed the poorest responsiveness among the three groups. A wide inter-individual variability of cerebrovascular and ventilatory reactivity to acute changes in P_{a,CO_2} was found between the investigated subjects. However, the present study showed a tendency of high cerebrovascular responses being accompanied by high

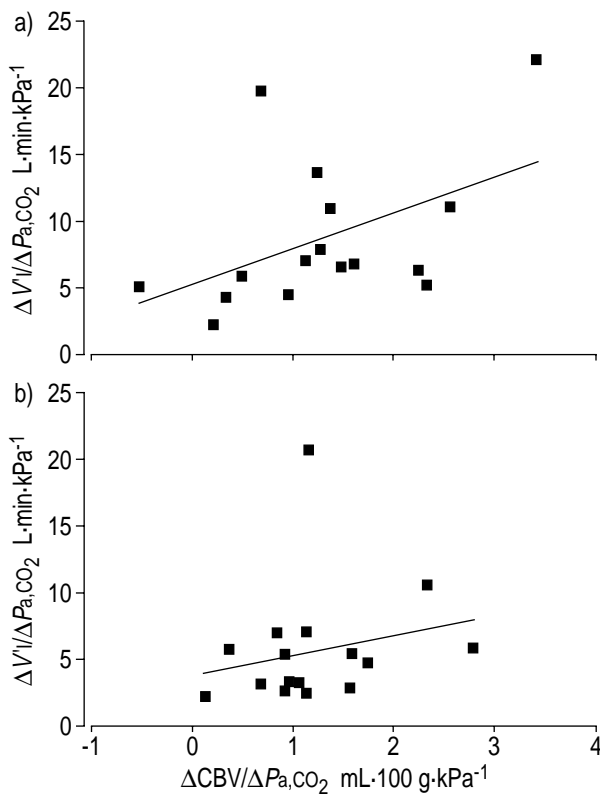


Fig. 4. – Correlation between ventilatory and cerebrovascular carbon dioxide (CO_2)-responsiveness in normocapnic and chronic hypercapnic chronic obstructive pulmonary disease (COPD) patients. The relationship between a) the individual ventilatory/ CO_2 tension in arterial blood ($\Delta V'/\Delta P_{a,\text{CO}_2}$) and cerebrovascular ($\Delta \text{CBV}/\Delta P_{a,\text{CO}_2}$) CO_2 -responsiveness in normocapnic and b) chronic hypercapnic patients. The regression equation, describing the inter-individual relationship between a) $\Delta V'/\Delta P_{a,\text{CO}_2}$ and $\Delta \text{CBV}/\Delta P_{a,\text{CO}_2}$ is $\Delta V'/\Delta P_{a,\text{CO}_2} = 2.66 \times \Delta \text{CBV}/\Delta P_{a,\text{CO}_2} + 5.22$ ($r=0.20$; $p=0.47$) and b) $\Delta V'/\Delta P_{a,\text{CO}_2} = 1.43 \times \Delta \text{CBV}/\Delta P_{a,\text{CO}_2} + 3.79$ ($r=0.21$; $p=0.41$). V' : inspired ventilation ($\text{L}\cdot\text{min}^{-1}$); CBV : cerebral blood volume ($\text{mL}\cdot 100 \text{ g}^{-1}$).

ventilatory responses to CO_2 , thus refuting the hypothesis of an inverse relationship between $\Delta \text{CBV}/\Delta P_{a,\text{CO}_2}$ and $\Delta V'/\Delta P_{a,\text{CO}_2}$ in COPD patients.

Ventilation and ventilatory responses

Ventilatory responsiveness to CO_2 were highest in healthy subjects and lowest in hypercapnic COPD patients. The results are in line with those of others [1, 8, 16], although the present study measured higher absolute values of responsiveness. The latter can be explained by various causes. Firstly, the present study used P_{a,CO_2} instead of $P_{\text{ET},\text{CO}_2}$ as an independent variable. Secondly, the (significantly) increased value of P_{a,O_2} during hypercapnic challenge may have resulted in an overestimated value of ventilatory CO_2 responses, as previous reports found a reduced CO_2 sensitivity during hyperoxia in healthy subjects [17]. Thirdly, chronic hypercapnic patients were exposed to chronic hypoxaemia (mean P_{a,O_2} value 8.31 kPa). Superimposed desaturation changes to

obtain absolute CBV values may have led to greater values of ventilation under both baseline conditions and during hypercapnic challenge, possibly leading to higher values of ventilatory slopes. Finally, all COPD patients have inhaled β_2 -adrenergic agonists, resulting in additional increases in ventilatory responses to hypercapnia, presumably by central chemoreceptor stimulation [18].

The sex ratio in healthy controls' and patients' groups is different. As all the subjects investigated were postmenopausal, this study is not predominantly biased by sex.

To ascertain whether and to what extent the reduced ventilatory response to a hypercapnic stimulus in COPD patients depends on a blunted chemoresponsiveness of central origin or to mechanical impairment, SCANO *et al.* [8] measured rebreathing CO_2 responses in normocapnic and hypercapnic COPD patients with similar degrees of airway obstruction and hyperinflation. Their study population was comparable to the present investigated group on pulmonary mechanics and arterial blood gas parameters. In contrast to GELB *et al.* [16] and the present study, they found a lower $P_{0.1}$ responsiveness ($\text{cmH}_2\text{O}\cdot\text{kPa}^{-1}$) in hypercapnics (1.08 ± 0.43) relative to normocapnics (2.72 ± 2.08) and healthy controls (2.57 ± 0.49). Conversely, when the normalization of $P_{0.1}$ for individual differences in muscle strength was performed by expressing $P_{0.1}$ as a percentage of MIP [15], a significant difference between the two groups did not occur, which is in line with the present results.

Cerebral blood volume and cerebrovascular responses

Cerebrovascular responsiveness was expressed as a change of CBV over a change in P_{a,CO_2} . It is important to consider the advantages of measurements of CBV over CBF measurements. Firstly, there is a close relationship ($r=0.9$) between CBV and CBF that has been extensively investigated [19]. Secondly, the use of CBV instead of CBF eliminates the problems related to the mean cerebral transit time [20]. Finally, near-infrared absorption changes reflect changes in the oxygenation of blood in the microvasculature, and thus the CBV of the brain tissue [21]. Changes of CBV also reflects capillary recruitment, which are considered a better reflection of cerebrovascular responses than CBF responses to acid-base stimuli [20].

CBV was measured in the frontal cortex, which may not react in the same way as the brain-stem region, where the central chemoreceptors are located [22]. However, HIDA *et al.* [23] used transcranial Doppler to determine changes in blood flow velocity and could not find any differences in CO_2 responses between the brain-stem artery and the middle-cerebral artery using transcranial Doppler. The latter paper would support the present measurements of frontal-lobe vasoresponsiveness to be representative of overall CBV changes. However, since there is no general agreement on cerebrovascular CO_2 -responsiveness, one has to be cautious to draw this conclusion.

Prior to this study, the reproducibility of CBV measurements during resting conditions using NIRS

was evaluated; an intra-individual coefficient of variation of $\pm 10\%$ was found [24]. These results are in agreement with others [25]. CBV values of the present study during normocapnia (range 1.60–4.30 mL·100 g⁻¹) are consistent with other studies using NIRS: 2.85 ± 0.97 mL·100 g⁻¹ [25].

Absolute values of CBV were lower in both COPD groups, relative to healthy subjects. Increased age [26], haematocrit [27] and HR may lower CBF and, therefore, CBV. HR was significantly increased in both COPD groups. HR responses primarily test the parasympathetic system. STEWART *et al.* [28] showed a parasympathetic autonomic dysfunction in 93% (28 out of 30) of severe hypoxaemic, hypercapnic COPD patients and in 65% (39 out of 60) of moderately to severely hypoxic, normocapnic COPD patients. Only 18% (four out of 22) of the control group had evidence of an age-related autonomic dysfunction. However, a correlation between absolute values of CBV and HR was not found in the present study. Additionally, no correlation was found between absolute values of CBV and age.

Medication, like theophyllines and systemic corticosteroids, may reduce CBV [29, 30]. Theophylline was chronically used by nine of 16 (56%) normocapnic and 11 of 17 (64%) hypercapnic patients, which may have contributed to the low CBV in both COPD groups. Systemic corticosteroids were used in four out of 16 normocapnic and four out of 17 hypercapnic patients. To assess the effect of medical intervention, average CBV was recalculated after subdividing both COPD groups in users and nonusers of theophyllines and/or oral corticosteroids. In contrast to others [29, 30], CBV was slightly, but not significantly higher in the group of theophylline users, relative to the nonusers in both COPD groups. In addition, CBV values measured in corticosteroid-users and nonusers were not different. Both the small size of the subgroups and the high variation of CBV values among the subjects may mask the well-documented effects of theophyllines. Intravenous salbutamol (1 $\mu\text{g}\cdot\text{kg}^{-1}$) leads to an increased CBV in rats [31]. Since the present study showed a low CBV in all COPD patients, it is unlikely that the inhaled salbutamol (≤ 400 μg) of the patients affected the CBV values substantially.

MABP was relatively higher in all COPD patients and remained unchanged during hypercapnia. Although their MABP values fell well within the range of autoregulation, pressure-dependent sensors may dominate flow-dependent sensors in the cerebral circulation during chronic elevated blood pressure, leading to a lowering of CBF and CBV. This might partly explain a blunted cerebrovascular responsiveness in both COPD groups, compared to healthy subjects.

There are only a few studies describing CBV reactivity in adults using NIRS. GUPTA *et al.* [32] used the same method as the present study to calculate CBV and found a higher mean CBV of 5.38 mL·100 g⁻¹ and a lower CBV reactivity of 1.25 mL·100 g⁻¹·kPa⁻¹, in young adults. However, they induced deeper desaturations ($\Delta 10$ –15%, instead of $\sim 5\%$), assumed equal Hb values for each individual and used the fractional concentration of CO₂ in expired gas to correlate with CBV. As they suggested, a deeper

desaturation possibly gives rise to concomitant hypoxic vasodilation and thereby, a higher CBV and different CBV reactivity. Other studies applied the same "O₂-desaturation-method" in neonates [33], or used O₂Hb derived reactivity values, and are therefore not comparable with this study [34].

Conclusions

Normocapnic and chronic hypercapnic COPD patients had lower absolute values of CBV relative to healthy subjects; autonomic dysfunction was suggested as a possible reason for this difference. There was a poor, but positive correlation between ventilatory and cerebrovascular CO₂ responsiveness ($\Delta\text{CBV}/\Delta P_{\text{a,CO}_2}$ and $\Delta V'/\Delta P_{\text{a,CO}_2}$) in COPD patients and healthy subjects, thus refuting the hypothesis concerning an inverse relationship between cerebrovascular and ventilatory responses to $P_{\text{a,CO}_2}$.

As compared to healthy subjects, both chronic obstructive pulmonary disease groups showed lower ventilatory as well as cerebrovascular carbon dioxide-responses, with significantly lower responses in the chronic hypercapnic group. Since similar mouth occlusion pressure reactivity was measured in both chronic obstructive pulmonary disease groups and cerebral blood volume- and inspired minute ventilation-reactivity were not significantly different, the present study was not able to elucidate why some patients with chronic obstructive pulmonary disease become hypercapnic, whereas others with the same degree of airway obstruction remain normocapnic.

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