Hyperventilation and Cerebral Blood Flow

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Abstract: Hypocapnic-hyperventilation has a profound, but probably temporary, effect on CBF, producing approximately a 2% decline in CBF for each 1 torr decline in $P_{CO_2}$. This effect appears to be mediated through changes in perivascular pH of the cerebral resistance vessels acting directly on the vessel wall. At low $P_{CO_2}$ the vasoconstrictor effect of short-term hypocapnic-hyperventilation is attenuated by resultant cerebral hypoxia. During prolonged hyperventilation CBF returns toward normal as the pH in the CSF is restored.

Short-term hypocapnic-hyperventilation can be lifesaving in the treatment of acute intracranial hypertension. On the other hand, prolonged hyperventilation has not been convincingly shown to benefit patients, whether with severe head injury or cerebral infarction, or during carotid endarterectomy without bypass.

Introduction

Hypocapnic-hyperventilation (HV) has a profound effect on cerebral blood flow in healthy man and animals. Because of this effect, it has played a central role in the development of our current understanding of the regulatory mechanism of the cerebral circulation. In addition, it has been employed in a variety of clinical situations where manipulation of cerebral circulation and brain acid-base metabolism has been sought. In this review we will consider first the relationship between hypocapnic-hyperventilation and cerebral blood flow (CBF), and second the clinical application of this tool.

Influence of Hyperventilation on Cerebral Blood Flow

Acute hypocapnic-hyperventilation (HV) in healthy animals and man causes an immediate cerebral vasoconstriction with a consequent rise in cerebral vascular resistance (CVR) and a fall in cerebral blood flow (CBF), changes that parallel the fall in arterial carbon dioxide tension ($P_{CO_2}$). It is generally accepted that the effect of HV is mediated by this change in $P_{CO_2}$, for it is the most potent cerebral vasoconstrictive agent known. Acute changes in $P_{CO_2}$ between 20 and 60 torr have been shown to change CBF 1 to 2 ml/min/100 gm of brain per 1 torr change in $P_{CO_2}$.

Mechanism of Action

The specific mechanism for the effect of $P_{CO_2}$ on CBF has been the subject of considerable controversy. It is well established that an acute rise in $P_{CO_2}$ causes a decrease in CVR which increases the CBF, and a fall in $P_{CO_2}$ has the opposite effect. However, during sustained alteration in $P_{CO_2}$ the CBF and absolute carbon dioxide tension often fail to correlate closely. This has led to the hypothesis that alteration of the pH of the brain extracellular space mediates the cerebral vascular response to carbon dioxide and hence HV, and that brain interstitial fluid pH is a major regulator of CBF.

One can marshal considerable indirect evidence that the pH of brain extracellular fluid is an important factor governing the response...
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of the cerebral vessels to $P_{CO_2}$. Underlying the premise is the fact that carbon dioxide diffuses readily and almost immediately across the blood-brain barrier, creating simultaneous pH changes in both blood and extracellular fluid (ECF), whereas charged ions are impeded in their passage across the barrier, creating considerable pH differences between the two compartments in systemic metabolic acidosis and alkalosis. If one alters the brain ECF pH by changing the bicarbonate concentration of the cortex as a whole or the CSF surrounding arterioles, vasodilatation and contraction are reported to occur in response to lowering and raising the ECF pH while the $P_{CO_2}$ remains constant.

By contrast, if the intravascular pH is acutely raised or lowered and the $P_{CO_2}$ is kept constant, the ECF pH stays the same, and CBF does not change. With more sustained acid-base disorders or changes in the blood carbon dioxide levels, brain ECF pH does shift, the change being mediated by more slowly changing influences than the quick respiratory adjustments that alter $P_{CO_2}$. Under these circumstances, the relation between CBF and ECF pH sometimes appears particularly strong. The examples are many: at high altitude the $P_{CO_2}$ is low but both the CSF pH and the CBF are normal. In severe diabetic acidosis, a condition in which an acidotic CSF has sometimes been found, CBF is increased above normal in spite of a low $P_{CO_2}$. Agnoli found that in chronic normoxic respiratory acidosis, CSF, pH, and CBF returned toward normal while $P_{CO_2}$ remained high, and Skinhoj reported that CBF was normal in patients with either hypocapnia or hypercapnia, so long as the pH in the CSF was normal. Most telling in this regard was the study of Fenc et al. in which steady-state metabolic acidosis or alkalosis was successively induced for several days in healthy men: CBF, estimated from cerebral arteriovenous differences, appeared to be a linear function of the lumbar CSF pH and not of the $P_{CO_2}$. According to Betz and Heuser cortical pH is low and CBF is high in the reactive cerebral hyperemia that follows transient hypoxia, even though the cortical $P_{CO_2}$ is low.

Conflicting with the interpretation of the above studies are the results of previous experiments using HV of several hours' duration. HV in man and animals causes an immediate rise in blood and CSF pH and a fall in CBF. With sustained HV the $P_{CO_2}$ remains low and blood pH high, but the brain ECF pH and bicarbonate as measured in the CSF and on the cortex progressively fall, because lactic acid accumulates in the brain and CSF. This accumulation of lactate with its accompanying reduction in CSF buffering capacity has been invoked to explain why, if the $P_{CO_2}$ is abruptly restored to normal after a period of HV, the CSF pH overshoots and transiently becomes relatively acidic. Such a situation creates a model to test whether the brain ECF pH or the $P_{CO_2}$ most affects CBF. If it is the $P_{CO_2}$, CBF should drop when hypocapnia begins, remain low until it ends, and return to normal as $P_{CO_2}$ is restored. If it is the pH of the brain ECF, CBF should drop when hypocapnia begins, rise during hypocapnia as the pH of the CSF and brain falls, and exceed control when the $P_{CO_2}$ is restored.

Different workers have used parts of this model but with discrepant results. At sea level Severinghaus and Lassen noted no return of CBF (estimated by cerebral arteriovenous blood gases) toward control in awake humans after 90 minutes of active HV; CSF pH was not recorded. With several hours of passive hyperventilation under general anesthesia, Wollman et al. using humans, Plum et al. using dogs, and Betz et al. using cats all found that CBF underwent no return toward normal during several hours of constant hypocapnia. McDowell and Harper, using anesthetized, paralyzed baboons, noted a significant increase in CBF over control after three hours of HV in association with a lowered pH of the CSF. However, the level of anesthesia had changed, making the data difficult to interpret, especially since CBF remained low during the antecedent period of HV despite a significant decline in CSF pH. Alexander and his associates observed that CBF in goats rose during continued HV only when the animals were hypoxic, and suggested that hypoxia had influenced the studies performed in man at high altitude.

In an attempt to resolve these discrepancies, Raichle, Posner, and Plum re-examined the effect of prolonged HV on CBF. We studied both awake men and anesthetized and awake animals with results that support the pH
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hypothesis and offer an explanation for the conflicting earlier experimental results. The results of our animal HV experiments are similar to many that one can find in the literature, and conflict with both our human data and the hypothesis that ECF pH controls CVR. The pattern of changes in P\textsubscript{CO\textsubscript{2}} predictably and significantly differed from observed changes in the CSF pH during and after HV, but CBF appeared to follow the P\textsubscript{CO\textsubscript{2}} rather than the CSF pH. However, there was also a significant decline in CBF of our control animals during five hours of general anesthesia, paralysis, and passive ventilation. McDowell and Harper\textsuperscript{23} also noted a progressive and significant decline in CBF over several hours of observation in paralyzed dogs under halothane anesthesia. Although they did not comment on it, Michenfelder and colleagues\textsuperscript{24} reported a similar decline in CBF in paralyzed dogs receiving halothane anesthesia measured both directly by collecting the cerebral venous effluent from an isolated sagittal sinus, and indirectly using \textsuperscript{85}Kr.

In order to eliminate general anesthesia, paralysis and passive ventilation, CBF was measured before, during, and after HV in four experiments in fully conscious, healthy men. In each study CBF fell with the onset of HV, gradually rose as HV continued, and exceeded control levels when ventilation returned toward normal. The P\textsubscript{CO\textsubscript{2}} fell initially, remained constantly low during HV, and returned toward control when HV ended. Figure 1 represents mean changes in CBF and P\textsubscript{CO\textsubscript{2}}. These results strongly suggest that some factor other than P\textsubscript{CO\textsubscript{2}} of arterial blood is responsible for cerebral vascular resistance.

Although the decline in CBF that occurs with time in anesthetized or paralyzed animals is unexplained, the phenomenon does clarify why different experiments studying the effect of HV on CBF have yielded contradictory results. Thus, if one corrects the CBF values of the animal hyperventilation experiments for the expected decline of CBF during a similar period of paralyzed, anesthetized eucapnia, one could speculate that the CBF actually rose above its predicted carbon dioxide-governed value during HV and significantly exceeded such a predicted value when P\textsubscript{CO\textsubscript{2}} was brought back to control levels. Such a postulate brings agreement between the results in animals and awake man and supports the increasing body of data that indicates that the pH of the brain interstitial fluid plays a major role in regulating CBF and mediating its response to hyperventilation.

**EFFECT OF HYPOXIA**

Considerable evidence suggests that cerebral anoxia occurs during severe hypocapnic-hyperventilation as the result of intense cerebral vasoconstriction and a shift of the oxyhemoglobin dissociation curve to the left, making the transfer of oxygen to the tissues more difficult (Bohr effect).\textsuperscript{28} Breathing low oxygen mixtures in the absence of hypocapnia reproduces most of the abnormal central neurological effects (slowing of electroencephalogram, mental confusion, and sometimes seizures) of low carbon dioxide tension. Studies employing electrodes to measure directly the oxygen tension of the exposed cerebral cortex have demonstrated substantially lower tensions during hypopcapnia.\textsuperscript{27, 28} When animals are passively hyperventilated with air at one atmosphere of pressure, the lactic acid concentration of the cerebrospinal fluid and brain rises along with a reduction in the NADH/NAD\textsuperscript{+} system of the brain.\textsuperscript{29} Giving the hyperventilating animals 10% oxygen to breathe nearly doubles the increase in brain and CSF lactate,\textsuperscript{14} while hyperventilating animals on 100% oxygen in a hyperbaric chamber at 3 atmospheres substantially reduces the lactate increase.\textsuperscript{30} A reduction in P\textsubscript{CO\textsubscript{2}} below 20 torr is also accompanied by a decreased aerobic and an increased

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**FIGURE 1**

Percentage change in CBF and P\textsubscript{CO\textsubscript{2}} in awake, actively ventilating human subjects. Broken line shows CBF corrected for failure of final P\textsubscript{CO\textsubscript{2}} to reach control.\textsuperscript{28}
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anaerobic utilization of glucose which is reversed during hypocapnic-hyperventilation on 100% oxygen at 3 atmospheres absolute. Several experiments demonstrate that the induced brain tissue hypoxia modifies the vasomotor response to HV at low P CO₂. Reivich and his colleagues demonstrated in humans that CBF was significantly lower at the same P CO₂ during HV on 100% oxygen at 2.0 atmospheres than at sea level pressures. Wollman et al. induced metabolic alkalosis in anesthetized subjects by sodium bicarbonate infusion and controlled P O₂ at 19 torr. The alkalosis intensified the degree of cerebral hypoxia through the Bohr effect, and resulted in a 17% increase in CBF. Haggendahl and Winso made similar observations.

Therapeutic Applications

The profound effect of HV on CBF has led to its use in several clinical situations. Four deserve particular mention: cerebral infarction, head injury, acute intracranial hypertension, and the operative setting of carotid endarterectomy. Before considering each of these situations separately, two general points about the use of HV as a clinical tool should be made.

First, in evaluating any proposal for the use of HV as a therapeutic tool, one must constantly bear in mind that if properly performed, it adds considerably to the complexity and expense of patient care. To give prolonged HV one must control the patient’s airway and constantly monitor the assistive breathing device. This requires intubation or tracheostomy and meticulous tracheobronchial toilet. If the patient is paralyzed, as is often necessary, even more skilled personnel are required.

Second, patients with severe brain injury frequently hyperventilate spontaneously. This has been correlated with a poor prognosis, possibly the result of the severity of the neurological injury itself. However, in such patients one almost universally finds a subnormal or moderately low arterial oxygen tension in addition to the low P CO₂ and elevated pH. Detailed examination of the lungs and airways usually reveals serious disease even when this has not been immediately obvious. Such a situation calls for treatment of the underlying hypoxia. If such treatment is delayed or never initiated, one cannot hope to improve the prognosis in these patients.

CEREBRAL INFARCTION

Strokes can severely disrupt the normal regulation of the cerebral circulation in man, as can experimentally occluding the middle cerebral artery in animals. In areas of infarction the CBF is usually reduced but occasionally it may be increased in or near the area of ischemia, particularly during the early stages of the lesion. This focal cerebral hyperemia, which may be relative or absolute, has been termed “luxury perfusion” by Lassen because of a presumably overabundant CBF relative to the metabolic needs of the tissue.

Normally, mechanisms intrinsic to the brain’s vascular bed maintain the CBF independent of the blood pressure within fairly wide limits—so-called autoregulation. Autoregulation frequently disappears in areas of infarction along with the normal response to acute changes in the arterial P CO₂. “Luxury perfusion” and loss of vascular autoregulation are postulated to result from an acute, metabolic acidosis localized within the brain, although the association is by no means proved. Whatever the cause, the focal loss of normal vasomotor responses, so-called vaso-paralysis, is thought to be the basis of paradoxical responses that vasodilator and vasoconstrictor agents occasionally induce, e.g., during vasodilatation produced by the inhalation of carbon dioxide CBF in the affected area decreases. Conversely, when generalized vasoconstriction is produced by hyperventilation, CBF in the affected region can increase at a time when flow elsewhere decreases. These paradoxical responses presumably occur because the vessels in the diseased region, being maximally dilated, are unable to respond to changes in P CO₂. As a result, with hypercapnia the resistance in normal vessels falls and blood is shunted away from the ischemic focus. With HV the reverse occurs. In addition to these focal changes, widespread loss of CBF autoregulation has been described in patients with stroke, occasionally affecting the opposite hemisphere.

Based on the above features of experimental and clinical cerebral infarction, hyperventilation has been proposed as a therapeutic...
tool to improve blood flow to the ischemic region and counteract the tissue acidosis, the hope being to restore normal CBF autoregulation, improve cell function, and prevent or reduce cerebral edema.\textsuperscript{38, 40, 41}

Unfortunately, the above predictions have not been borne out by either controlled animal experiments or observations of patients. Solo-way and his colleagues,\textsuperscript{47} commencing hyperventilation before arterial occlusion and continuing after occlusion for three hours, observed a significant reduction in the size of the infarct when compared to controls. Obviously the experiment has no applicability to the medical problem of stroke. No effect was observed by the same authors when hyperventilation was started one hour after occlusion.\textsuperscript{49} Similar negative results were obtained by Yamaguchi et al.\textsuperscript{40} when they initiated hyperventilation four to six hours after arterial occlusion. Brock et al.\textsuperscript{40} found that CBF and neurological signs actually worsened in a patient who received hyperventilation for the first time 36 hours after onset of symptoms. Meyer et al.\textsuperscript{51} observed a reduction in CBF in the infarcted hemisphere in all patients during hyperventilation, and on no occasion did they encounter a paradoxical increase in CBF. The authors\textsuperscript{49, 51} concluded that hyperventilation in cerebral infarction was potentially dangerous because collateral vessels feeding the ischemic area, although naturally dilated, retained the responsiveness to P co2 and constricted during hyperventilation. This view is supported by the work of Yamamoto et al.\textsuperscript{52} and Yamaguchi\textsuperscript{40} in experimental animals.

In contrast to the above studies, Battistini et al.\textsuperscript{58} reported that in cats the area of an experimental infarction was reduced to about one-third of control when they initiated hyperventilation one-half hour after occlusion and continued for four to six hours. The same authors were able to demonstrate an increase in tissue pH to near normal values and a significant reduction in the water content of the damaged hemisphere. However, the blood gas values reported for their experiment reveal that they called Pco2 25 to 30 torr hyperventilation. Since this is the normal Pco2 for the cat, it means that their control group at Pco2 40 torr was actually hypocapnic and they never really tested feline hypocapnia. In a single patient with cerebral infarction, Paulson\textsuperscript{54} was able to restore autoregulation with hyperventilation, but the patient's neurological condition did not change. In the only controlled study of patients, conducted by Christensen,\textsuperscript{58} artificial hyperventilation to 25 torr for 72 hours did not appear to influence the clinical neurological deficit of the patients. There was no significant difference in mortality in the hyperventilated group, which was high in both the paralyzed and passively ventilated subjects and controls.

Several theoretical reasons argue against hyperventilating patients with stroke. First, during hyperventilation of even a few hours' duration there is a return of CSF pH and CBF toward prehyperventilation values,\textsuperscript{72, 22} limiting the duration of the intended therapeutic effects. Furthermore, upon discontinuation of hyperventilation, particularly if abrupt, one has a sudden state of hypercapnia,\textsuperscript{21} which could theoretically negate the therapeutic advantages gained in the antecedent period of hyperventilation. As has already been mentioned, there is evidence that the hyperemia surrounding areas of infarction include dilated collateral vessels\textsuperscript{48, 52} supplying the infarcted region. These vessels appear to retain their responsiveness to carbon dioxide and may constrict during HV, reducing blood flow to the ischemic region. Finally, hyperventilation, when properly carried out for a prolonged period of time, is complicated and enhances the risk of pulmonary infection.\textsuperscript{55}

HEAD INJURY

Both experimental and clinical observations have demonstrated that head injury can abolish cerebral autoregulation.\textsuperscript{50-59} Often one can also find brain swelling with increased intracranial pressure,\textsuperscript{60-62} regional increases in CBF, \textit{luxury perfusion}\textsuperscript{56, 58, 62} and a CSF lactic acidosis.\textsuperscript{56} The overall CBF is variably affected\textsuperscript{63} and may be normal in the face of the preceding abnormalities.\textsuperscript{57} As yet, a good correlation has not been established between the quantity of trauma and the development of these abnormalities, or between the dependence of one abnormality on another. However, it has been proposed that the loss of CBF autoregulation exposes the brain capillaries and veins to an increased intraluminal pressure, forcing fluid into the extracellular space of the brain.\textsuperscript{50, 61} Increases in systemic arterial pressure, transmitted directly to the capillaries...
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because of the loss of autoregulation, are postulated to cause an immediate worsening of the brain edema.06

Hyperventilation has been advocated in the treatment of severe head injuries in order to reduce tissue acidosis, restore autoregulation, and reduce increased intracranial pressure, presumably by reducing cerebral blood volume and decreasing CSF production.54, 62, 64-68

The effectiveness of short-term hyperventilation along with withdrawal of ventricular CSF for the relief of transient increases in intracranial pressure in head-injured patients has been clearly demonstrated by Johnston and his co-workers.64 They point out, however, that only by continuously monitoring intracranial pressure can this form of therapy be effectively used.

Gordon and Rossanda69-71 report the only large series of patients treated with prolonged hyperventilation. Their work is a retrospective evaluation of 251 patients with severe head trauma, 51 of whom were hyperventilated (Pco2 25 to 30 torr) from between six hours to 41 days (mean ten days). Few details of their case selection are given, but they found a reduction in mortality from 32.8% to 9.8%. The number of surviving patients with severe neurological sequelae increased substantially in the treated group, but the percentage recovering completely did not differ in the two groups. One must question both the social utility and specific effectiveness of hyperventilation in this study, particularly since most patients with severe head injury hyperventilate spontaneously anyway.69

Respiratory abnormalities frequently complicate severe head injuries, often contributing to increased morbidity and mortality.56, 68, 69 Conventional measures aimed at improving pulmonary toilet, airway, and oxygenation reduced mortality from 90% to 40% in one series.70

ACUTE INTRACRANIAL HYPERTENSION

There is much evidence, recently summarized by Langfitt,71 that when acute intracranial hypertension is caused by a space-occupying lesion or brain swelling, short-term hyperventilation can be lifesaving. Langfitt’s concept is that within finite limits the brain can accommodate a gradually expanding mass lesion or swelling by a reduction of its CSF compartment. When these limits have been reached or when sudden increases in volume occur, slight changes in the size of the mass, the brain, or the blood volume can cause a marked increase in intracranial pressure, accompanied by tentorial herniation and sudden neurological deterioration. Hypocapnic-hyperventilation, by reducing the cerebral blood volume through cerebral vasoconstriction, can promptly reduce this pressure below a critical level, allowing one time to initiate more permanent corrective action. However, hyperventilation can be a two-edged sword under these circumstances. Kitahata et al.,72 using positive pressure breathing, observed that the intracranial pressure declined until the Pco2 reached 23 torr. Beyond this point the intracranial pressure increased because of an elevated airway pressure; applying negative expiratory airway pressure further reduced the intracranial pressure.

CAROTID ENDARTERECTOMY

To perform carotid endarterectomy without bypass necessitates the temporary occlusion of the internal carotid artery. Most patients tolerate this uneventfully, but signs of focal cerebral ischemia and infarction develop in a few. Various techniques have been employed to determine which patients are intolerant to cross clamping. The one receiving widest attention has been to measure the pressure in the internal carotid artery distal to the clamp (so-called “stump pressure” or carotid artery back pressure), on the premise that it directly reflected the perfusion pressure to the affected hemisphere. Moore and Hall73 found a good correlation between such pressures and clinical tolerance: all patients who had ischemic symptoms had pressures less than 25 torr, while all those who tolerated the procedure had pressures greater than 25 torr.

Based on “stump pressure” measurements at the time of endarterectomy, Fourcade et al.74 proposed the use of hyperventilation during this procedure. Working on the premise that occlusion would lead to cerebral ischemia, vasomotor paralysis, and paradoxical responses, they employed hyperventilation and observed a significant increase in stump pressure over control. They concluded that this represented an increased perfusion pressure, and hence shunting of blood to the affected hemisphere. They did not present data on the
tolerance of their hyperventilated patients compared with controls.

Boyesen et al. and Ladegaard-Pedersen combined measurements of “stump pressure” with regional CBF measurements and described a more complex, although useful, relationship between “stump pressure” and CBF. They found that if stump pressures were high during hypocapnia (above 70 torr), hypercapnia induced a significant increase in mean rCBF and a moderate fall in stump pressure. If the hypocapnic occlusion pressure was about 50 torr, hypercapnia induced a similar decrease in occlusion pressure but only a moderate increase in mean rCBF. Finally, if the hypocapnic stump pressure was 30 torr or less, regional impaired flow responses were encountered. It was concluded that patients maintaining high stump pressures (greater than 50 torr with hypercapnia or 65 torr with hypocapnia) could tolerate any level of Pco2. Patients whose pressure was below these levels might benefit from moderate hypocapnia and certainly should not be subjected to hypercapnia.

Agnoli et al. and Pistolese et al. observed a 42% reduction in mean hemispheric CBF with carotid clamping at normocapnia. An additional 18% reduction in flow occurred when clamping occurred during hypocapnia, partially due to a fall in mean systemic blood pressure. They saw no evidence of an improved blood flow induced by hyperventilation, and concluded that although hyperventilation was not harmful in terms of CBF, it did not offer clear benefit.

As already mentioned, Soloway’s experimental study indicated that hyperventilation counteracts cerebral tissue hypoxia during reduced cerebral perfusion: hyperventilation initiated before occlusion of the middle cerebral artery of the cat reduced the incidence and size of the consequent infarct compared with normocapnic controls.

The above observations leave unclear the role of hyperventilation in carotid endarterectomy. When the internal carotid artery stump pressure is below a critical level (about 30 torr), blood flow to the affected hemisphere is likely to be marginal and steps must be taken to ensure adequate CBF. A shunt or bypass has proved its effectiveness in this regard (see Discussion, ref. 74). Whether hyperventilation is a dependable substitute remains to be seen.

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