Transient Responses of Cerebral Blood Flow and Ventilation to Changes in Paco$_2$ in Normal Subjects and Patients With Cerebrovascular Disease

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SUMMARY In the present study, the dynamics of the cerebral blood flow (CBF) and ventilatory response to hypercapnia was investigated in a group of patients with cerebrovascular disease and compared to responses measured in a group of normal volunteers. There was a significant correlation between the rapidity of the transient CBF and ventilatory responses and the severity of the cerebrovascular disease. While the steady state CBF response showed no such correlation, the steady state ventilatory response was reduced in patients with severe cerebrovascular disease. Various explanations for the differences in the dynamic responses of CBF and ventilation in patients with mild or severe cerebrovascular disease compared to normal subjects are considered. Measurement of these circulatory and ventilatory responses may be sensitive means for assessing the changing status of patients with cerebrovascular disease.

THE CLOSELY COORDINATED ADJUSTMENTS in ventilation and cerebral blood flow (CBF) which guard the acid-base balance of the brain may be upset in cerebrovascular disease. Cerebrovascular disease may significantly affect the usual increase in CBF that occurs with hypercapnia.1-4 It may also alter the steady state ventilatory response to CO$_2$ either by interfering specifically with the function of respiratory neurons or by causing generalized ischemia, thus interfering with brain metabolism.5-10

Besides disturbing steady state responses, it seems reasonable to expect that cerebrovascular disease can produce more subtle functional changes, interfering with the rapidity of CBF and ventilatory responses to the addition and removal of CO$_2$ from the inspired air, sometimes even before obvious changes in the magnitude of the steady state response can be observed.11

In the present study, the dynamics of the CBF and ventilatory response to hypercapnia was investigated in a group of patients with cerebrovascular disease and compared to responses measured in a group of normal volunteers.

Methods

The ventilatory and CBF response to 5% CO$_2$ inhalation and its removal were determined in four normal subjects and 18 patients with mild to severe cerebrovascular disease as determined by clinical and angiographical findings. The patients had had their neurological deficit for at least five days prior to study.

In the normal subjects, a catheter was placed in the brachial artery and internal jugular vein under local anesthesia. The venous catheter was advanced into the jugular bulb with fluoroscopic guidance. A steady state CBF measurement was then performed by the Kety-Schmidt technique using Kr$_{85}$ after waiting 30 minutes for the subject to stabilize.12 The blood samples containing Kr$_{85}$ were measured in a liquid scintillation counter.13 During the measurement of control CBF, the subject breathed 30% O$_2$ in N$_2$ through a one-way valve. Ventilation was determined in this steady state period by measuring expired gas collected for three minutes with a dry gas meter. The inspired gas was then abruptly switched to 5% CO$_2$-30% O$_2$ in N$_2$, and arterial and cerebral venous samples were obtained intermittently for pH, PCO$_2$, and O$_2$ content. A blood gas analyzer with appropriate electrodes (Radiometer PHM-71, Copenhagen, Denmark) and an oximeter (Cooximeter Model 182, Instrumentation Laboratories, Springfield, Massachusetts) were used for these determinations. The ventilation of the subject was continuously monitored by electronically integrating the airflow signal obtained from a pneumotachograph connected to the expired gas port of the breathing valve. End-tidal PCO$_2$ was continuously monitored with an infrared CO$_2$ analyzer (Beckman LB-1, Palo Alto, California). Continuous measurements were also made of blood pressure and EKG. The on-transient response was followed for 20 minutes and then a second steady state determination of ventilation and CBF was made with K$_{85}$ while the subject continued to breathe 5% CO$_2$. The inhaled gas was then abruptly switched back to 30% O$_2$ in N$_2$ and the off-transient monitored as before for 20 minutes. Finally, a third steady state determination of ventilation was made and CBF determined with Kr$_{85}$.

In the patients, total and regional cerebral blood flows were measured in the steady state by the $^{133}$Xe arterial injection technique during and either before or after 5% CO$_2$ inhalations as previously described.14 In ten patients, the ventilation and CBF were measured as above during the on-transient, and in eight other patients, during the off-transient. In both patients and normal subjects, the reciprocal of the arterial-cerebral venous difference in O$_2$ content was used as a measure of CBF during the transient studies. This is only a valid measure of changes in CBF if the cerebral metabolic rate for oxygen (CMRO$_2$) does not change significantly with changes in CO$_2$. In normal subjects, this has been shown to be true under conditions similar to those of the present study.3 In the 18 patients studied, no statistically significant change in CMRO$_2$ during hypercapnia was observed: mean CMRO$_2$ was 2.23 ml/100 gm per minute during hypercapnia and 2.35 ml/100 gm per minute in the absence of hypercapnia.

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Results

Table 1 lists the clinical and angiographical data in the 18 patients studied. On the basis of this information, the patients were divided into two groups: Group 1, patients with mild disease, and Group 2, patients with severe disease. The age range of the patients in these two groups was similar. Patients with mild disease were 37 to 61 years old, while those with severe disease were 29 to 76 years of age. Average steady state data for cerebral oxygen consumption and cerebral blood flow and ventilatory response to CO₂ are shown in table 2. Results in the four normal individuals (age range 20 to 25) were within the limits reported by other investigators for similar subjects.¹⁵⁻¹⁹

Table 2 shows that the CMRO₂ is significantly reduced in the patients with severe disease (p < 0.001) compared to either the patients with mild disease or the normal subjects. The ventilatory response to CO₂ was significantly less in the patients with more severe clinical cerebrovascular disease than it was in either the patients with milder illness or the control subjects. Also, the steady state CBF response was nearly identical in the two patient groups. Correlation between CMRO₂ and the steady state CBF or ventilatory response to CO₂ was likewise poor (r = 0.32 and 0.25 respectively).

Examples of the time course of the increases in arterial and cerebral venous PcO₂, CBF and ventilation with 5% CO₂ inhalation are illustrated in figure 1 in patients from the two clinical groups and in normal subjects.

In the normal subjects the time course of the increase in CBF was similar to that of arterial PcO₂, but an overshoot occurred in the CBF response in the patients with mild cerebrovascular disease that was not present in the arterial PcO₂. The rise in ventilation in both these groups was much slower than that of CBF, and the rate of increase of cerebral venous PcO₂ is slower yet.

In contrast, in the patients with severe cerebrovascular disease, the rate of change of CBF was much slower than that of arterial PcO₂, while ventilation and arterial PcO₂ rose at about the same rate and there were no overshoots.

In order to more easily compare the transient ventilatory and cerebral blood flow response in the two groups of patients with the normal response, the response to a step change in arterial PcO₂ was calculated by standard techniques.²⁰ In this way, any difference in the CBF or ventilatory response caused by difference in the arterial PcO₂ input function was eliminated.

The average change in CBF for a step change in PaCO₂ is illustrated in figure 2. The CBF response was faster in the mild than in the severe cases. Three of the four normal subjects also showed a slight overshoot (8% on the average) in the CBF response. The 90% response time of the CBF for the mild cases (Group 1) was 0.4 ± 0.1 minute, and for the severe cases (Group 2), 3.9 ± 0.8 minute. This difference is significant at the p < 0.005 level. There was also a significant direct correlation between the 90% response time of the CBF in the patients and their CMRO₂ (r = 0.68 and p < 0.025).

Figure 3 shows the average on-ventilatory response as calculated for a step increase in PaCO₂. No overshoot was present in the ventilatory response of normals or patients with mild cerebrovascular disease, but was present in patients with severe disease. The 90% response time is significantly less (p < 0.01) in patients with severe disease (1.8 ± 0.5 minutes) than in patients with mild cerebrovascular disease (5.3 ± 0.76 minutes). There is a significant inverse correlation between the 90% response time of the ventilatory response and the CMRO₂ (r = 0.76 and p < 0.025).

Figure 4 shows the average time course of the changes in arterial and jugular venous PcO₂ in CBF and in ventilation in the normal volunteers, and in the patients from each of the two clinical groups when 5% CO₂ in the inspired gas was suddenly removed. Again, CBF changed more rapidly than

![Normal Subjects](image)

![Severe Cerebrovascular Disease](image)

![Mild Cerebrovascular Disease](image)

**Figure 1.** Changes with time during 5% CO₂ inhalation in arterial PcO₂, cerebral venous PcO₂, ventilation and CBF in (A) normal subjects, (B) patients with severe cerebrovascular disease, and (C) patients with mild cerebrovascular disease. Changes are plotted as a percent of the total changes.
<table>
<thead>
<tr>
<th>Pt./age/sex</th>
<th>BP</th>
<th>Clinical Findings</th>
<th>Angiographical Findings</th>
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<tr>
<td>HW/50/M</td>
<td>160/100</td>
<td>Mild L hemiparesis and dysarthria 1 mo prior to study</td>
<td><em>R</em> carotid angiogram: no extracranial disease, minor atherosclerotic changes in cavernous portion of ICA, focal narrowing of lenticulostriate arteries</td>
</tr>
<tr>
<td>RP/47/F</td>
<td>220/135</td>
<td>Mild L hemiparesis 3 mos prior to study</td>
<td><em>R</em> carotid angiogram: no extracranial disease, some irregularity of lenticulostriate arteries, mild arteriosclerotic changes in branches of ACA and MCA, no occlusions</td>
</tr>
<tr>
<td>DM/51/M</td>
<td>100/60</td>
<td>Mild dementia of 1 yr duration</td>
<td><em>L</em> carotid angiogram: normal extracranial vessels, moderate stenosis of the cavernous portion of the ICA</td>
</tr>
<tr>
<td>GJ/63/M</td>
<td>190/90</td>
<td>Mild R hemiparesis 3 wk prior to study</td>
<td><em>L</em> carotid angiogram: normal except for atherosclerotic changes of lenticulostriate arteries</td>
</tr>
<tr>
<td>RC/42/M</td>
<td>120/90</td>
<td>Mild R hemiparesis 3 wk prior to study</td>
<td><em>L</em> carotid angiogram: no extracranial disease, mild to moderate atherosclerosis of the cavernous portion of the ICA, MCA and posterior cerebral artery</td>
</tr>
<tr>
<td>EMcC/61/M</td>
<td>125/85</td>
<td>Moderate L hemiparesis 10 days prior to study</td>
<td><em>R</em> carotid angiogram: mild atherosclerotic changes in lenticulostriate arteries, other branches of ICA are normal</td>
</tr>
<tr>
<td>ES/54/M</td>
<td>130/95</td>
<td>TIA involving R arm and leg</td>
<td><em>L</em> carotid angiogram: minor atherosclerotic changes present in supraclinoid portion of ICA, minimal changes present in MCA branches and moderate changes in lenticulostriate arteries</td>
</tr>
<tr>
<td>GH/37/M</td>
<td>180/120</td>
<td>TIA involving R arm and leg 2 wk prior to study</td>
<td><em>L</em> carotid angiogram: plaque at origin of ICA, moderately occlusive; no intracranial atherosclerosis present</td>
</tr>
<tr>
<td>JMcK/29/M</td>
<td>125/85</td>
<td>SAH</td>
<td>*Bilateral carotid &amp; L vertebral angiograms: marked spasm of supraclinoid portions of ICA, bilaterally</td>
</tr>
<tr>
<td>AD/62/F</td>
<td>220/110</td>
<td>Moderate R hemiparesis 22 days prior to study</td>
<td><em>L</em> carotid angiogram: severe diffuse atherosclerotic changes with multiple focal atheroembolic intracranial lesions in MCA distribution and supraclinoid portion of ICA</td>
</tr>
<tr>
<td>FS/76/F</td>
<td>160/100</td>
<td>Marked R hemiparesis and dysarthria 5 days prior to study</td>
<td>*Bilateral carotid angiograms: 60% stenosis at origin L ICA; 40% stenosis of supraclinoid portion of L ICA; marked narrowing of MCA at bifurcation from ICA on L, atherosclerotic changes in ACA, severe stenosis of intracavernous portion of R ICA</td>
</tr>
<tr>
<td>RT/62/F</td>
<td>140/90</td>
<td>R hemiparesis 10 yr prior to study, R pontine infarction 3 yr prior to study, marked L hemiparesis 7 mo prior to study</td>
<td><em>R</em> carotid angiogram: no extracranial disease, moderate atherosclerotic changes in MCA branches</td>
</tr>
<tr>
<td>CV/66/M</td>
<td>160/95</td>
<td>Syncopeal episode 2 wk prior to study, mild CVA 1 yr prior to study</td>
<td><em>R</em> carotid angiogram: severe atherosclerotic changes in supraclinoid portion of ICA and lenticulostriate arteries</td>
</tr>
<tr>
<td>WW/66/M</td>
<td>200/100</td>
<td>Moderate L hemiparesis 1 mo prior to study</td>
<td><em>R</em> carotid angiogram: 50% stenosis at origin of ICA; 70% to 80% stenosis of supraclinoid portion of ICA, multiple areas of moderate to marked stenosis of MCA and ACA</td>
</tr>
<tr>
<td>EW/50/M</td>
<td>170/110</td>
<td>R hemiplegia and aphasia 2 mo prior to study</td>
<td><em>L</em> carotid angiogram: moderate diffuse atherosclerotic changes involving the supraclinoid portion of ICA and ACA and lenticulostriate artery</td>
</tr>
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ventilation in the normal volunteers and in the patients with mild cerebrovascular disease; the CBF changes were only slightly slower than the decrease in Paco₂. In contrast, ventilation falls more rapidly than CBF in the patients with severe cerebrovascular disease.

Because the arterial CO₂ input functions differed in the two patient groups, responses to a step reduction in Paco₂ were also calculated. Average changes in CBF for a step decrease in Paco₂ are compared for the two clinical groups and the normal subjects in figure 5, while average ventilatory changes are compared in figure 6. Patients with mild cerebrovascular disease showed an undershoot in their CBF response which averaged 29%. A smaller undershoot was observed in normal volunteers, but none at all was noted in patients with severe disease. There is a good correlation between CMRO₂ and 90% response time of CBF (r = 0.752, p < 0.05). As shown in figure 6, the rate of change of ventilatory responses was greater in the patients with more severe disease than in either normal patients or patients with mild cerebrovascular disease, but the correlation between 90% response time of ventilation and CMRO₂ is not significant.

**Discussion**

In the present study, the steady state level and the rapidity of the ventilatory and CBF response to the addition and removal of 5% CO₂ from the inspired air were measured in 18 patients with cerebrovascular disease; the results were compared to similar data obtained in four normal volunteers. Steady state CBF responses to CO₂ were only slightly decreased in the patients with cerebrovascular disease; there was no relation between the blunting of the response and the clinical severity of the disease. In contrast, there was a significant correlation in the patients between the rapidity of the CBF responses and the severity of vascular abnormalities in the brain as indicated by the cerebral oxygen consumption. The worse the disease, the more sluggish was the change in CBF. Steady state ventilatory responses were at the lower limit of normal in the group with severe vascular disease of the brain. However, the rapidity of ventilatory response was greater in these patients and correlated directly with the CMRO₂.

Blunting of the steady state CBF response to hypercapnia and hypocapnia has been reported in some but not in all studies of patients with vascular disease of the brain. The effect of cerebrovascular disease seems to be uneven and in patients with acute strokes, both ischemic and hemorrhagic, foci have been described. In some areas, vascular responses to changes in blood gas tensions appear to be preserved; in others, only the response to hypocapnia persists; and in still others, paradoxical changes have been observed so that CBF decreases as Pco₂ is increased. Both the fact that the usual methods of assessing CBF measure only the average flow per volume of cerebral tissue and the fact that relatively great variability is seen even in the responses of normal individuals interfere with the clinical usefulness of the steady state CO₂ response. Only a few studies have tried to evaluate the dynamics of the CBF response to blood gas changes and none have attempted to correct the transient response for differences in the time course of the input function, the Paco₂ change. The results of the present study suggest that the time course of CBF changes to step changes in Paco₂ may be clinically useful since abnormalities in this response are detectable even before abnormal steady state responses are present.

The differences in the speed of the transient CBF response in patients with mild or severe cerebrovascular disease can be explained in several ways, because it is uncertain whether changes in arterial, extracellular or intracellular Pco₂ (or pH) are responsible for the brain blood flow changes that oc-
cur with CO₂ inhalation. While Shapiro has presented experimental evidence indicating the importance of intracellular PCO₂ changes, the study by Severinghaus and Lassen would be compatible with CBF regulation by changes in arterial PCO₂. Comparison of levels of CBF in individuals with chronic hypocapnia (high altitude natives) and studies during acid-base derangements suggest that CBF depends mainly upon the pH of the brain extracellular fluid.

Blood flow seems to be highest in those areas of the brain with the greatest metabolic rate, and in the normal brain, the ratio of blood flow to metabolism is nearly the same throughout the brain. If CBF is controlled by a single factor such as extracellular fluid (ECF) pH, the increase in the rapidity of the transient CBF response seen in patients with mild cerebrovascular disease could be explained by increas-
The difference in O₂ content would narrow more rapidly than it rate is high would equilibrate more rapidly with CO₂ metabolism in the brain caused by the vascular lesions. Consequently, these high blood flow regions would contribute disproportionately more to the decreasing rather than increasing with hypercapnia. Initially, the high flow regions would contribute more to the AV-O₂ difference in O₂ content would narrow more rapidly than it would if flow, metabolic and hence CO₂ equilibration rates were more uniform. Apparent overshoots in the CBF response would occur if there were areas in which CBF responded paradoxically to CO₂ changes — blood flow decreasing rather than increasing with hypercapnia. Initially, the high flow regions would contribute more to the AV-O₂ difference and tend to narrow it, while later when the flow areas were represented more in proportion to their true weight the mean AV-O₂ difference would widen. As increasingly severe disease interfered more extensively with gas exchange across capillaries, changes in ECF PCO₂ and pH would be uniformly slowed throughout the brain, reducing the speed of the CBF response. Also, with extensive vascular lesions, the ability of the smooth muscle in the blood vessel wall to shorten might be affected, further diminishing the rate with which vascular dilatation and contraction occurred with CO₂.

Recent studies by Greenberg et al. suggest that CBF responses to CO₂ have a rapid component and a slower component. The slow component may depend on changes in ECF pH or brain PCO₂, while the rapid component may depend on changes in PaCO₂. Alternatively, other studies have suggested that the cerebrovascular response to CO₂ may involve a neural component which is presumably rapid. Both these ideas would be compatible with the observations made in the present study which show that CBF in normal subjects responds more rapidly than changes in cerebral venous PCO₂ but more slowly than changes in arterial PCO₂.

If the rapidity and the degree of the CBF response to CO₂ depend on changes at two sites, the differences in the transient CBF response in patients with mild or severe cerebrovascular disease could be explained as follows: In mild disease, a decrease in the sensitivity of the vascular response to the slow component would tend to accelerate the transient CBF response; however, with more severe disease, as shortening of the vascular smooth muscle was mechanically slowed, the rate of the transient response would decrease.

In the present study, the steady state ventilatory response to CO₂ was reduced in subjects with the most severe cerebrovascular disease. However, the ventilatory response to CO₂ is variably affected in stroke patients depending on the location of the cerebrovascular lesions. Heightened steady state ventilatory responses to CO₂ have been observed in vascular disease affecting the cortex, while a depressed response has been noted in patients with medullary lesions.

Abnormalities in the transient as well as the steady state ventilatory responses to CO₂ were observed in the present study. The significant inverse relationship between the rapidity of the ventilatory response to CO₂ inhalation and the clinical severity of the vascular disease suggests that measurements of these ventilatory responses may be a useful noninvasive way for assessing the changing status of these patients.

While CBF dynamics were depressed with severe cerebrovascular disease, ventilatory dynamics seemed to be accelerated. Although 70% to 90% of the ventilatory response to CO₂ is determined by the pH of brain ECF, 10% to 30% of the ventilatory response to CO₂ in normal individuals arises in the peripheral chemoreceptors which respond rapidly to hypercapnia. Cerebrovascular disease would be expected to depress respiratory neuron function in the brain, reduce the sensitivity to the centrally mediated response to CO₂, and consequently produce a blunting of total CO₂ response as was observed in the patients with severe stroke. This reduction in the role of central CO₂ receptors would increase the relative contribution of the peripheral arterial chemoreceptors to CO₂ response which in turn would accelerate the rate of ventilatory response to CO₂ as observed in this study. Although this hypothesis requires further experimental con-
firmation, an increase in peripheral chemoreceptor contribution to CO₂ response could also decrease the stability of ventilatory control. The decrease in stability could contribute to production of the periodic breathing sometimes observed in patients with severe cerebrovascular disease. Additional experimental study is needed to evaluate the stability of ventilatory control in these patients.

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Transient responses of cerebral blood flow and ventilation to changes in PaCO2 in normal subjects and patients with cerebrovascular disease.
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