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Carbon Dioxide and the Cerebral Circulation

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THE arterial partial pressure of carbon dioxide (P_{aCO_2}) is an important regulator of the cerebral circulation, and a large body of literature describes this relation. This review summarizes the current state of knowledge of the effect of CO_2 on cerebral physiology, focusing first on mechanisms of CO_2 -induced alteration of vascular tone, then on the effect of CO_2 on cerebral vascular regulation, and finally on CO_2 manipulation in patient care.

Mechanisms

This section summarizes information regarding the site of action of CO_2 on the cerebral circulation and cellular mechanisms important in CO_2 -mediated changes in cerebral vascular tone. The CO_2 -mediated alteration of brain extracellular pH is the initial step leading to changes in vascular tone. The effect of pH on cerebral vascular tone is mediated by nitric oxide (NO), prostanoids, cyclic nucleotides, potassium channels, and intracellular calcium. Most data available support an important role for each of these mediators in the response of the cerebral circulation to CO_2 . However, contradictory data exist, and there is no comprehensive understanding of how these mediators interact to control cerebral vascular tone. Further, mechanisms differ in neonates and adults.

Site of Action of Carbon Dioxide

Increased carbon dioxide tension (P_{CO_2}) relaxes cerebral arteries *in vitro*, which indicates that CO_2 can

cause cerebral vascular relaxation independent of extravascular cells.^{1,2} *In vivo*, cerebral arteries respond to highly localized perivascular alteration of P_{CO_2} and pH, which indicates that the mechanisms that affect cerebral vascular tone are localized to the area of the blood vessel wall.³⁻⁵ Cellular elements that could contribute to the cerebral vascular response to CO_2 include vascular cells (endothelium and smooth muscle) and extravascular cells (perivascular nerves, parenchymal neurons, and glia). In adult animals, removal of the endothelium *in vitro*¹ or endothelial damage *in vivo*⁶ does not alter the response of cerebral arteries to hypercapnia. This suggests that in adults the endothelium is not involved in the response to CO_2 . In neonates, however, the endothelium does contribute to cerebral vasodilation during hypercapnia.^{7,8} Tetrodotoxin, which blocks sodium channels and prevents neuronal depolarization, does not reduce CO_2 -mediated cerebral vasodilation, indicating that depolarization of perivascular nerves or parenchymal neurons is not important.^{6,9} Selective destruction of cortical neurons also does not alter the cerebral vascular response to hypercapnia.¹⁰ Although these data in adults suggest that the endothelium, parenchymal neurons, and perivascular nerves are not important during hypercapnia-induced cerebral vasodilation, it is also possible that these cells produce overlapping vasodilator messengers, and removal of an individual messenger is not sufficient to alter the response. No data exist regarding a potential role for glia in the CO_2 response of the cerebral circulation.

In vitro data suggest that extravascular cells are not important in the response of cerebral arteries to increased P_{aCO_2} . However, the relative contribution of vascular and extravascular cells to CO_2 -mediated vasodilation cannot be assessed by comparing *in vivo* and *in vitro* studies. Although isolated cerebral vessels relax with increased P_{CO_2} , technical differences between *in vivo* and *in vitro* studies make it impossible to know if vasodilation is equal in isolated vessels compared with

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in vivo blood vessels. Thus, *in vivo*, it is possible that dilation is larger, and some of the effect of CO₂ on cerebral vessels is mediated by extravascular cells.

pH

When cerebral vascular tone is altered by a change in P_{CO₂}, it is possible that CO₂ itself, a CO₂-mediated change in pH, or both are signals leading to a change in vascular tone. Applying acidotic or alkalotic solutions to the brain dilates or constricts cerebral arteries *in vivo*, which indicates that pH can affect cerebral vascular tone.⁴ In humans, Severinghaus *et al.*¹¹ showed that cerebral blood flow (CBF) was normal during chronic hypocapnia, which suggests that CO₂ itself does not alter cerebral vascular tone. Kontos *et al.*^{3,12} offered the best evidence that pH rather than CO₂ is the controlling messenger for CO₂-mediated alterations of cerebral vascular tone. Applying artificial cerebrospinal fluid (CSF) topically to the cerebral cortex of anesthetized cats, they showed that the diameter of cerebral arterioles responded only to changes in pH, regardless of fluid P_{CO₂}. During alterations of fluid P_{CO₂}, the pH of the artificial CSF was held constant by altering its bicarbonate concentration. Because CO₂ diffuses freely through cell membranes and bicarbonate does not, these data suggest that extracellular pH is more important than intracellular pH in altering cerebral vascular tone. Data in isolated cerebral arteries also indicate that extracellular pH is more important than intracellular pH in hypercapnic-induced dilation of cerebral arteries.¹³ However, changes in extracellular pH do affect intracellular pH in cerebral vascular smooth muscle,¹³ and due to complex interactions between extracellular and intracellular pH,¹⁴ it is not known whether extracellular or intracellular pH controls cerebral vascular tone.

Cellular Mechanisms

Changes in pH can exert effects on smooth muscle tone through second messenger systems and by altering vascular smooth muscle calcium concentration directly. This section reviews the role of prostanoids, NO, cyclic nucleotides, potassium channels, and intracellular calcium concentration in CO₂-mediated changes in cerebral vascular tone.

Prostanoids. Production of prostaglandins is controlled by the availability of arachidonic acid, which is cleaved from membrane lipids by phospholipase. Cyclo-oxygenase converts arachidonic acid to prostaglandin H₂, which is subsequently modified by other enzymes

to yield both vasoconstrictor and vasodilator prostanoids. The principle vasoactive prostanoids in the brain are prostaglandin E₂ (PGE₂) and prostacyclin (PGI₂), both dilator prostanoids, and the constrictor prostanoid prostaglandin F_{2α} (PGF_{2α}).¹⁵ In adult humans and animals, some studies reported that indomethacin, a cyclo-oxygenase inhibitor, reduces hypercapnia-induced cerebral vasodilation.¹⁶⁻¹⁹ However, other studies reported that indomethacin does not reduce hypercapnia-induced cerebral vasodilation.²⁰⁻²³ Although indomethacin reduces hypercapnia-induced increase in CBF in humans, aspirin and naproxen have no effect, even when there is an equal degree of cyclo-oxygenase inhibition.¹⁶ Other have reported in animals and humans that the cyclo-oxygenase inhibitors aspirin, sulindac, amfenac, and diclofenac do not alter the response of the cerebral circulation to hypercapnia.^{19,20,24,25} In adult humans and animals, brain arachidonic acid, PGI₂, and PGE₂ concentrations do not increase during hypercapnia.^{16,26-28} Overall, data in adults indicate that cyclo-oxygenase products are not responsible for cerebral vasodilation during hypercapnia. The effect of indomethacin on hypercapnia-induced cerebral vasodilation is difficult to resolve. However, indomethacin does inhibit enzymes other than cyclo-oxygenase, including phosphodiesterase, phospholipase A₂, and cyclic adenosine monophosphate (cAMP)-dependent protein kinase, which indicate that the effect of indomethacin is nonselective.²⁶

The neonatal and adult cerebral circulation responds to CO₂ in a similar way, although the magnitude of the response may be less in neonates (see below). In neonates, prostanoids are important in regulating the cerebral circulation.²⁹ In neonatal animals, damage *in vivo* to cerebral vascular endothelium prevents hypercapnia-mediated increases in CSF PGI₂ concentration and dilation of cerebral blood vessels.⁸ Inhibition of phospholipase, which prevents the release of arachidonic acid and the production of prostanoids, abolishes the response of the neonatal circulation to hypercapnia and extracellular acidosis.³⁰ Further, indomethacin inhibits hypercapnia-induced cerebral vasodilation and increases in CSF PGI₂ and PGE₂ concentrations in newborn animals.^{31,32} In human neonates, indomethacin abolishes hypercapnic-induced increases in CBF.³³ These data support the concept that in neonates, vasodilator prostaglandins derived from the vascular endothelium are important in the response to hypercapnia. However, an alternative role for prostaglandins has

been suggested by some investigators, who report in newborn animals that after inhibition of cyclo-oxygenase or endothelial injury, application to the brain of a very low concentration of vasodilator prostanoids restores hypercapnia-induced cerebral vasodilation.^{7,34} These data suggest that prostanoids may not be direct mediators of hypercapnia-induced cerebral vasodilation, but rather that a basal level of prostanoids is necessary to "permit" hypercapnia to dilate cerebral blood vessels. Overall, data indicate that cyclo-oxygenase products are important regulators in the hypercapnic response of the newborn but not adult cerebral circulation.

Nitric Oxide. Nitric oxide is an important regulator of cerebral vascular tone and is produced by a family of NO-synthase enzymes in brain vascular endothelial cells, some perivascular nerves, parenchymal neurons, and glia.^{35,36} Nitric oxide activates guanylate cyclase in vascular smooth muscle, increasing the intracellular concentration of cyclic guanosine monophosphate (cGMP), causing vasorelaxation.³⁶ In adult animals, inhibition of NO-synthase activity reduces cerebral vasodilation during hypercapnia³⁷⁻⁴¹ and extracellular acidosis-mediated cerebral vasodilation.³⁹ This indicates that NO is one vasodilator important in the response of the cerebral circulation to hypercapnia and acidosis. Although these studies indicate that NO is important in CO₂-induced cerebral vasodilation, they also suggest that NO is not the only vasodilator signal, because after inhibition of NO-synthase, 10-70% of hypercapnia-mediated cerebral vasodilation remains. The wide range in the reduction of cerebral vasodilation may reflect use of different NO-synthase inhibitors, doses of inhibitors, timing of doses, degree of hypercapnia, and species differences. During severe hypercapnia (Pa_{CO₂} >100 mmHg), CO₂-mediated dilation of cerebral arterioles cannot be reduced by inhibition of NO-synthase, which indicates that cerebral vasodilation during severe hypercapnia does not depend on NO.³⁷ In contrast to adults, NO does not play a role in hypercapnia-induced cerebral vasodilation in neonatal animals.³²

Although it might be surmised from these studies that hypercapnia increases the synthesis of NO, which leads to cerebral vasodilation, some investigations suggest an alternative explanation. The brain tonically produces NO, creating a constant vasodilator signal.³⁶ Inhibition of NO-synthase removes tonic NO and increases the resting tone in cerebral blood vessels, which could alter the response to other vasoactive signals, such as hyper-

capnia. Thus inhibition of NO-synthase could cause a direct effect by preventing hypercapnia-mediated activation of NO-synthase and indirect effects by reducing basal NO and cGMP levels and increasing resting tone of blood vessels. After inhibition of NO-synthase, low concentrations of NO-dependent and NO-independent vasodilators can restore cerebral vascular tone to baseline.⁹ However, NO-dependent but not NO-independent vasodilators can restore the response to hypercapnia.⁹ Furthermore, a cell-permeable cGMP analog can also restore basal vascular tone and the response to hypercapnia after inhibition of NO-synthase.⁹ These data suggest that changes in basal tone are not important, because NO-independent vasodilators cannot restore the response to hypercapnia. These data indicate that NO and cGMP are important in CO₂-mediated dilation of cerebral blood vessels. However, NO and cGMP may not be the final mediators of vasodilation, but rather that basal levels of NO and cGMP "permit" hypercapnia to dilate cerebral vessels. Nitric oxide may also function in a "permissive" role for other vasodilators in the cerebral circulation.^{42,43}

In the brain, vascular endothelium expresses the endothelial isoform of NO-synthase, and some perivascular nerves, parenchymal neurons, and glia express the neuronal isoform of NO-synthase.^{36,44-46} All are potential sources of NO important for hypercapnia-induced cerebral vasodilation.³⁶ Damage to vascular endothelium *in vivo* does not reduce hypercapnia-induced vasodilation,⁶ which indicates that the endothelial isoform of NO-synthase is not the source of NO involved in hypercapnia-induced cerebral vasodilation. Selective inhibition of the neuronal isoform of NO-synthase reduces hypercapnia-induced cerebral vasodilation, which indicates that the activity of neuronal NO-synthase is important.⁴⁷ Cerebral perivascular nerves originating from the sphenopalatine ganglia release NO but do not appear to be important in hypercapnia, because destruction of these nerves does not alter the cerebral vascular response to hypercapnia.⁴⁸ Furthermore, tetrodotoxin, which blocks sodium channels and prevents neuronal depolarization, does not reduce hypercapnia-induced cerebral vasodilation.⁹ This indicates that the activation of neuronal NO-synthase by depolarization of perivascular nerves or parenchymal neurons is not important in hypercapnia-induced cerebral vasodilation. The NO responsible for hypercapnia-induced cerebral vasodilation could arise either from parenchymal neurons producing NO in the absence of depolarization or from

glia. However, selective destruction of cortical neurons does not alter hypercapnia-induced cerebral vasodilation, which indicates that parenchymal neurons are not involved in the response to hypercapnia.¹⁰ Thus data suggest that, in adult animals, the vascular endothelium, parenchymal neurons, and perivascular nerves are not the source of NO important in hypercapnia-mediated vasodilation. Neuronal NO-synthase appears to be the source of NO involved in hypercapnia-induced cerebral vasodilation, but the cellular location is not known. Glia, which express neuronal NO-synthase, could be the source of NO, but it is also possible that multiple, overlapping sources of NO may be involved in hypercapnia-induced cerebral vasodilation.

In contrast to hypercapnia, alterations in cerebral vascular tone during hypocapnia do not depend on NO. In adult rabbits and rats, cerebral vasoconstriction during hypocapnia is not altered by inhibition of NO-synthase.^{38,49}

Cyclic Nucleotides. Changes in cyclic nucleotide concentrations are important in the signaling cascade leading from *pH* to changes in vascular smooth muscle tone. Nitric oxide activates guanylate cyclase in vascular smooth muscle, increasing the cGMP concentration while vasodilator prostanoids (PGE₂, PGI₂) activate adenylylate cyclase and increase the cAMP concentration.^{32,36} In adult rats, hypercapnia increases brain cGMP concentration, consistent with the theory that hypercapnia increases NO production, which then increases cGMP.⁴⁰ However, in isolated cerebral arteries from adult rats, increased P_{CO₂} relaxes arteries but does not increase cGMP, consistent with the "permissive" hypothesis in which increases in NO and cGMP are not required for CO₂-mediated dilation of cerebral blood vessels.¹ Cyclic GMP is important in hypercapnia; however, as after inhibition of NO-synthase, infusion of a low concentration of a stable cGMP analog restores hypercapnia-induced vasodilation in the brain.⁹ As with NO, it is not clear in adult animals whether cGMP functions as a vasodilator mediator during hypercapnia or whether basal levels of cGMP are necessary to "permit" hypercapnia-induced cerebral vasodilation to occur.

In neonatal pigs, hypercapnia causes cerebral vasodilation and increased brain PGI₂ and cAMP concentration; inhibition of cyclo-oxygenase prevents these changes.³² These data suggest that cAMP mediates vasodilation during hypercapnia in neonates. Although vasodilator prostanoids can act permissively for hypercapnia

in neonates, it is not known whether cAMP can play a similar permissive role.

Potassium Channels. Recent evidence suggests that vascular smooth muscle potassium channels play an important role in regulating cerebral vascular tone.⁵⁰ In vascular smooth muscle, the opening of potassium channels allows potassium (the major intracellular cation) to diffuse out of the cell, making the interior of the cell more negative (hyperpolarized). When the cell is hyperpolarized, voltage-gated calcium channels reduce the influx of extracellular calcium, decreasing intracellular calcium concentration and reducing vascular smooth muscle tone.

One subgroup of potassium channels is ATP sensitive (K_{ATP}). Decreasing *pH* increases the open-state probability of K_{ATP} channels (which would hyperpolarize cells), supporting the concept that during hypercapnia, activation of K_{ATP} channels could cause vascular smooth muscle hyperpolarization and cerebral vasodilation.⁵¹ Furthermore, extracellular acidosis hyperpolarizes cerebral vascular smooth muscle, also supporting the concept that changes in vascular smooth muscle membrane potential are important during hypercapnia.² In large cerebral arteries *in vitro*, acidosis-induced relaxation depends partially on activation of K_{ATP} channels.⁵² In adult animals, cerebral vasodilation during modest (Pa_{CO₂} ≈ 55 mmHg), but not marked, hypercapnia can be attenuated by blockade of K_{ATP} channels.^{41,53}

A second potassium channel is the large conductance calcium-activated potassium channel. This channel can be activated by cGMP and NO, hyperpolarizing vascular smooth muscle and reducing intracellular calcium.^{54,55} It contributes to cGMP-dependent vasodilation in small cerebral arterioles⁵⁶ but not in large cerebral arteries.⁵⁷ In contrast to K_{ATP} channels, large conductance calcium-activated potassium channels do not contribute to acidosis-induced vasodilation in isolated large cerebral arteries.⁵² The lack of importance of these channels during acidosis-induced vasodilation in large cerebral arteries may reflect the regional heterogeneity of potassium channel distribution.

A third potassium channel is the delayed rectifier potassium channel (K_v). This channel is normally activated by membrane depolarization, resulting in repolarization by allowing potassium to exit the cell.⁵⁰ In cerebral vascular smooth muscle, K_v channels are *pH* sensitive, and acidosis increases K_v conductance, hyperpolarizing the cell.⁵⁸ This suggests that K_v channels should be activated during hypercapnia and contribute to dilation.

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However, in isolated large cerebral arteries, blockade of K_v channels does not alter dilation to acidosis.⁵² As with large conductance calcium-activated potassium channels, this discrepancy may reflect regional differences in potassium channel distribution in the cerebral circulation.

Intracellular Calcium. Vascular smooth muscle tone is controlled by intracellular calcium concentration. Under baseline conditions, intracellular calcium is approximately 0.1 μ M, which is 10,000 times less than extracellular calcium. Small changes in plasma membrane calcium conductance may have a significant effect on both intracellular calcium concentration and vascular smooth muscle tone. During alkalosis, cerebral vascular smooth muscle intracellular calcium concentration increases, which increases tone.⁵⁹ In cerebral vascular smooth muscle, changes in extracellular pH affect intracellular calcium concentration and vascular tone.⁶⁰ Extracellular acidosis-induced dilation of cerebral arterioles can be prevented by elevation of extracellular calcium, which suggests that reduced entry of calcium into vascular smooth muscle is important in the reduction of vascular tone by acidosis.⁵ Cyclic nucleotides (cAMP and cGMP) affect vascular tone in part by altering smooth muscle calcium concentration.^{54,61} Both cAMP and cGMP appear to activate their respective protein kinases and phosphorylate calcium channels, which reduces the entry of calcium into vascular smooth muscle.^{61,62} Cyclic nucleotides also activate potassium channels, leading to membrane hyperpolarization and inactivation of voltage-gated calcium channels, reducing intracellular calcium concentration.⁶¹

Summary of Mechanisms

The system of mediators that link extracellular pH to cerebral vascular tone is complex and interrelated (fig. 1). The initial step is alteration of extracellular pH, and the final common mediator is intracellular calcium concentration. In adults, cerebral vasodilation during hypercapnia is mediated in part by NO, which increases cGMP concentration. Cyclic GMP exerts several effects to decrease intracellular calcium, including activation of K_{ATP} channels and the direct reduction of calcium entry through calcium channels. Nitric oxide can also activate potassium channels directly and thereby hyperpolarize and relax vascular smooth muscle. Some data suggest that NO and cGMP are not the direct mediators during hypercapnia but rather function in a "permissive" way to allow vasodilation. The cellular source

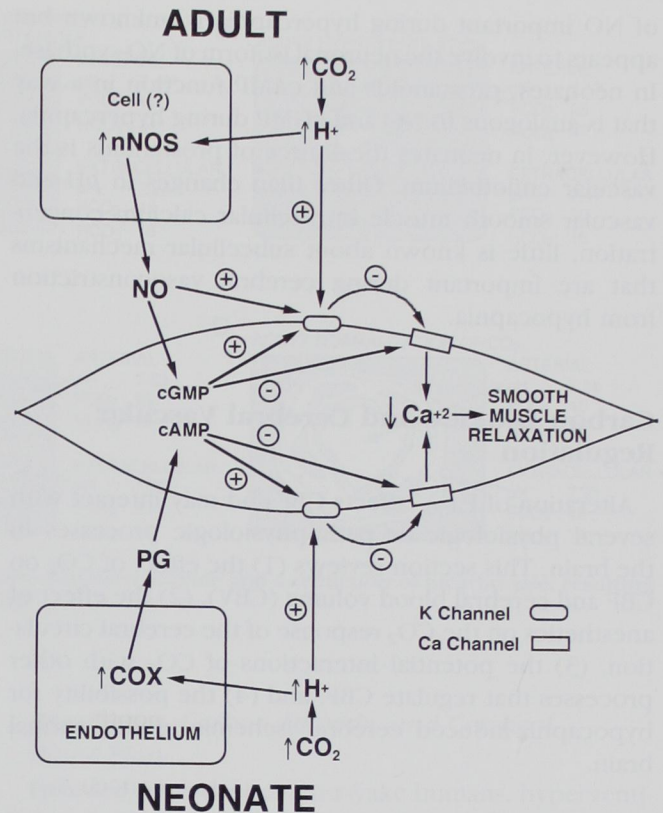


Fig. 1. Altering the partial pressure of carbon dioxide in arterial blood (P_{aCO_2}) changes extracellular pH, which is the initial step leading to changes in vascular smooth muscle (VSM) intracellular calcium concentration and vascular tone. In adult animals, hypercapnia may activate the neuronal isoform of NO-synthase (nNOS), increasing NO production and cyclic guanosine monophosphate (cGMP) concentration in VSM. Both NO and cGMP can activate potassium channels, which hyperpolarize VSM. Membrane hyperpolarization inhibits voltage-gated calcium channels, which reduces VSM intracellular calcium concentration and causes vascular relaxation. In addition, cGMP can inhibit calcium channels directly and reduce intracellular calcium concentration in VSM. In adult humans, the cellular location of nNOS is not known. Further, some data suggest that in adults, NO and cGMP may not function as vasodilators during hypercapnia, but rather basal levels of NO and cGMP are necessary to "permit" hypercapnic vasodilation (see the text for further details). Extracellular acidosis can also activate potassium channels directly, hyperpolarizing VSM and reducing intracellular calcium concentration. During hypercapnia in neonates, cyclo-oxygenase, located in the vascular endothelium, may increase the production of vasodilator prostaglandins, which then activate adenylate cyclase, producing cyclic adenosine monophosphate (cAMP) in VSM. However, as with NO in adults, prostaglandins may function in a permissive role for hypercapnic-induced cerebral vasodilation in neonates. Little is known about the mechanism of hypocapnic-induced cerebral vasoconstriction, other than changes in extracellular pH and VSM intracellular calcium concentration.

of NO important during hypercapnia is unknown but appears to involve the neuronal isoform of NO-synthase. In neonates, prostanoids and cAMP function in a way that is analogous to NO and cGMP during hypercapnia. However, in neonates the source of prostanoids is the vascular endothelium. Other than changes in pH and vascular smooth muscle intracellular calcium concentration, little is known about subcellular mechanisms that are important during cerebral vasoconstriction from hypocapnia.

Carbon Dioxide and Cerebral Vascular Regulation

Alteration of Pa_{CO_2} affects CBF and may interact with several physiologic or pathophysiologic processes in the brain. This section reviews (1) the effect of CO_2 on CBF and cerebral blood volume (CBV), (2) the effect of anesthetics on the CO_2 response of the cerebral circulation, (3) the potential interactions of CO_2 with other processes that regulate CBF, and (4) the possibility for hypocapnia-induced cerebral ischemia in the normal brain.

Carbon Dioxide and Cerebral Blood Flow

The relative change in CBF during variations of Pa_{CO_2} depends on several factors, including baseline CBF, cerebral perfusion pressure, and anesthetic drugs. However, in a wide variety of subjects and conditions, most studies report a change in global CBF of 1–2 $ml \cdot 100 g^{-1} \cdot min^{-1}$ for each 1 mmHg change in Pa_{CO_2} .^{24,63–82} Reducing Pa_{CO_2} to 20–25 mmHg decreases the global CBF by 40–50%, and further reductions of Pa_{CO_2} do not reduce CBF any further.^{83,84} Increasing the Pa_{CO_2} to 80 mmHg or more produces a maximal increase in CBF of 100–200% in anesthetized animals.^{37,83} In awake animals, however, increasing the Pa_{CO_2} to 80 mmHg increases CBF by six times, but one half of the increase in CBF is a result of endogenous catecholamine release and activation of neuronal metabolism.⁸⁵ This suggests that in awake subjects, severe hypercapnia may increase the flow by two mechanisms, with a direct effect of CO_2 on cerebral blood vessels and an indirect effect by increasing brain metabolism and blood flow.

Brain blood flow is not homogeneous, and areas of the brain that receive more blood flow have a steeper flow response to changes in Pa_{CO_2} . For example, in cats with a baseline cortical blood flow of 86 $ml \cdot 100$

$g^{-1} \cdot min^{-1}$, the slope of the CO_2 response was a 1.7-ml change in CBF for each 1-mmHg change in Pa_{CO_2} . In contrast, spinal cord blood flow was 46 $ml \cdot 100 g^{-1} \cdot min^{-1}$ with a slope of 0.9.⁶⁷ Similar findings have been reported in animals⁶⁸ and humans.⁷⁶ The observation that baseline CBF influences the response of CBF to changes in Pa_{CO_2} also holds true when CBF is elevated artificially, as by inhalational anesthetics.

Sustained Hypocapnia and Cerebral Blood Flow

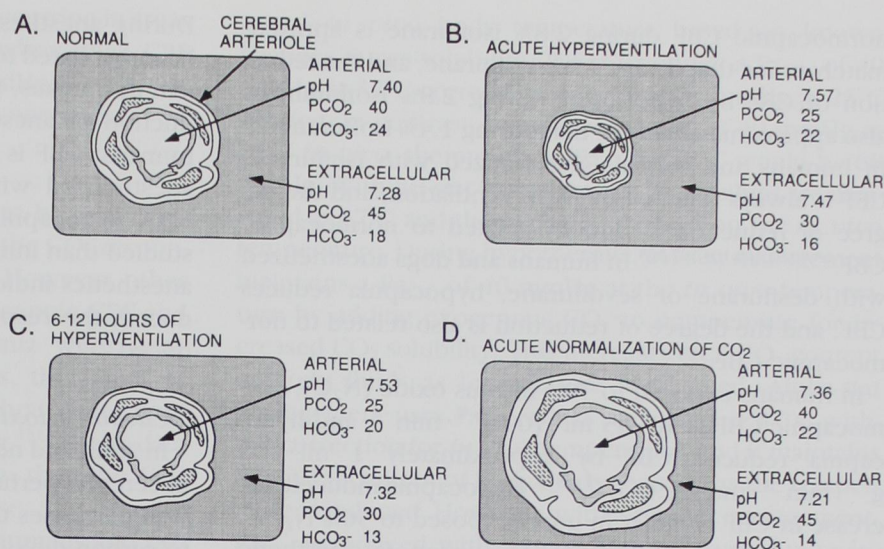
In awake humans, active hyperventilation to a Pa_{CO_2} of 16 mmHg initially reduced CBF by 40%, but during 4 h of sustained hypocapnia, CBF recovered to within 10% of baseline.⁸⁶ Similar findings have been demonstrated in goats⁸⁷ and piglets.⁸⁸ Recovery of CBF during sustained hypocapnia appears to be mediated by a reduction in CSF (and extracellular) bicarbonate concentration and correction of extracellular pH (fig. 2).⁸⁹ Glial cells appear to be important in the regulation of extracellular bicarbonate concentration because these cells contain large amounts of carbonic anhydrase, which can convert bicarbonate to CO_2 and water.⁹⁰ Bicarbonate is the only buffer in extracellular brain fluid, and the reduction of bicarbonate concentration during sustained hypocapnia leads to a greater reduction in brain extracellular pH and a greater increase in CBF during any subsequent increase in CO_2 . In support of this concept, after 6 h of sustained hypocapnia in awake goats, normocapnia caused marked cerebral hyperemia.⁸⁷ Chronic hypocapnia in awake rabbits reduces the bicarbonate concentration of CSF and enhances the dilation of cerebral vessels to hypercapnia.⁹¹ Thus, in humans, acute termination of sustained hyperventilation could result in cerebral hyperemia and increased intracranial pressure (ICP). To avoid these events, termination of sustained hypocapnia is best accomplished by normalizing Pa_{CO_2} over a period of hours, which allows the brain to increase the extracellular bicarbonate concentration and buffer the change in extracellular pH .

Sustained Hypercapnia and Cerebral Blood Flow

In anesthetized dogs, CBF returned to baseline values during 6 h of sustained hypercapnia, accompanied by an increase in CSF bicarbonate concentration and partial correction of CSF pH .⁹² In awake rabbits, chronic hypercapnia increased CSF bicarbonate concentration and attenuated the response of the cerebral circulation to further hypercapnia.⁹¹ In unanesthetized animals, however, hypercapnia can increase brain catechol-

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Fig. 2. The effect of prolonged hyperventilation on brain extracellular pH, the partial pressure of carbon dioxide (P_{CO₂}), and bicarbonate concentration. These values are a composite from those available in the literature.^{86,87} (A) Under normal conditions, brain P_{CO₂} is slightly higher, and pH and bicarbonate are slightly lower than arterial values. (B) When acute hyperventilation is initiated, brain alkalosis results in cerebral vasoconstriction, reducing cerebral blood flow (CBF), cerebral blood volume (CBV), and intracranial pressure (ICP). (C) After 6–12 h of sustained hypocapnia, extracellular brain pH recovers nearly to baseline levels due to a reduction of bicarbonate. At this point, cerebral vascular tone has recovered to baseline, which restores CBF and CBV to baseline. The ICP may not increase if other compensatory changes have occurred during hyperventilation. (D) If hyperventilation is acutely terminated, marked brain extracellular acidosis occurs due to both elevations of the partial pressure of carbon dioxide and a reduction of bicarbonate, resulting in cerebral vasodilatation and increased CBF, CBV, and possibly ICP.



amines and activate cerebral metabolism, indirectly causing an increase in CBF.^{85,93} Anesthetics may influence the response to hypercapnia by suppressing catecholamine release and preventing increased cerebral metabolism.

Carbon Dioxide and Cerebral Blood Volume

When hypocapnia is used to reduce ICP, it does so by reducing CBV and not CBF *per se*. Technical difficulties have limited the number of studies of Pa_{CO₂} and CBV. Evidence indicates that during alterations of Pa_{CO₂}, changes in CBV are qualitatively similar to changes in CBF. In humans, baseline CBV is 3 or 4 ml per 100 g⁹⁴⁻⁹⁶ and is similar to values reported in baboons and monkeys when measurement techniques are similar.^{71,97} Other investigators have reported that CBV was larger in monkeys, dogs, and goats^{78,98,99} and smaller in rats.¹⁰⁰ In humans, hyperventilation reduces CBV by 0.049 ml · 100 g⁻¹ · mmHg CO₂⁻¹,⁹⁶ which is similar to values in monkeys⁷¹ and goats.⁷⁸ Smaller changes in CBV have been reported in rats¹⁰⁰ and dogs.⁹⁹ Variations in CBV measurements likely reflect the intrinsic difficulty of measuring CBV and the measurement techniques. During sustained hyperventilation in dogs, CBV returns to baseline during a period of 4 h.¹⁰¹ The effect of Pa_{CO₂} on CBV is attenuated during hypotension.⁹⁸

Anesthetics, Carbon Dioxide, and Cerebral Blood Flow

Inhaled Anesthetics. In awake humans, hyperventilation decreased CBF by 0.9 ml · 100 g⁻¹ · min⁻¹ · mmHg CO₂⁻¹, and during anesthesia with 1% halothane (and nitrous oxide), hyperventilation decreased CBF by 2 ml · 100 g⁻¹ · min⁻¹ · mmHg CO₂⁻¹.⁸¹ Although hyperventilation caused a greater reduction of CBF during anesthesia with halothane because halothane increased normocapnic CBF from 53 to 88 ml · 100 g⁻¹ · min⁻¹, absolute CBF was greater during hyperventilation with halothane compared with hyperventilation in the awake state.⁸¹ In halothane-anesthetized humans with a normocapnic CBF of 50 ml · 100 g⁻¹ · min⁻¹, CBF was reduced by 1.4 ml for each 1 mmHg reduction in Pa_{CO₂}.⁶³ In halothane-anesthetized animals, hyperventilation always reduces CBF, and the slope of the reduction is directly related to the normocapnic CBF.^{68,73,86,102-104} These data indicate that the cerebral circulation responds to hyperventilation during halothane anesthesia, and the response is increased when normocapnic CBF is increased.

In humans, reductions in CBF by hyperventilation was greater during isoflurane anesthesia than in the awake state.¹⁰⁵ The importance of normocapnic CBF in determining the response to hyperventilation during isoflurane anesthesia was demonstrated in dogs, where

normocapnic CBF during 2.8% isoflurane is approximately twice that during 1.4% isoflurane, and the reduction of CBF by hypocapnia during 2.8% isoflurane is also approximately twice that during 1.4% isoflurane.¹⁰⁶ In humans and animals anesthetized with isoflurane, CBF is always reduced by hyperventilation, and the degree of reduction is directly related to normocapnic CBF.^{68,80,82,102,104,107,108} In humans and dogs anesthetized with desflurane or sevoflurane, hypocapnia reduces CBF, and the degree of reduction is also related to normocapnic CBF.¹⁰⁹⁻¹¹²

In humans exposed to 70% nitrous oxide (N_2O), normocapnic CBF is $40-45 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, and hypocapnia reduced CBF by approximately $1 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg CO}_2^{-1}$.^{69,72} Hypocapnia-induced decrease in CBF is intact in goats exposed to 50% N_2O .⁷⁸ In humans, the addition of N_2O to a propofol anesthetic does not alter middle cerebral artery flow velocity or the response of the cerebral circulation to hypocapnia.¹¹³ However, the addition of N_2O to a halothane anesthetic in rabbits increased normocapnic CBF and the slope of the response to hypocapnia.¹⁰⁴

Several studies support the concept that by increasing normocapnic CBF, inhaled anesthetics enhance the response of the cerebral circulation to hypocapnia.^{68,102,105,106} Although the slope of the response to hypocapnia can be increased by inhalational anesthetics, this does not mean that CBF can be reduced to lower absolute values during inhalational anesthesia (i.e., greater vasoconstriction produced). Increased normocapnic CBF during inhaled anesthetics results in greater absolute values in CBF during hypocapnia, despite the increased relative response to hypocapnia. During inhaled anesthesia when normocapnic CBF is comparable with the awake state, the reduction of CBF by hypocapnia is similar to that in the awake state.

Intravenous Anesthetics. During thiopental anesthesia in humans, hypocapnia reduces CBF, but as anesthetic depth increases and normocapnic CBF is reduced, the response of CBF to reduction of Pa_{CO_2} also decreases.^{69,114} Similar findings have been reported for thiopental in baboons and dogs.^{115,116} During anesthesia with propofol in humans, the cerebral circulation responds to hypocapnia and hypercapnia.⁶⁶ However, compared with the awake state in humans, propofol anesthesia reduces middle cerebral artery flow velocity and the hypocapnic reduction of flow velocity.¹¹³ Further, the hypocapnia response of the cerebral circulation is less during deep levels of propofol anesthesia.¹¹⁷

During anesthesia with etomidate in humans, CBF is linearly related to Pa_{CO_2} .¹¹⁸ During sedation with midazolam in humans, hypercapnia increases CBF.¹¹⁹ After induction of anesthesia with fentanyl and diazepam in humans, CBF is linearly related to Pa_{CO_2} .¹²⁰ In animals anesthetized with either morphine or fentanyl with N_2O , hypocapnia reduces CBF.^{68,79} Although less well studied than inhaled anesthetics, data with intravenous anesthetics indicate that when normocapnic CBF is reduced, the response of CBF to hypocapnia is also reduced.

Carbon Dioxide and Cerebral Autoregulation

In adult and neonatal animals, a progressive reduction in cerebral perfusion pressure by hemorrhagic hypotension decreases the response of the cerebral circulation to carbon dioxide, and when perfusion pressure is less than the lower limits of cerebral autoregulation, the response to CO_2 is abolished.^{121,122} Other methods of producing hypotension generally yield a similar effect on the CO_2 response of the cerebral circulation.^{74,75,103,108} However, hypocapnia-induced reductions of CBF are present but attenuated during hypotension with isoflurane, in contrast to other hypotensive agents.^{74,108} This may reflect the greater CBF during isoflurane, despite equal levels of hypotension. In these studies, CBF exceeded the value associated with rapid neuronal death ($10 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$) during hypocapnia and normocapnia. Patients are rarely subjected to the profound degree of hypotension used in most of these studies and will likely maintain some response to hypocapnia during the lesser degree of hypotension used clinically. These studies suggest that in the normal brain, hypocapnia combined with hypotension does not reduce CBF to levels associated with cerebral injury.

Elevation of Pa_{CO_2} to 50–60 mmHg attenuates cerebral autoregulation, and elevation of Pa_{CO_2} to 70–90 mmHg abolishes autoregulation in primates and dogs.^{64,123} The cerebral circulation adapts during chronic hypercapnia, with autoregulation returning toward normal over several days, despite continued elevation of the Pa_{CO_2} level.¹²³ In contrast, in primates and dogs, hypocapnia does not appear to alter autoregulation, although absolute CBF is reduced by hypocapnia.^{64,124}

Carbon Dioxide Response in Neonates

In sheep, the response of the cerebral circulation to Pa_{CO_2} increases during development from fetus to adult.¹²⁵ In newborn dogs, hypocapnia has a minimal

effect on CBF, with the greatest effect occurring in areas of the brain with more flow.^{126,127} In newborn pigs, CBF is reduced only when PaCO₂ is <15 mmHg.^{128,129} However, hypercapnia does increase CBF in neonates.¹²⁷⁻¹³⁰

Carbon Dioxide Response in Aging

Normocapnic gray matter blood flow has been reported to decrease during aging, as has the CO₂ responsiveness of gray matter blood flow.^{131,132} However, other investigators have reported that normocapnic CBF and hypercapnia-induced cerebral hyperemia were unaltered with aging.¹³³ In awake humans, the effect of hypo- and hypercapnia on middle cerebral artery flow velocity was not different during aging.¹³⁴ These data indicate that if CBF declines with aging, then the CO₂ responsiveness of CBF will also decrease.

Some investigators have reported in humans and primates that atherosclerosis reduces hypercapnia-induced cerebral hyperemia.^{135,136} However, others report that the response of the cerebral circulation to hypercapnia is normal in humans with atherosclerosis.¹³⁷ Occlusive atherosclerosis could limit the vasodilator reserve of the cerebral circulation by limiting maximal blood flow to the brain, thus reducing hypercapnia-induced hyperemia. Conflicting data may arise from the variable nature of atherosclerosis. Similar data assessing the effect of atherosclerosis on the response of the cerebral circulation to hypocapnia are not available.

Carbon Dioxide Response and Hypertension

It is generally accepted that chronic hypertension does not alter baseline CBF in either humans or animal models of hypertension. In hypertensive rats, baseline CBF and the reduction in CBF during hypocapnia are not different than in normotensive rats.¹³⁸ In humans with essential hypertension but without atherosclerosis, changes in CBF during hypocapnia and hypercapnia are similar to those in normotensive humans.^{70,139}

Carbon Dioxide Response and Hypothermia

Brain temperature affects CBF and thus the response of the cerebral circulation to changes in PaCO₂. An important issue in the study of temperature effects on CBF is the method by which PaCO₂ is managed. As blood is cooled anaerobically, PaCO₂ decreases due to the increased solubility of CO₂, even though total CO₂ content remains constant. Blood gas tensions measure partial pressures of gas and are typically measured at 37°C. Gas tension measured at 37°C can be "corrected" to

actual *in vivo* body temperature based on known changes in gas solubility.¹⁴⁰ For example, a PaCO₂ of 40 mmHg at 37°C corrects to a PaCO₂ of 24 mmHg at 25°C *in vivo*. In contrast, to achieve a PaCO₂ of 40 mmHg at 25°C *in vivo*, the measured PaCO₂ at 37°C would be 68 mmHg. With pH-stat management, PaCO₂ values are measured at 37°C and then corrected based on the *in vivo* temperature. During hypothermia, pH-stat management maintains a PaCO₂ of 40 mmHg at the *in vivo* temperature by adding exogenous CO₂ to compensate for increased CO₂ solubility. This increases total CO₂ content of body fluids as temperature is reduced. Alpha-stat management uses PaCO₂ values measured at 37°C without correction for *in vivo* temperature, and it maintains total CO₂ content of body fluids constant as the temperature is reduced. However, with alpha-set management, PaCO₂ is reduced with reduced temperature due to increased CO₂ solubility. Thus pH-stat management results in relative hypercapnia at reduced body temperatures compared with alpha-stat management.

The cerebral circulation responds to changes in PaCO₂ during hypothermic cardiopulmonary bypass.^{141,142} However, hypothermic cardiopulmonary bypass reduces CBF and the slope of the CBF/PaCO₂ relation.¹⁴² During pH-stat blood gas management, CBF is greater than during alpha-stat management,^{143,144} and autoregulation of CBF is attenuated compared with alpha-stat management.^{144,145} This suggests that the relative hypercapnia of pH-stat management impairs cerebral autoregulation.

Hypocapnia-induced Cerebral Ischemia in the Normal Brain

In humans, when PaCO₂ is reduced to 20–25 mmHg, CBF is reduced to 20–25 ml·100 g⁻¹·min⁻¹.^{63,69,70,72} However, CBF remains >20 ml·100 g⁻¹·min⁻¹ even during extreme hypocapnia in anesthetized (PaCO₂ = 10 mmHg)⁷² and nonanesthetized humans (PaCO₂ = 16 mmHg).⁸⁶ In animals, reducing PaCO₂ <20 mmHg does not reduce CBF further.^{71,121,138} In nonanesthetized, normothermic humans and primates, the earliest signs and symptoms of cerebral ischemia such as confusion, inability to follow commands, focal neurologic deficits, and slowing of the electric activity of the brain, measured by an electroencephalogram (EEG), occur at global CBF levels of 20–30 ml·100 g⁻¹·min⁻¹.^{146,147} However, CBF must be reduced to <10 ml·100 g⁻¹·min⁻¹ to cause acute neuronal death.¹⁴⁷ Hyperventilation can reduce CBF to a level associated with mild

cerebral ischemia, and in humans and animals, reducing the Pa_{CO_2} to 20–25 mmHg slows the EEG^{148,149} and impairs mental function,^{150,151} which suggests the occurrence of mild cerebral ischemia. In addition to reducing CBF, marked alkalosis shifts the oxyhemoglobin dissociation curve to the left, further limiting oxygen delivery to the brain. Thus many investigators assume that hypocapnia-induced changes in EEG and mental activity result from cerebral ischemia.

A preliminary study in humans reported that hyperventilation-induced slowing of the EEG could be reversed by hyperbaric oxygen, which suggests that hyperventilation reduces oxygen delivery and limits cerebral metabolism.¹⁴⁹ Brain lactate concentration increases during severe hypocapnia and is inversely proportional to Pa_{CO_2} , which suggests insufficient oxygen to maintain oxidative metabolism.^{87,152–154} Cortical oxygen tension is reduced during hypocapnia, and severe hypocapnia (10 mmHg Pa_{CO_2}) can reduce cortical oxygen tension even while CBF remains constant, which suggests that increasing alkalosis further limits oxygen delivery.^{155,156}

Although hyperventilation slows the EEG, hyperventilation-induced changes in the EEG may not represent cerebral ischemia. In humans, hypocapnia and hypoxia produce different changes in spectral power bands of the EEG.¹⁵⁷ Further, because hyperbaric oxygen can increase the frequency of the EEG, and cause seizures, it is not clear if reversal of hyperventilation-induced EEG changes represent a specific or nonspecific effect.¹⁵⁸ Brain lactate production is pH-dependent, and as pH increases, lactate production increases independent of oxygen availability.^{153,159}

In animals and humans, hypocapnia to a Pa_{CO_2} 10–20 mmHg does not change cerebral metabolic rate of oxygen use, which suggests that the brain is receiving sufficient oxygen to maintain oxidative metabolism.^{65,86,160,161} Most,^{152–154} but not all,^{162–164} studies report that brain levels of high-energy compounds such as adenosine triphosphate (ATP) and phosphocreatine are unchanged during severe hypocapnia, which suggests that sufficient oxygen is reaching the brain to maintain oxidative phosphorylation. In newborn animals, cerebral metabolism is not impaired during severe hypocapnia ($\text{Pa}_{\text{CO}_2} < 20$ mmHg),¹⁶¹ and brain high energy stores are not reduced.¹²⁶

Overall, these studies indicate that, in the normal brain, hypocapnia can reduce CBF to the threshold of cerebral ischemia, but not to CBF associated with

rapid neuronal death. If hypocapnia causes cerebral ischemia in the normal brain, it must be mild, and not associated with gross disturbances of brain oxidative metabolism. However, the long-term effect of hyperventilation on the normal brain are not known, because no data are available regarding hyperventilation-induced loss of neurons or permanent functional alterations.

Summary of Carbon Dioxide and Cerebral Vascular Regulation

The cerebral circulation is very responsive to changes in CO_2 ; at approximately 20–80 mmHg Pa_{CO_2} , CBF changes $1–2 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg CO}_2^{-1}$ in many species under various conditions (table 1). The response of the cerebral circulation to changes in Pa_{CO_2} depends on resting CBF, and the slope of the response to CO_2 increases as normocapnic CBF increases. At both extremes of Pa_{CO_2} , the response of the cerebral circulation is attenuated or abolished. During sustained alteration of Pa_{CO_2} , CBF recovers to baseline during a period of hours as brain extracellular pH corrects. During alterations in Pa_{CO_2} , CBV changes in parallel with changes in CBF, but the relative change is less marked. The cerebral circulation maintains its response to CO_2 during administration of anesthetics, but the relative response of the cerebral circulation to change in Pa_{CO_2} may be altered if anesthetics alter normocapnic CBF. Hypotension to less than the lower limit of autoregulation can abolish the response of CBF to hypocapnia, and hypercapnia can attenuate or abolish cerebral autoregulation. The response of the cerebral circulation to CO_2 increases during development from neonate to adult. However, aging does not alter the response to changes in Pa_{CO_2} as long as normocapnic CBF is unchanged. Hypertension does not affect the response of the cerebral circulation to Pa_{CO_2} , but atherosclerosis may limit hypercapnia-induced cerebral vasodilation. Hypothermia reduces CBF and the response of CBF to changes in Pa_{CO_2} . Many studies have tried to demonstrate hypocapnia-induced cerebral ischemia in the normal brain, but clear evidence for this is lacking.

Clinical Use of Hypocapnia and Hypercapnia

Manipulation of Pa_{CO_2} is common in both the operating room and the intensive care unit, with hypocap-

CO₂ AND THE CEREBRAL CIRCULATIONTable 1. Summary of CO₂ and Cerebral Physiology

Cerebral Blood Flow (CBF)	Cerebral Blood Volume (CBV)	Cerebral Autoregulation	CO ₂ Response and Anesthetics	CO ₂ Response and Disease/Injury
CBF changes 1–2 ml · 100 g ⁻¹ · min ⁻¹ for each 1 mmHg change in CO ₂ between 20 and 80 mmHg CO ₂	CBV changes 0.05 ml/100 g for each 1 mmHg change in CO ₂	Modest hypercapnia impairs and marked hypercapnia abolishes autoregulation	CO ₂ response is maintained during inhaled and intravenous anesthetics	Hypercapnic response intact with hypertension
Slope of the response depends on normocapnic CBF	CBV returns to baseline during sustained alteration of CO ₂	Hypotension below the lower limit of autoregulation abolishes	Relative response to hypocapnia depends on normocapnic CBF	Hypocapnic response present with brain injury, but may be attenuated
CBF returns to baseline during sustained alteration of CO ₂		hypocapnic cerebral vasoconstriction		

nia being used to treat increased ICP and both hypocapnia and hypercapnia used to treat cerebral ischemia. This section reviews the clinical and experimental evidence regarding the manipulation of Pa_{CO₂} in patient care.

Carbon Dioxide in the Management of Cerebral Ischemia

The pathophysiology and therapy of cerebral ischemia is complex and poorly understood, and a full overview of cerebral ischemia is beyond the scope of this review. In an attempt to enhance blood flow to ischemic brain, Pa_{CO₂} has been manipulated during cerebral ischemia. However, manipulation of Pa_{CO₂} affects not only CBF but also brain pH, which may affect cerebral ischemia independent of CBF.¹⁶⁵ Further, small variations in brain temperature can significantly affect the severity of a cerebral ischemic insult, and many studies did not adequately control brain temperature.¹⁶⁶ It is difficult to retrospectively assess the interactions of these factors during studies of Pa_{CO₂} manipulation and cerebral ischemia. However, this section will focus on the effect of Pa_{CO₂} manipulation on CBF during cerebral ischemia, and on how such changes in CBF may affect cerebral ischemia and patient care.

Focal Cerebral Ischemia. Cerebral embolization or occlusion of cerebral vessels results in focal cerebral ischemia. Hyperventilation is proposed to be beneficial during focal cerebral ischemia by constricting the non-ischemic brain and diverting blood flow to the ischemic brain (known as Robin Hood or inverse steal). This hypothesis assumes that the ischemic brain lacks hypo-

capnic-induced vasoconstriction. An early study in dogs reported that hyperventilation reduced the volume of brain infarction after middle cerebral artery occlusion, which suggests a favorable redistribution of blood flow by hyperventilation.¹⁶⁷ However, the same investigators¹⁶⁸ and others¹⁶⁹ later reported in cats and primates that hyperventilation did not reduce the volume of brain infarction after middle cerebral artery occlusion. In cats with middle cerebral artery occlusion, hyperventilation does not increase blood flow to the ischemic brain.^{77,170} Furthermore, during focal cerebral ischemia in primates, hyperventilation exacerbated the reduction in brain high-energy compounds and impaired oxidative metabolism in the ischemic brain, which suggests that hyperventilation exacerbated cerebral ischemia.^{171,172} In rats with middle cerebral artery occlusion, hyperventilation enlarges the area of the ischemic brain.¹⁰⁷ In humans who have had a stroke, CBF in the ischemic brain is low and can be further reduced by hyperventilation.^{173,174} However, blood flow to the ischemic brain is increased in approximately 10% of patients who have had a stroke.¹⁷⁴ Hyperventilation of humans with acute, focal stroke does not alter patient outcome.¹⁷⁵

Temporary focal cerebral ischemia may be induced in humans during carotid cross-clamping for endarterectomy. Hypocapnia during carotid cross-clamping does not reduce the incidence of new neurologic deficits after carotid endarterectomy, which suggests that CBF is not favorably redistributed by hypocapnia.¹⁷⁶ When CBF was measured during carotid cross-clamping in humans, hypocapnia decreased the CBF in the ischemic cerebral hemisphere in three of seven patients but in-

creased CBF in one of seven patients.¹⁷⁷ A case report also indicates that hypocapnia combined with hypertension was effective in reversing ischemic EEG changes during carotid cross-clamping.¹⁷⁸

Thus, although an early animal study suggested that hyperventilation was beneficial during focal cerebral ischemia, other experimental studies indicate that hyperventilation is not beneficial and may be harmful by further reducing CBF in the ischemic brain. In humans with focal cerebral ischemia, hyperventilation appears to cause a favorable redistribution of CBF (inverse steal) in approximately 10% of patients. Assessment of whether hyperventilation is helpful or harmful in individual patients with focal cerebral ischemia requires measurement of CBF, cerebral function, or both. Furthermore, because of the transient effect of Pa_{CO_2} alterations on CBF, any enhancement of CBF will likely be temporary.

Hypercapnia has been proposed to be beneficial in focal ischemia by vasodilating the ischemic brain and increasing blood flow. Hypercapnia may also decrease blood flow to the ischemic brain by vasodilating the normal brain and diverting blood flow from the ischemic brain, which cannot be further dilated by hypercapnia (intracerebral steal). In animals with middle cerebral artery occlusion, hypercapnia does not change or decreases blood flow in the ischemic brain.^{77,170,179,180} In animals with focal ischemia, hypercapnia does not dilate arteries in the ischemic brain cortex.^{77,181} In humans who have had acute stroke, hypercapnia does not increase blood flow in the ischemic brain.^{182,183} Several days after the onset of focal stroke in humans, the response of CBF to hypercapnia is more heterogeneous, with some patients demonstrating increased and others decreased flow in the ischemic brain.¹⁸⁴ However, in dogs with focal cerebral ischemia, modest hypercapnia increased blood flow in the ischemic brain and improved somatosensory evoked potentials.¹⁸⁵ The positive outcome of both hypercapnia and hypocapnia studies in dogs may reflect differences in the collateral cerebral circulation in dogs, which predisposes these animals to benefit from alterations of Pa_{CO_2} . Overall, however, data indicate that hypercapnia is not beneficial in focal cerebral ischemia.

Global Ischemia. Global cerebral ischemia occurs during cardiac arrest; after resuscitation, cerebral hyperfusion or hypoperfusion can occur. In an attempt to enhance CBF in the post-arrest state, Pa_{CO_2} has been manipulated. However, after global cerebral ischemia

in animals, the response of the cerebral circulation to hypocapnia is attenuated or abolished,^{130,186,187} and the response to hypercapnia is markedly attenuated.^{130,187,188} In newborn piglets, CBF can be reduced by hypocapnia, but hypercapnia does not increase CBF after global ischemia.^{130,189} However, after global ischemia in juvenile pigs, the CO_2 reactivity of the cerebral circulation is normal 2 h after ischemia.¹³⁰ In rabbits subjected to global cerebral ischemia, hypocapnia decreases the release of glutamate and glycine during ischemia, which suggests less severe neuronal damage.¹⁹⁰ After global cerebral ischemia in dogs, hypercapnia but not hypocapnia delayed electrophysiologic recovery,¹⁹¹ which suggests that hypercapnia was detrimental. Also in dogs, hyperventilation improved the brain histopathology score after 15 min of cardiac arrest.^{192,193} Thus, although some data suggest that hypocapnia can be beneficial after global ischemia, it is not possible to draw a definitive conclusion regarding potential benefits. Furthermore, most studies indicate that the response of the cerebral circulation to CO_2 is markedly attenuated or abolished immediately after global cerebral ischemia. Similar data addressing manipulation of Pa_{CO_2} after cardiac arrest in humans are not available.

Hyperventilation and Intracranial Pressure

Hyperventilation is a common component in the management of increased ICP. Most evidence regarding hyperventilation in the management of increased ICP is derived from studies of head-injured patients. In the late 1960s and early 1970s, hyperventilation was proposed to decrease the mortality rate in patients after head injury.¹⁹⁴⁻¹⁹⁶ However, these reports are difficult to interpret because often the Pa_{CO_2} was not measured. More importantly, the control patients in these studies breathed spontaneously with a native airway. Thus it is impossible to assess the degree of hyperventilation achieved and the contribution of airway maintenance and possible improved oxygenation on the outcomes of these studies.

During the late 1970s and 1980s, several authors reported that the mortality rate for head injury was reduced if a multimodal treatment approach was used that included hyperventilation.^{197,198} However, other investigators¹⁹⁹ reported that mechanical ventilation did not affect outcome in patients with head injury. In 1991, a randomized, prospective trial of head injured patients reported that hyperventilation initially worsened outcome in a subset of patients, but by 1 yr after injury

there was no difference between hyperventilated and nonhyperventilated patients.²⁰⁰ Due to inherent problems with this study, including hyperventilation of patients with normal ICP and relatively small differences in PaCO₂ between the hypocapnic and normocapnic groups, it is difficult to draw conclusions about the effect of hyperventilation on outcome in head injured patients.²⁰⁰

After head injury, CSF lactate concentration increases,²⁰¹ and hyperventilation has been proposed as beneficial by correcting brain acidosis.²⁰² However, in cats with severe fluid-percussion brain injury, brain intracellular pH decreases only transiently after injury,²⁰³ and hyperventilation increases brain lactate production.²⁰⁴ Thus brain intracellular acidosis appears limited after injury, and hyperventilation may exacerbate acidosis by increasing lactate production.

Cerebral blood flow can be low and ICP normal after head injury, especially in the first hours after injury.²⁰⁵ Some authors have proposed that decreased CBF after head injury represents cerebral ischemia.²⁰⁵ However, cerebral metabolism is also decreased after head injury, and the reduction in CBF may not represent cerebral ischemia but rather may reflect appropriate flow-metabolism coupling.²⁰⁶ Because the cerebral circulation usually retains some responsiveness to CO₂ after head injury, hyperventilation can reduce CBF further.^{173, 206-208} However, reduction in CBF alone is not sufficient to produce cerebral ischemia, because the threshold for ischemia depends not only on flow but also on metabolism. In some patients with head injury, hyperventilation reduces CBF, increases arteriovenous oxygen extraction, and reduces the cerebral metabolic rate of oxygen, which suggests the onset of cerebral ischemia.²⁰⁶ In animals with ICP elevated to the threshold of cerebral ischemia, hyperventilation reduced brain phosphocreatine, which suggests cerebral ischemia.²⁰⁹ Thus cerebral metabolic evidence suggests that after head injury, hyperventilation can reduce CBF to the point of cerebral ischemia.

Acute hyperventilation is effective in controlling increased ICP,^{210,211} and in contrast to the studies just noted, hyperventilation can increase CBF by reducing ICP.²¹² However, because hyperventilation has transient effects on CBF and CBV, it is only a temporary measure to control increased ICP.²⁰⁵ Current recommendations for PaCO₂ management after brain injury discourage the use of prophylactic hyperventilation and suggest that

hyperventilation should be used only when increased ICP is refractory to other methods of control.²⁰⁵

Recent reports suggest that measurement of an objective parameter of cerebral oxygenation or CBF can assess the effect of hyperventilation on the brain metabolic state in head injured patients.^{213,214} The ability to optimize cerebral perfusion would allow more rational treatment of individual patients. However, the methods proposed have not been evaluated prospectively, and their effect on patient outcome is unknown.

Based on clinical experience and experimental data, increased ICP can be reduced by acute hyperventilation. As ICP is reduced, cerebral perfusion pressure is increased and CBF may be increased. However, after head injury, despite the presence of coma, some patients may have reduced CBF and normal ICP. When ICP is normal, there is no benefit to hyperventilation, and there may be detriment by further reducing CBF. Prophylactic or indiscriminate use of hyperventilation in head injured patients should be avoided, and hyperventilation should be reserved for the acute treatment of increased ICP. Because the effect of hyperventilation on CBF, CBV, and ICP is transient, other interventions are necessary for long-term control of ICP.

Hyperventilation and Subarachnoid Hemorrhage

In primates, subarachnoid hemorrhage resulting in coma and hemiparesis does not alter the response of the cerebral circulation to hypocapnia, although the hypercapnia-induced increase in CBF was reduced by 50%.¹¹⁵ In humans with subarachnoid hemorrhage, those with no or mild angiographic vasospasm have a normal response to hypocapnia.²¹⁵ However, in patients with severe vasospasm documented by angiography, CBF responded less to hyperventilation.²¹⁵ All patients in this study, including those with relatively low normocapnic CBF (<25 ml · 100 g⁻¹ · min⁻¹), responded to hyperventilation, even though the response was attenuated in patients with low normocapnic CBF. In patients with severe cerebral vasospasm, attenuation of hypocapnia-induced cerebral vasoconstriction may be due to preexisting constriction from vasospasm.

Intraoperative Hyperventilation

Hyperventilation is considered an integral component of the anesthetic management of patients undergoing intracranial surgery. Hypocapnia is proposed to be beneficial by reducing CBV and ICP, thus allowing brain tissue to be retracted with less force, thereby enhancing

operative exposure. Hyperventilation was proposed as an adjunct to anesthetic management in intracranial operations in the late 1950s. Before then, most patients undergoing intracranial operations breathed spontaneously while they were anesthetized. Although it was recognized that hypercapnia increased CBV and ICP,²¹⁶ early discussions of anesthetic management of patients having neurosurgery do not mention controlled ventilation or hyperventilation.^{217,218} In 1957, a subjective report detailed the use of intraoperative hyperventilation to improve intracranial operating conditions.²¹⁹ Later, when ICP and Pa_{CO_2} were measured in anesthetized patients having intracranial surgery, Pa_{CO_2} and ICP were frequently elevated ($\text{Pa}_{\text{CO}_2} > 60$ mmHg) and "hyperventilation" only restored Pa_{CO_2} to normal levels.²²⁰ Subsequent reports supported the use of intraoperative hyperventilation, but these reports are subjective rather than critical evaluations of the technique.^{221,222} All of these reports compare spontaneous ventilation to hyperventilation, with hyperventilation usually defined based on delivered minute ventilation rather than measurement of Pa_{CO_2} .

In the early 1960s, hyperventilation of patients undergoing craniotomy was reported to reduce tension of the dura, as assessed in an unblinded fashion by surgeons.^{223,224} However, Pa_{CO_2} was not measured, anesthetic agents were not standardized, and hyperventilation was compared with spontaneous ventilation.^{223,224} These investigators also reported that in spontaneously breathing patients, osmotic dehydrating agents were as effective as hyperventilation in reducing dural tension.²²⁴ Although these anecdotal reports do not indicate if hyperventilation resulted in hypocapnia or normocapnia, they began the tradition of hyperventilation for patients undergoing intracranial surgery.

By the mid-1960s, investigators reported that halothane could increase CBF and ICP.^{225,226} Hyperventilation before administration of halothane was proposed as a method to attenuate halothane-induced increases in ICP.^{227,228} Isoflurane was later reported to increase CBF and ICP,^{229,230} and hyperventilation was again proposed as a method to offset isoflurane-induced increases in ICP.²²⁹ In contrast to halothane, isoflurane-mediated elevations of ICP could be prevented when hyperventilation was instituted concomitantly with the administration of isoflurane.^{229,231} In dogs, 2% isoflurane significantly increased CBV, and hyperventilation attenuated this effect.⁹⁹ However, in dogs with supratentorial space-occupying lesions, administration of isoflurane

after induction of hyperventilation does not increase ICP further.²³²

In humans undergoing craniotomy, the degree of hyperventilation required to prevent an inhaled anesthetic-induced increase in ICP appears to vary, which reflects individual variability in intrinsic mechanisms to compensate for increased CBV. In one study of patients with intracranial tumors, ICP was not different (12–15 mmHg) during modest hypocapnia ($\text{Pa}_{\text{CO}_2} \approx 30$ mmHg) during anesthesia with either isoflurane with nitrous oxide or propofol with fentanyl.²³³ However, other investigators reported in patients with intracranial tumors that isoflurane increased ICP from 14 to 22 mmHg despite hyperventilation to an end-tidal CO_2 level of 26 mmHg.²³⁴ In patients undergoing CSF shunt procedures, isoflurane increased ICP from 4 to 26 mmHg, and subsequent hyperventilation reduced ICP to 2 mmHg.²³¹ Although hyperventilation is commonly used in patients undergoing intracranial surgery, the effect of hyperventilation on patient outcome has not been evaluated objectively. Furthermore, the relative degree of hyperventilation required also has not been determined. Hyperventilation can reduce increased ICP and can offset the effect of inhaled anesthetics on ICP. However, due to the variable nature of intracranial disease, the degree of hyperventilation required in individual patients can only be assessed on an individual basis. The need for and degree of hyperventilation in patients should be guided by preoperative signs and symptoms of increased ICP, by inspection of intracranial contents during craniotomy, and by measurement of ICP.

Summary of the Clinical Use of Hypocapnia and Hypercapnia

During permanent focal cerebral ischemia, hyperventilation does not improve outcome in humans and can exacerbate cerebral ischemia in animals. In a minority of patients, hyperventilation can increase blood flow during temporary and permanent focal cerebral ischemia. Hypercapnia also does not appear to be beneficial with focal cerebral ischemia. Manipulation of Pa_{CO_2} after global ischemia has been studied less, and definite conclusions regarding the use of Pa_{CO_2} manipulation are not available. However, immediately after global ischemia, the response of the cerebral circulation to CO_2 is attenuated or abolished. After head injury, acute hyperventilation can reduce increased ICP and increase cerebral perfusion. However, head injury can reduce CBF in humans, and hyperventilation can further reduce CBF. In

animals with elevated ICP, hyperventilation can reduce both CBF and brain energy stores. Although control of elevated ICP is an important goal after head injury, there is no objective evidence that hyperventilation improves outcome in patients with head injury. Current recommendations are to avoid prophylactic hyperventilation in brain injured patients and to reserve hyperventilation to treat increased ICP that cannot be controlled by other methods.

Intraoperative hyperventilation appears to be a clinically useful intervention to control ICP, to offset the effect of inhaled anesthetics, and to enhance operative exposure. However, intraoperative hyperventilation has not been evaluated rigorously, and the overall effect on patient outcome is unknown. The degree of intraoperative hyperventilation necessary in individual patients requires assessment of preoperative signs and symptoms of increased ICP, intraoperative inspection of intracranial contents, and measurement of ICP. Excessive or indiscriminate use of intraoperative hyperventilation may not be innocuous, because some evidence suggests that hyperventilation can further reduce CBF in the brain with low normocapnic blood flow.

Conclusions

In the past 100 yr, a great deal has been learned regarding CO₂ and the cerebral circulation. Today much is known about the mechanisms of CO₂-mediated changes in cerebral vascular tone. A key step in CO₂-mediated signaling is alteration of extracellular brain pH. After alterations in pH, changes in intracellular calcium concentration are the final common mediator in both hypercapnia and hypocapnia. In adults animals, NO and cGMP contribute to modest but not marked hypercapnia-induced dilation of cerebral blood vessels. However, NO and cGMP may not be the direct vasodilators, but rather may function in a "permissive" role. In neonates, cyclo-oxygenase products and cAMP are important in hypercapnia-induced cerebral vasodilation, but they also may not be the direct vasodilators. Finally, activation of K_{ATP} channels is important in cerebral vasodilation to modest hypercapnia in adults.

Between Pa_{CO₂} values of 20 and 80 mmHg, CBF changes 1 to 2 ml · 100 g⁻¹ · min⁻¹ for each 1 mmHg change in Pa_{CO₂}. The change in CBF is related to the normocapnic CBF, and when flow is increased, the relative response to hypocapnia is increased. During sus-

tained alterations of Pa_{CO₂}, CBF returns to baseline over several hours due to a correction of brain extracellular pH. Anesthetics that increase CBF enhance the reduction of CBF by hypocapnia, and anesthetics that reduce CBF reduce the response. Cerebral blood volume changes in a manner that is similar to CBF, but the relative change is less marked. Hypotension less than the lower limit of autoregulation attenuates or abolishes the response of the cerebral circulation to changes in Pa_{CO₂}. Hypercapnia can attenuate or abolish autoregulation. The response of CBF to changes in Pa_{CO₂} increases during development from neonate to adult. However, during aging the response to hypocapnia does not change as long as normocapnic CBF is unchanged. Untreated hypertension does not affect the response of the cerebral circulation to changes in Pa_{CO₂}. Hypothermia reduces normocapnic CBF and the response of CBF to changes in Pa_{CO₂}. Many studies have tried to demonstrate hypocapnic-induced ischemia in the normal brain, but clear evidence for this is lacking.

During temporary focal cerebral ischemia, neither hypercapnia nor hypocapnia improve and in fact may worsen outcome. Hypocapnia has been reported to increase blood flow to the ischemic brain during temporary and permanent focal cerebral ischemia in a minority of patients. Animal data suggest that hyperventilation can improve some indicators of cerebral well-being after global cerebral ischemia. However, no data are available to assess the effect of hyperventilation after global ischemia in humans. When ICP is increased, acute hyperventilation can reduce ICP and may increase CBF. However, the effect of hyperventilation on patient outcome is uncertain. Current recommendations are to reserve hyperventilation for the treatment of increased ICP that cannot be controlled by other methods. After subarachnoid hemorrhage, the cerebral circulation responds to reductions in Pa_{CO₂}, although the response may be attenuated if vasospasm is present. Intraoperative hyperventilation appears to be useful in controlling ICP, offsetting the effect of inhaled anesthetics, and improving intracranial operating conditions. However, objective data on intraoperative hyperventilation and operative exposure or patient outcome are lacking. In the clinical care of patients in the operating room, the need for and degree of hyperventilation can be guided only by assessment of the signs and symptoms of increased ICP, inspection of intracranial contents during craniotomy, and measurement of ICP. As in the inten-

sive care unit, it would be prudent to avoid unnecessary hyperventilation in the operating room.

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