Cerebral Vascular Responsiveness in Chronic Hypercapnia*

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To assess the responsiveness of the cerebral vessels to chronic hypercapnia, we measured middle cerebral artery flow velocity by transcranial Doppler ultrasound in 20 normal subjects and in 14 COLD patients before and after stimulation by progressive hypercapnia (rebreathing test) or by intravenous administration of an acetazolamide bolus. The results showed no statistically significant difference in baseline flow velocity between the normal subjects and the COLD patients. The COLD patients showed a reduced cerebral vascular responsiveness to both stimuli. Cerebral blood flow is normal in chronic hypercapnia and the mechanism by which compensation is achieved leads to a decrease in cerebral vascular responsiveness.

(Chest 1992; 102:135-38)

CBF = cerebral blood flow; CCA = common carotid artery;
ICA = internal carotid artery; MCA = middle cerebral artery;
TCD = transcranial Doppler ultrasound

The dependence of cerebral blood flow (CBF) on PaCO₂ variations is well known in man and in laboratory animals. During acute hypercapnia, the CBF more than doubles, according to a sigmoid curve, and decreases by about 50 percent vs control values when the PaCO₂ falls by about 10 mm Hg.¹

During hypercapnia, pulmonary ventilation increases by some 2 to 5 L/min per mm Hg of PaCO₂ to reach 70 to 80 mm Hg of PaCO₂,² whereas during pronounced hypocapnia, the decrease in pulmonary ventilation is limited by lactic acid accumulation in brain tissue. Hence, CO₂ accumulation in brain tissue leads to an increase in CBF, which in turn tends to lower the tissue concentration of CO₂.³,⁴

The CBF-PaCO₂ relationship is even more complex, for the brain PaCO₂ affects the activity of nervous structures that regulate pulmonary ventilation.⁵ Yet, in the advanced stages of respiratory failure secondary to chronic obstructive lung disease, stable hypercapnia is known to be associated with a normal CBF.⁶

Middle cerebral artery blood flow velocity can be measured by means of transcranial Doppler ultrasound.⁷ Since the diameter of the large cerebral arteries is known to remain constant during hypercapnia,⁸,⁹ the variations in blood velocity reflect changes in blood flow, which can thus be monitored through time. It has therefore been possible to study MCA flow in man and vascular responsiveness during experimentally induced PaCO₂ variations ("cerebral vascular reserve").¹¹,¹²

This study aims to investigate cerebral vascular responsiveness in patients with chronic hypercapnia secondary to COLD.

Subjects and Methods

Thirty four subjects were assigned to four groups. The first group (G1) was made up of 12 normal subjects aged 47 to 51 years with PaCO₂ and PaO₂ values of 38.12±3.01 and 98.32±1.11 mm Hg, respectively (mean value±SD). The second group (G2) consisted of eight patients with COLD and stable hypercapnia aged 60 to 70 with a PaCO₂ of 56.22±6.07 and a PaO₂ of 54.42±4.27 mm Hg (mean value±SD).

All the subjects of these two groups were studied before and after hypercapnia induced by the rebreathing test (test A). The third group (G3) was made up of eight normal subjects aged 48 to 54 with PaCO₂ and PaO₂ values of 40.07±4.36 and 96.15±1.33 mm Hg, respectively (mean value±SD). The fourth group (G4) consisted of six patients with COLD and stable hypercapnia aged 60 to 74 with PaCO₂ of 56.67±4.15 and PaO₂ of 56.45±3.17 mm Hg (mean value±SD). The subjects of these two groups were investigated before and after intravenous administration of acetazolamide (test B). All the groups were made up of different subjects.

The selection criteria for the COLD patients were as follow: clinical history of cough, chronic dyspnea, and irreversible obstructive changes in spirometric tests. None of the patients was a smoker at the time of our study, the smokers having stopped at least five years before. In Table 1, some spirometric values for each group studied are shown.

None had atheromatous changes, other than age-related (ie, parietal sclerosis without vascular stenosis) of the common carotid artery or of the internal carotid artery detectable on echo-Doppler ultrasound study of the neck vessels, or any other disease. None of the patients studied had taken drugs during the 24 h preceding the study. Patients with an MCA flow velocity side-to-side asymmetry of more than 15 percent were excluded. Informed consent was obtained from all taking part in the study.

The spirometry measurements were analyzed by lung function analyzer and the lung volume by the nitrogen dilution method. Blood gas analysis was done on an ABL gas analyzer. The carotid arteries were investigated by 7.5 MHz duplex Doppler ultrasound scanner.

The MCA blood velocities were measured by a pulsed TCD velocimeter after the subject had been comfortably placed in the supine position for at least 10 min. The 2 MHz probe was positioned on the temporal window, and the MCA was imaged at a depth of 5.0 to 5.5 cm. The mean velocity was expressed in centimeters per

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**Table 1—Spirometric Data of the Four Populations Studied**

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects</th>
<th>VC, % Pred</th>
<th>FEV1, % Pred</th>
<th>RV, % Pred</th>
<th>TLC, % Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>1-12</td>
<td>102.50</td>
<td>105.83</td>
<td>98.83</td>
<td>99.00</td>
</tr>
<tr>
<td></td>
<td>± SD</td>
<td>2.06</td>
<td>3.10</td>
<td>0.92</td>
<td>0.71</td>
</tr>
<tr>
<td>G2</td>
<td>13</td>
<td>31</td>
<td>14</td>
<td>269</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>± SD</td>
<td>14</td>
<td>22</td>
<td>160</td>
<td>89</td>
</tr>
<tr>
<td>G3</td>
<td>21-28</td>
<td>104.10</td>
<td>111.60</td>
<td>94.50</td>
<td>97.90</td>
</tr>
<tr>
<td></td>
<td>± SD</td>
<td>3.82</td>
<td>4.39</td>
<td>2.18</td>
<td>1.69</td>
</tr>
<tr>
<td>G4</td>
<td>29</td>
<td>62</td>
<td>26</td>
<td>180</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>± SD</td>
<td>3.82</td>
<td>4.39</td>
<td>2.18</td>
<td>1.69</td>
</tr>
</tbody>
</table>

*G1 and G3, normal subjects; G2 and G4, COLD patients; VC, vital capacity; pred, percent of the predicted value; FEV1, forced expiratory volume in 1 s (75 percent of predicted VC); RV, residual volume; and TLC, total lung capacity.

**Table 2—MCA Flow Velocities Before and After the Rebreathing Test in Normal Subjects and in COLD Patients**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mean Baseline MCA Flow Velocity, cm/s</th>
<th>Mean MCA Flow Velocity/Paco2</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>60.41 ± 9.27 SD</td>
<td>3.17 ± 1.48 SD</td>
</tr>
<tr>
<td>G2</td>
<td>58.97 ± 4.08 SD</td>
<td>1.45 ± 0.46 SD</td>
</tr>
</tbody>
</table>

*G1, normal subjects; G2, COLD patients; MCA flow velocity/ Pco2, increase in MCA flow velocity (cm/s) per unit CO2 increase (mm Hg) during rebreathing test.

**Discussion**

The subjects of this series were not matched for age and the COLD patients were older. Thus, it could be supposed that the differences observed may be related to aging. However, in our experience (unpublished data), we did not find any significant difference in the cerebrovascular CO2 reactivity in normal subjects of various ages up to 65 years. Thus, these findings seem to suggest that cerebrovascular responsiveness to CO2 is decreased in chronic hypercapnia.

The finding that chronic hypercapnia attenuates the cerebrovascular responses to CO2 is not new since previous studies in animals have demonstrated this. However, to our knowledge, the confirmation in patients with COLD is a novel clinical finding.

An increase in the H+ concentration in the cerebral interstitial tissue leads to vasodilatation, and this is **Table 3—MCA Flow Velocities Before and After Acetazolamide in Normal Subjects and in Patients with COLD**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mean Baseline MCA Flow Velocity, cm/s</th>
<th>Mean MCA Flow Velocity After Acetazolamide and Percentage Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3</td>
<td>54.52 ± 5.70 SD</td>
<td>79.17 ± 9.03 SD (42% ± 9% SD)</td>
</tr>
<tr>
<td>G4</td>
<td>60.11 ± 17.13 SD</td>
<td>73.21 ± 16.25 SD (22% ± 10% SD)</td>
</tr>
</tbody>
</table>

*G3, normal subjects; G4, COLD patients.
the final common mechanism of many substances or metabolites acting on the CBF, including CO₂.

Since H⁺ and HCO₃⁻ do not easily cross the blood-brain barrier, the pH of the cerebrospinal fluid, equitable within limits to the cerebral interstitial fluid, undergoes only small variations during metabolic pH changes.²⁰,²¹

Acid-base variations of respiratory origin, on the other hand, are reflected immediately in the CSF, because of the high diffusibility of CO₂ and the low buffering power of the CSF.²² In the stable phases of COLD with hypercapnia, the CSF pH usually follows the changes in plasma pH.²³ The HCO₃⁻ concentrations also present a trend parallel to that of the plasma, even though it takes hours or days before an equilibrium situation is attained.²⁴,²⁵

While acute changes in PaCO₂ are followed by a rapid rise in CBF, a stable increase in PaCO₂ is not accompanied by a rise in CBF, and patients with chronic hypercapnia secondary to COLD have CBF values within normal limits.²⁶

In line with these data, we found that patients with chronic hypercapnia presented MCA flow velocities similar to those of normal subjects.

An acute increase in PaCO₂ in response to the rebreathing test, however, induces a significantly smaller increase in MCA flow velocity in COLD patients with hypercapnia than in normal subjects. A reduced response is observed also after acetazolamide.

The Read rebreathing method involves the use of a hyperoxic gas mixture. Since the COLD patients were hypoxic, the lesser response to CO₂ could reflect a relief of the effects of hypoxemia on the brain blood flow. Surely, the relief of the hypoxemia may have in some extent reduced the MCA flow velocity, but the reduction of the CO₂ vascular reactivity in COLD patients is confirmed by the results obtained after acetazolamide, a drug which induces a "factitious" hypercapnic effect inhibiting the carbonic anhydrase of the erythrocytes.

Reduced cerebral vascular responsiveness might be due to the following: (1) changes in neurotransmitter production secondary to hypercapnia;²⁷,²⁸ (2) a chronic increase in interstitial fluid; (3) increased venous resistance to venous return; (4) inability to increase cardiac output; and (5) reduced increase in tissue H⁺ concentration secondary to an increase in the buffering capacity of the brain substance. In hypercapnia, the deamination of alanine may give rise to increased production of NH₃ followed by an increase in glutamic acid from alpha ketoglutaric acid,²⁹ the direct consequence of which is an increased capacity of an important intracellular buffering system. Further, in prolonged hypercapnia, an alteration in responsiveness of pial arterioles to CO₂ was shown to be due to a change in the chemical composition of the CSF bathing these vessels, involving an adjustment in the concentration of bicarbonate ions.³⁰

Acetazolamide causes a rapid inhibition of erythrocyte carbonic anhydrase, an enzyme that normally catalyses the last step in the chemical reaction:

\[ \text{H}^+ + \text{HCO}_3^- = \text{H}_2\text{CO}_3 = \text{CO}_2 + \text{H}_2\text{O} \]

The lowering of the pH in the cerebrospinal fluid and in the cerebral tissue is explained by the higher concentration of H₂CO₃ due to inhibition of carbonic anhydrase in the erythrocytes, impeding the removal of CO₂ in the brain tissue by the bloodstream.³¹

Alternatively, the effect might occur through a direct inhibition of the carbonic anhydrase located within the brain tissue, where it has been demonstrated in large quantities in the glia cells, in the choroid plexus³² and in the endothelium of the capillaries scattered throughout the brain tissue.³³

In conclusion, we can confirm that flow velocity in the basal cerebral arteries is normal during hypercapnia and that cerebral vascular responsiveness to the capnic stimulus is significantly reduced. This may be explained by the different status of the feedback mechanism of CBF regulation.

The latter depends not so much on the PCO₂ value as on the interstitial H⁺ concentration. A greater buffering capacity of the brain tissue makes possible the coexistence of hypercapnia, a normal CBF, and the possibility of its regulation around the new chronically stabilized PaCO₂ value.

The flow variations induced by acute CO₂ variations will, of course, be smaller than in normal subjects.

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