Effects of Acetazolamide and Furosemide on Ventilation and Cerebral Blood Volume in Normocapnic and Hypercapnic Patients With COPD*

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Study objectives: Effects of chronic metabolic alkalosis and acidosis and their relation to central chemoregulation may differ between normocapnic and chronic hypercapnic patients with COPD. The relationship between responses of inspired ventilation (Vi), mouth occlusion pressure (P0.1), and cerebral blood volume (CBV), to short-term changes in arterial PCO2 was measured.

Patients and methods: Seventeen patients with chronic hypercapnia and COPD (PaCO2 > 6.0 kPa) and 16 normocapnic patients with COPD (PaCO2 ≤ 6.0 kPa) [FEV1 27% predicted] were studied under baseline metabolic conditions and after 1 week of treatment with oral furosemide, 40 mg/d, or acetazolamide, 500 mg/d. Hypercapnia (change in end-tidal carbon dioxide > 1 kPa) was induced by administering adequate amounts of carbon dioxide in the inspired air. CBV was measured using near-infrared spectroscopy.

Results: Compared with baseline metabolic condition, chronic metabolic acidosis and alkalosis did not change ventilatory (ΔVi/ΔPaCO2) and cerebrovascular (ΔCBV/ΔPaCO2) reactivity. Base excess (BE) decreased by 6.8 ± 1.1 mEq/L and 6.9 ± 1.6 mEq/L, respectively, in the normocapnic and chronic hypercapnic COPD groups during metabolic acidosis, resulting in a not-quite-significant leftward shift of both the ventilatory and cerebrovascular carbon dioxide response curve. BE increased by 2.3 ± 1.2 mEq/L and 1.2 ± 1.3 mEq/L, respectively, during chronic metabolic alkalosis in both COPD groups, without concomitant shift. Poor correlations between ventilatory and cerebrovascular carbon dioxide responsiveness (ΔCBV/ΔPaCO2 and ΔVi/ΔPaCO2, ΔCBV/ΔPaCO2 and ΔP0.1/ΔPaCO2, respectively) were found irrespective of baseline, respiratory condition, and induced metabolic state.

Conclusions: Normocapnic and chronic hypercapnic COPD patients have the same ventilatory and cerebrovascular carbon dioxide responsiveness irrespective of induced metabolic state.

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Key words: acid-base; central chemosensitivity; cerebral blood volume; control of breathing; COPD; metabolic acidosis; metabolic alkalosis; mouth occlusion pressure; near-infrared spectroscopy

Abbreviations: BE = base excess; CBF = cerebral blood flow; CBV = cerebral blood volume; MAP = mean arterial pressure; MIP = maximal inspiratory pressure; NIRS = near-infrared spectroscopy; P0.1 = mouth occlusion pressure; RR = respiratory rate; Vd/Vt = dead space ventilation; Vi = inspired ventilation
percapnia, however, is associated with a blunted cerebrovascular reactivity to short-term PCO₂ alterations.⁶,⁹ As a result, only minor changes in CBF and CBV can be expected during the latter condition, an inability to attenuate the short-term hypercapnic stimulus to the central chemoreceptors, and a tendency toward an elevated PCO₂ in the cerebral interstitial fluid (see Appendix). Consequently, an elevated ventilatory drive could be expected during chronic hypercapnia; however, the opposite, a lowered ventilatory drive, is found.⁵,¹⁰

Cerebrovascular responses to hypercapnia, expressed as a ΔCBV, were studied in their relationship to ventilatory responses in normocapnic and chronic hypercapnic patients with COPD, using the noninvasive technique of near-infrared spectroscopy (NIRS). We hypothesized an inverse relationship between cerebrovascular reactivity (ΔCBV/ΔPCO₂) and ventilatory reactivity (change in inspired ventilation [VI/ΔPCO₂]). Patients with chronic hypercapnia are thought to have a high vasodilatory response to PCO₂/pH, keeping the extracellular fluid of the brain less hypercapnic, thus keeping the central chemoreceptor-mediated ventilatory drive relatively low, and resulting in systemic hypercapnia. In the normocapnic group, the cerebrovascular response to carbon dioxide might be less, leading to a higher extracellular fluid PCO₂ and resulting in a normal (high) ventilatory drive.

Because chronic respiratory acidosis is usually compensated via metabolic pathways, in the present study we investigated the effects of superimposed chronic metabolic acid-base changes on the control of cerebrovascular and ventilatory responses. Therefore, a chronic metabolic acidosis and alkalosis was induced by orally administered acetazolamide and furosemide, respectively. P₀₁ and its response to changes of PCO₂ (ΔP₀₁/ΔPCO₂) were measured to approximate the ventilatory drive independent of airway resistance and related to CBV responsiveness.

**Materials and Methods**

**Subjects**

The study was performed on 33 patients with COPD as defined by the American Thoracic Society. Ten men and 6 women, aged 60 ± 11 years, were normocapnic (Paco₂ ≤ 6.0 kPa); 15 men and 2 women, aged 63 ± 8 years, were hypercapnic (Paco₂ > 6.0 kPa). Patients were excluded if they: (1) had evidence of obstructive sleep disorders or restrictive pulmonary function, or had a history of cardiopulmonary, cerebrovascular, or other chronic diseases; (2) had an exacerbation in the 6 weeks before enrollment; and (3) received additional 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. A description of the patients is presented in Table 1.

**Table 1—Characteristics of Normocapnic and Chronic Hypercapnic Patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normocapnic COPD</th>
<th>Hypercapnic COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>59.8 ± 10.7</td>
<td>62.8 ± 8.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.9 ± 2.54</td>
<td>21.5 ± 2.4</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>28.8 ± 9.6</td>
<td>24.3 ± 7.5</td>
</tr>
<tr>
<td>IVC, % predicted</td>
<td>79.3 ± 13.5</td>
<td>64.1 ± 9.3</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>109.9 ± 20.1</td>
<td>97.8 ± 16.4</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>147.6 ± 38.2</td>
<td>137.4 ± 27.3</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>171.3 ± 47.2</td>
<td>167.2 ± 39.4</td>
</tr>
<tr>
<td>MIP, % predicted</td>
<td>87.9 ± 39.9</td>
<td>77.2 ± 29.8</td>
</tr>
<tr>
<td>MEP, % predicted</td>
<td>69.6 ± 28.7</td>
<td>59.4 ± 25.7</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. BMI = body mass index; IVC = inspiratory vital capacity; TLC = total lung capacity; RV = residual volume; FRC = functional residual capacity; MEP = mean expiratory pressure.†p < 0.001 normocapnic COPD group compared to chronic hypercapnic COPD group.

At least 2 h before the experiments, all participants had to abstain from caffeine drinks and cigarettes, but were allowed to continue their pulmonary medications. All volunteers gave informed consent. The study was approved by the ethical committee of the Department of Pulmonology Dekkerswald, University Medical Center Nijmegen, The Netherlands.

Patients were studied on 3 separate days, during induced-acidosis, induced-alkalosis, and baseline (control) conditions, respectively, in random order. Metabolic acidosis was induced by orally administered acetazolamide, 250 mg q12h for 1 week. Metabolic alkalosis was induced by orally administered furosemide, 40 mg/d for 1 week.

**Measurements**

**Ventilation Measurements:** The subjects were positioned 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 (Vd/Vt) was measured using the Bohr equation. Expired air was collected in a Douglas bag for 10 min for measurements of mean expiratory PCO₂ (Capnograph N1000; Nellcor Puritan Bennett; St. Louis, MO). Next, the inspiratory port of the mask was connected via a Fleisch No. 3 pneumotachograph to an inspiratory reservoir. The flow signal was electrically integrated into volume to calculate inspired ventilation (Vt). End-tidal carbon dioxide (kilopascals) and respiratory rate (RR) [breaths per minute] were measured at the expiratory port of the mask. Changes in the inspiratory gas mixture of oxygen, nitrogen, and carbon dioxide were induced using a computer-controlled mass-flow system (Bronchiol-Hitex, Veenendaal, The Netherlands). The fraction of inspired oxygen was monitored continuously using an oxygen analyzer (OM-11; Beckmann; Fullerton, CA). Fast changes in inspiratory gas mixture could be induced; the aimed changes were reached within one breath. Hypercapnia (change in end-tidal carbon dioxide > 1 kPa) was induced by administering adequate amounts of carbon dioxide (fraction of inspired carbon dioxide, 3 to 5%) in the inspired air.

**CBV Measurements:** NIRS has been developed to monitor brain oxygenation and dynamics.¹¹ The theory of NIRS has been described extensively.¹² The technique is based on oxygenation-dependent absorption changes in the blood caused by chromophores, mainly oxyhemoglobin and deoxyhemoglobin. Near-infrared light was carried to and from a pulsed continuous-wave
NIRS instrument (Oxymon; Artinis Medical Systems; The Netherlands) through two fiber optic bundles (optodes) on the left side of the forehead. One optode emits near-infrared light at three different wavelengths, which penetrates through the skull and brain. The receiving optode is positioned at a distance of 5.5 cm from the emitting optode. This distance ensures that most of the extracranial circulation is excluded from the detected signal.13

Calculation of CBV was described by Elwell et al14 and Wyatt et al.15 A slight change of saturation (approximately 5%) is necessary to quantify CBV. The change of saturation is related to the difference of concentration of hemoglobin chromophores at two levels of saturation. CBV can be calculated when the individual hemoglobin concentration and a fixed constant are taken into account. This constant accounts for the molecular weight of hemoglobin, the cerebral tissue density, and the cerebral vessel/large vessel hematocrit ratio.

\( P_{0.1} \) Measurements: Ventilatory effort during inspiration was determined by occlusion pressure at 0.1 s after the start of inspiration. A solenoid valve was positioned in the inspiratory line of the circuit.16 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 carbon dioxide condition. \( P_{0.1} \) was expressed both as an absolute value and as a percentage of maximal inspiratory pressure (MIP) to normalize \( P_{0.1} \) for the individual differences in inspiratory muscle strength.17

Protocol

All patients underwent routine spirometry and analysis of hemoglobin, hematocrit, and resting arterial blood gases to assign the individual patients into the normocapnic and chronic hypercapnic COPD groups. On each of 3 study days, a cannula was introduced in the left brachial artery to collect arterial blood samples during normocapnia and to control the level of induced respiratory hypercapnia (Rapid Lab 855; Chiron Diagnostics Corporation; East Walpole, MA). Arterial oxygen saturation and heart rate were monitored with a pulse oximeter (N200; Nellcor Puritan Bennett), with the sensor attached to the right-frontal forehead.

Duplicate measurements of CBV and \( P_{0.1} \) during normocapnia and hypercapnia were performed after a period of 10 min of equilibration. Arterial pressure was measured manually during each carbon dioxide condition. Mean arterial pressure (MAP) was calculated as follows: diastolic pressure + 1/3 × (systolic − diastolic) pressure. All data (except MAP) were linked directly to the NIRS computer for real-time display and simultaneous storage with the NIRS data.

Statistical Analysis

During the whole experiment, time-averaged values of \( V_i \), arterial oxygen saturation, heart rate, and RR were recorded and expressed as mean ± SD during each carbon dioxide challenge. The latter parameters, anthropometric characteristics, pulmonary function, MAP, and arterial blood gas values under control condition were compared between the two COPD groups using the Mann-Whitney test for two independent samples. Within the COPD groups, values measured under control conditions were compared with values during chronic metabolic acidosis (acetazolamide) and during chronic metabolic alkalosis (furosemide) using the Wilcoxon matched-pair signed-ranks test. For each individual, \( CBV \), \( V_i \), and \( P_{0.1} \) were plotted against corresponding Paco2 values during each metabolic condition and were subjected to linear regression analysis. Because the statistical method of Kolmogorov and Smirnov, as described in the software (GraphPad Instat; GraphPad Software; San Diego, CA), showed a Gaussian distribution, a paired t test could be used to compare the slopes and intercepts of the linear regression equations during control conditions and both metabolic conditions. The level of statistical significance was set at \( p < 0.05 \). All tests should be regarded as explorative because of the multiplicity of tests.

RESULTS

Comparison Between the Normocapnic and Hypercapnic COPD Groups: Control Condition

The anthropometric characteristics and respiratory function data of the patients are summarized in Table 1. The degree of airway obstruction was the same in both COPD groups. Other ventilatory parameters (\( V_i \), RR, tidal volume, maximal voluntary ventilation, Vd/Vt) were similar in both groups (Table 2). Mean ± SD values of Paco2 were 5.26 ± 0.27 kPa and 6.27 ± 0.45 kPa in the normocapnic and chronic hypercapnic COPD groups, respectively, under baseline metabolic conditions. The hypercapnic COPD group showed significantly lower resting Pao2 values. Values of CBV were lower in the normocapnic patients relative to chronic hypercapnic patients (\( p < 0.01 \); Table 2).

An equal number of patients in both COPD groups were receiving inhaled salbutamol (5 of 16 normocapnic patients and 6 of 17 chronic hypercapnic patients). To account for medical intervention, average CBV and \( V_i \) were recalculated after subdividing both COPD groups into users and nonusers of theophyllines and/or oral corticosteroids. Long-term theophylline was received by 9 of 16 normocapnic patients (56%) and by 11 of 17 hypercapnic patients (64%). Four of 16 normocapnic patients and 4 of 17 hypercapnic patients received systemic corticosteroids. In both COPD groups, \( V_i \) values were not significantly different for users and nonusers of theophylline (10.3 mL/min and 8.9 mL/min in the normocapnic group and 8.5 mL/min and 9.8 mL/min in the chronic hypercapnic group, respectively). In addition, values of \( V_i \) were not significantly different for users and nonusers of corticosteroids (11.2 mL/min and 9.3 mL/min in the normocapnic group and 8.8 mL/min and 10.0 mL/min in the chronic hypercapnic group, respectively). CBV was not significantly different in our group of theophylline users, relative to the nonusers in both COPD groups. Furthermore, CBV values measured in corticosteroid users and nonusers were not different.

Both cerebrovascular and ventilatory responses to carbon dioxide (\( \Delta CBV/\Delta Paco2 \) and \( \Delta V_i/\Delta Paco2 \)) were the same for the chronic hypercapnic group as the normocapnic group (Table 3; Fig 1, 2). Both absolute values of \( P_{0.1} \) (Table 2) and its reactivity (\( \Delta P_{0.1}/\Delta Paco2 \); Table 3; Fig 1, 2) were the same in both COPD groups, even after correction for MIP.

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However, the x-intercept (Paco$_2$ at zero Pa$_{CO_2}$) was higher (p < 0.05) in the hypercapnic COPD group.

**Effects of Chronic Metabolic Acidosis**

The degree of metabolic acidosis was reflected in a mean decrease of base excess (BE) of −6.8 ± 1.1 mEq/L in the normocapnic COPD group and −5.9 ± 1.6 mEq/L in the chronic hypercapnic COPD group (both p < 0.001). Oral acetazolamide administration induced significant changes of Paco$_2$ compared with the control condition in both COPD groups despite unchanged ventilation in the hypercapnic COPD group. In addition, only the normocapnic COPD group showed a simultaneously significant increased PaO$_2$ value (p < 0.05). Ventilatory (ΔVt/ΔPaco$_2$), mouth pressure (ΔP$_{o,1}$/ΔPaco$_2$), and cerebrovascular (ΔCBV/ΔPaco$_2$) reactivity and corresponding intercepts did not change significantly during metabolic acidosis (Table 3; Fig 1, 2) in both COPD groups.

**Table 2—Outcome Parameters During Three Metabolic Conditions in Normocapnic and Chronic Hypercapnic Patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normocapnic COPD</th>
<th>Hypercapnic COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paco$_2$, kPa</td>
<td>5.26 ± 0.27</td>
<td>4.69 ± 0.35</td>
</tr>
<tr>
<td>PaO$_2$, kPa</td>
<td>9.05 ± 0.59</td>
<td>9.50 ± 0.75</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 ± 0.02</td>
<td>7.35 ± 0.02</td>
</tr>
<tr>
<td>HCO$_3^-$, mEq/L</td>
<td>25.2 ± 1.2</td>
<td>18.96 ± 1.19</td>
</tr>
<tr>
<td>BE, mEq/L</td>
<td>0.8 ± 1.2</td>
<td>−6.0 ± 1.1</td>
</tr>
<tr>
<td>CBV, mL/100 g</td>
<td>2.41 ± 0.66</td>
<td>2.95 ± 0.80</td>
</tr>
<tr>
<td>Vt, L/min</td>
<td>9.7 ± 2.5</td>
<td>11.1 ± 1.8</td>
</tr>
<tr>
<td>P$_{o,1}$, cm H$_2$O</td>
<td>5.12 ± 5.57</td>
<td>5.12 ± 2.48</td>
</tr>
<tr>
<td>Po$_{2}$, % of MIP</td>
<td>7.72 ± 4.53</td>
<td>7.90 ± 3.00</td>
</tr>
<tr>
<td>MVV, % predicted</td>
<td>33.1 ± 12.7</td>
<td>37.4 ± 13.1</td>
</tr>
<tr>
<td>Vn/Vt, %</td>
<td>48 ± 11</td>
<td>52 ± 5</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>16 ± 4</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>Vt, mL</td>
<td>648 ± 200</td>
<td>710 ± 140</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>83 ± 31</td>
<td>82 ± 14</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>106 ± 12</td>
<td>111 ± 15</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. MVV = maximal voluntary ventilation; Vt = tidal volume; HR = heart rate.

†p < 0.01.

‡p < 0.001 normocapnic COPD group compared to chronic hypercapnic COPD group.

§p < 0.01 no medication compared to acetazolamide or furosemide, Mann-Whitney test.

#p < 0.01 no medication compared to acetazolamide or furosemide, Mann-Whitney test.

Table 3—Linear Regression of CBV, Vt, and P$_{o,1}$ to Hypercapnia in Normocapnic and Chronic Hypercapnic Patients*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normocapnic COPD</th>
<th>Hypercapnic COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBV slope, mL/100 g/kPa</td>
<td>1.59 ± 0.91</td>
<td>1.61 ± 0.90</td>
</tr>
<tr>
<td>Vt slope, L/min/kPa</td>
<td>8.2 ± 4.9</td>
<td>7.5 ± 3.1</td>
</tr>
<tr>
<td>r value</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Vt$_{o,1}$, kPa</td>
<td>3.63 ± 1.12</td>
<td>2.99 ± 0.57</td>
</tr>
<tr>
<td>r value</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>P$_{o,1}$ slope, cm H$_2$O/kPa</td>
<td>3.02 ± 1.73</td>
<td>4.51 ± 3.19</td>
</tr>
<tr>
<td>r value</td>
<td>0.66</td>
<td>0.90</td>
</tr>
</tbody>
</table>

*Linear regression analysis of CBV (CBV, Vt, and P$_{o,1}$ value) as a function of Paco$_2$ was performed on each subject, based on four measurements (duplicated normocapnia, duplicated hypercapnia). Mean (± SD) slopes, x-intercepts, and coefficient of correlation (r) of the groups are displayed. The x-intercept is the Paco$_2$ value at zero CBV (CBV$_o$), zero Vt (Vt$_o$), and zero P$_{o,1}$ (P$_{o,1}$). An intercept of Paco$_2$ at zero CBV (CBV$_o$) was higher (p < 0.05) in the hypercapnic COPD group.

†p < 0.01 normocapnic COPD group compared to chronic hypercapnic COPD group.

‡p < 0.01 no medication compared to acetazolamide or furosemide, Mann-Whitney test.
Effects of Chronic Metabolic Alkalosis

Orally administrated furosemide induced a chronic metabolic alkalosis, with a mean increased ΔBE of 2.3 ± 1.2 mEq/L (p < 0.001) in the normocapnic COPD group and mean increased ΔBE of 1.2 ± 1.3 mEq/L (p < 0.05) in the chronic hypercapnic COPD group (Table 2). The mean value of PaCO₂ increased (p < 0.01) in the normocapnic group despite unchanged ventilation. Furosemide administration lowered PaO₂ (p < 0.05) in the hypercapnic COPD group. Normocapnic COPD patients showed the same reactivity of both ΔV̇/
\( \Delta P_{\text{aco}} \) and \( \Delta \text{CBV}/\Delta P_{\text{aco}} \) as the chronic hypercapnic group (Table 3; Fig 1, 2). Absolute values of \( P_{0.1} \) did not differ between both the control condition and metabolic alkalosis, however, its reactivity \( (\Delta P_{0.1}/\Delta P_{\text{aco}}) \) was significantly higher \((p < 0.05)\) during metabolic alkalosis in the chronic hypercapnic COPD group.

**Correlation Between the Different Reactivity Parameters**

Poor, not significantly different correlations were found between the individual CBV and \( V_i \) responses to acute hypercapnia \((\Delta \text{CBV}/\Delta P_{\text{aco}} \) and \( V_i/\Delta P_{\text{aco}}; r \leq 0.44, p > 0.1)\) for both COPD patients (Fig 3) under control condition and during metabolic acidosis; a weak but significant correlation was found during metabolic alkalosis in both COPD groups \((r = 0.58; p < 0.05)\). Correla-

tions between the individual CBV and \( P_{0.1} \) slopes \((\Delta \text{CBV}/\Delta P_{\text{aco}} \) and \( \Delta P_{0.1}/\Delta P_{\text{aco}}) \) were poor and not significant in both COPD groups in three metabolic conditions (Fig 4).

**DISCUSSION**

Cerebrovascular responses were studied and correlated with ventilatory reactivity in normocapnic conditions.
and chronic hypercapnic COPD patients. Chronic hypercapnic patients showed the same CBV and Vt reactivities to short-term carbon dioxide changes under baseline metabolic conditions as did normocapnic patients. P0.1 was the same in both COPD groups, even after correction for MIP. The influence of superimposed chronic metabolic alkalosis were more pronounced in the normocapnic COPD group, with (tendency to) lower ventilatory and cerebrovascular carbon dioxide responses in the latter group. In addition, P0.1 reactivity was significantly increased in the chronic hypercapnic group. Ventilatory and cerebrovascular carbon dioxide responsiveness were correlated and showed a wide interindividual variability of cerebral vascular and ventilatory reactivity to short-term changes in PCO2, thus refuting the hypothesis of an inverse relationship between ΔCBV/ΔPCO2 and ΔVt/ΔPCO2 in patients with COPD.

**Critique of Methods**

Before this study, the reproducibility of CBV measurements during resting conditions using NIRS was evaluated, and an intrapatient coefficient of variation of ±10% was found. These results are in agreement with others. CBV values of the present study under baseline metabolic conditions in both COPD groups (2.41 ± 0.66 mL/100 g and 2.90 ± 0.60 mL/100 g, respectively) are consistent with other investigators using NIRS in healthy subjects (2.85 ± 0.97 mL/100 g).

It is important to consider the advantages of measurements of CBV over measurements of CBF. First, there is a close relationship between CBV and CBF that has been extensively investigated by Grubb et al and by van Zijl et al. Second, the use of CBV instead of CBF eliminates the problems related to the mean cerebral transit time. Finally, near-infrared absorption changes reflect changes in the oxygenation of the microvasculature, and thus the CBV of the brain tissue. Changes of CBV reflect capillary recruitment, which is considered, by some, a better reflection of cerebrovascular responses than CBF responses to acid-base stimuli. We measured CBV in the frontal cortex region because present techniques do not allow measures of CBV or CBF in the brainstem of conscious humans. Moreover, Hida et al could not find any differences in carbon dioxide responses between the brainstem artery and the middle cerebral artery, supporting the assumption that our frontal lobe CBV measurements may be a good reflection of overall CBV changes in the brain.

**Baseline Metabolic Control Conditions**

Absolute values of CBV were lower in the normocapnic COPD group. Age, Hematocrit, MAP, and heart rate are established factors that affect CBV. However, both COPD groups were age matched, and all other parameters were not significantly different. The influence of medication was evaluated to find an explanation for the differences of CBV values between the COPD groups. Theophylline and corticosteroids are known to lower CBV. To account for medical intervention, average CBV and Vt was recalculated after subdividing both COPD groups in users and nonusers of theophyllines and/or oral corticosteroids. In contrast to others, CBV was not significantly different in our group of theophylline users, relative to the nonusers in both COPD groups. In addition, no differences were seen in ventilation. Furthermore, CBV values and Vt values measured in corticosteroid users and nonusers were not different. Buchweitz and Weiss described that IV salbutamol (1 μg/kg) leads to an increased CBV in
rats. In addition, the influence of inhaled salbutamol is likely to be less important on CBV regulation. An equal number of patients in both COPD groups received inhaled salbutamol. This study did not show any significant effect of inhaled salbutamol in both COPD groups on both CBV and V1.

CBV responsiveness to carbon dioxide was not reduced in the chronic hypercapnic COPD group compared with the normocapnic group. This is probably because of the power of the study. A reduced cerebral vascular responsiveness to a carbon dioxide challenge is in line with the findings of others, and is suggested to be the resultant of several factors, including: (1) a reduced increase in tissue hydrogen ion concentration secondary to an increased buffering capacity of the brain substance; (2) changes in the chemical composition of the CSF bathing the cerebral vessels (arterioles), involving an adjustment in the concentration of bicarbonate ions; (3) changes in neurotransmitter production secondary to chronic hypercapnia; (4) a chronic increase in interstitial fluid; (5) increased venous resistance to venous return; and (6) an inability to increase cardiac output.

Ventilatory responsiveness to carbon dioxide administration was highest in normocapnic COPD patients compared with chronic hypercapnic COPD patients. This result was expected and is in agreement with results of others. Because serum bicarbonate levels are higher in patients with chronic hypercapnia than patients with normocapnia, pH changes at the central chemoreceptor, caused by acute respiratory hypercapnia, are lower for a given increment in PaCO₂. This could explain the lower ventilatory responses in the first group. The lack of statistically significant may be explained by the relatively small size of the group.

Similar to the findings of Gelb et al. and Montes de Oca and Celli, but in contrast to others, the present study found the same values of P₂,₁ responsiveness in the hypercapnic group relative to the normocapnic group. The present study agreed with the results of Scano et al. that even after normalization of P₂,₁ for individual differences in muscle strength was performed (P₂,₁ as percentage of MIP), no differences between both COPD groups were seen.

**Effects of Chronic Metabolic Acidosis**

Acetazolamide is used in patients with COPD to improve blood gas values, especially in cases with a metabolic alkalosis related to the use of steroids and diuretics. The beneficial effect of acetazolamide in these patients is probably primarily caused by an increase in ventilatory drive, secondary to a metabolic acidosis induced by effective inhibition of renal carbonic anhydrase. A clinical dose of acetazolamide (250 mg po q8h for 3 days) leads to increased ventilation, resulting in a lowered PaCO₂. However, in the present study, results of ventilation after acetazolamide administration differed in normocapnic patients relative to chronic hypercapnic patients. This might be caused by the relatively flat carbon dioxide response curve, which is a common observation in the latter group. A change in BE would shift the carbon dioxide response curve leftward, without much measurable change in ventilation and in ventilatory responsiveness (ΔV̇/ΔPaco₂). Earlier studies found different effects of acetazolamide administration on the ventilatory carbon dioxide sensitivity in humans, with variations from no change to an increase after long-term application. It is suggested that differences in drug regimens and methodology to determine slopes of carbon dioxide responses curves (e.g., steady-state methods vs rebreathing) may account for these variable study outcomes.

The increase in ventilation caused a rise in PaO₂ in the normocapnic group. The presence of many lung regions with low ventilation/perfusion ratios may have mainly contributed to the lack of increase of ventilation and increase of PaO₂ in the chronic hypercapnic group. However, the degree of ventilation-perfusion mismatch was only slightly higher in the latter group.

Because of its physical/chemical properties, acetazolamide does not easily cross the blood brain barrier, even at higher doses. However, even after one low dose of acetazolamide (4 mg/kg), a decrease of carbon dioxide sensitivity of the central chemoreflex loop was found in carotid body denervated cats, which the investigators thought to be an altered relationship between brain blood flow and brain tissue PCO₂. However, the present study could not support differences in cerebrovascular reactivity and, thus, altered relationships between cerebral blood volume and PaCO₂ after long-term acetazolamide administration in both COPD groups.

**Effect of Chronic Metabolic Alkalosis**

It is interesting to note the different effects of furosemide administration in both COPD groups, with reduced effects on ΔBE in the hypercapnic COPD group. This may be caused by the preexisting metabolic compensated alkalosis in the latter group, relative to the normocapnic group (mean control value of BE, 2.4 mEq/L vs 0.8 mEq/L) and, therefore, difficulties to induce a further metabolic alkalosis. Ventilatory and cerebrovascular slopes were not different in the normocapnic group after the induction of metabolic alkalosis. Values of PaCO₂...
(despite unchanged ventilation) are only significantly elevated in the normocapnic group. Despite minor BE changes, PaO₂ deteriorated significantly in the chronic hypercapnic group. The higher P₀.₁ slope with a concomitant unchanged ventilation slope in chronic hypercapnic COPD patients is probably caused by an ensuing increased airway resistance as seen during alkalosis.⁴⁰

Mean values of CBV did not alter during metabolic alkalosis. Earlier studies¹¹ suggest lower cerebral blood flows during maintained steady chronic metabolic alkalosis in healthy humans. Assuming similarities in CBF between healthy subjects and normocapnic patients with COPD, the present study suggest only a tendency to a lower CBV reactivity in normocapnic patients with COPD.

**Correlation Between the Different Reactivity Parameters**

Other investigators pointed out the importance of measuring ventilation and cerebrovascular reactivity simultaneously.³⁴,⁴² The present study showed a wide variety in ventilatory and cerebrovascular carbon dioxide responsiveness, albeit showing some positive correlation and thereby refuting the hypothesized inverse relationship.

In conclusion, chronic hypercapnic patients showed the same CBV and Vᵢ reactivities under baseline metabolic conditions compared with patients with normocapnia. The effect of superimposed chronic metabolic acidosis on mean CBV reactivity and Vᵢ reactivity was not significantly different in both COPD groups. However, different effects on arterial blood gas values were seen between the COPD groups. In addition, superimposed chronic metabolic acidosis was more obvious in the normocapnic COPD group and led to some tendency to a lower ventilatory and cerebrovascular carbon dioxide responses in the latter group. P₀.₁ was similar in both COPD groups, even after correction for MIP during control condition and metabolic acidosis. The increased P₀.₁ reactivity during superimposed chronic metabolic acidosis in the chronic hypercapnic group was probably caused by increased airway resistance. The poor, but positive correlation between ventilatory and cerebrovascular carbon dioxide responsiveness (ΔCBV/ΔPaCO₂ and ΔVᵢ/ΔPaCO₂) during all metabolic conditions argued against our hypothesis concerning an inverse relationship between cerebrovascular and ventilatory responses to PaCO₂, and differences in neuroventilatory reactivity between normocapnic and hypercapnic COPD groups.

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**Appendix**

We describe a simple linearized static model of the interaction between CBF and ventilation (V) in response to changes in PaCO₂. Consider a certain volume of brain tissue with a metabolic rate of M (liters [standard temperature and pressure, dry] of carbon dioxide per minute) and perfused by Q (liters per minute) of blood entering the tissue with a PaCO₂.

According to Fick’s law, the venous partial carbon dioxide pressure (PvCO₂) in steady state then is,

\[ P_{vCO_2} = P_{aCO_2} + M/(c \times Q)(1) \]

where c is solubility.

For reasons of simplicity, the index carbon dioxide will now be dropped. We now make the simplifying assumption that during normoxia, perfusion around the operating point is linearly dependent on arterial pressure (Pₐ); therefore,

\[ Q = Q₀ + a \times Pₐ(2) \]

Next, we assume that the normoxic central ventilatory drive is a simple linear combination of arterial pressure and venous pressure (Pᵥ),

\[ V = V₀ + a \times Pₐ + β \times Pᵥ(3) \]

Substituting equations 1 and 2 in equation 3 yields,

\[ V = V₀ + (α + β) \times Pₐ + βM/(c(Q₀ + (α \times Pₐ))(4) \]

Equation 4 consists of three terms. Because the ventilatory drive V = 0 at some non-zero, positive value of arterial pressure, term 1 must be a negative constant. Term 2 increases linearly with arterial pressure. Term 3 represents the larger part of the interaction between CBF and ventilatory drive and has an inverse response (ΔV/ΔPₐ < 0). It decreases with increasing arterial pressure, thus damping the ventilatory response to an increase in arterial pressure. At lower arterial pressure values, this term is the more important one, increasing with decreasing values of arterial pressure. Depending on the balance of terms 2 and 3, term 3 may even induce hyperventilation. The blunted response of patients with COPD can be modeled here with relative small values for α and β in equation 3, making term 3 more important.

**References**

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