Review Article

Medical Progress

HYPOCAPNIA

JOHN G. LAFFEY, M.D., AND BRIAN P. KAVANAGH, M.B.

ARTERIAL carbon dioxide tension represents the balance between the production and elimination of carbon dioxide, and in healthy persons, it is maintained within narrow physiologic limits. Hypocapnia, even when marked, is normally well tolerated, often with few apparent effects. Transient induction of hypocapnia can lead to lifesaving physiological changes in patients with severe intracranial hypertension or neonatal pulmonary-artery hypertension, but hypocapnia of longer duration in critically ill patients may adversely affect outcomes.[1,2] Despite concern about adverse effects, the induction of hypocapnia has commonly been recommended for diverse disease states.[3-5] Thus, hypocapnia, whether produced deliberately[3-5] or accidentally,[6,7] remains prevalent in clinical practice (Table 1). In addition, hypocapnia is a common component of many acute illnesses, although its importance is often underestimated.[8-12] The prevalence of hypocapnia may be exacerbated by the belief held by some clinicians that hypocapnia is inherently safer than — or at least preferable to — hypercapnia.

DEVELOPMENT OF ARTERIAL HYPOCAPNIA

In its simplest form, the partial pressure of arterial carbon dioxide ($PaCO_2$) reflects the balance between the production and elimination of carbon dioxide (CO_2), as described by the following formula:

$$PaCO_2 \text{ is proportional to } \frac{CO_2 \text{ production}}{CO_2 \text{ elimination}} + \text{inspired } CO_2.$$

The volume of inspired carbon dioxide is usually negligible, whereas reduced carbon dioxide production is an unusual, but possible, contributor to hypocapnia. Therefore, for practical purposes, a low partial pressure of arterial carbon dioxide reflects the rate of elimination of carbon dioxide. Thus, the principal physiologic causes of hypocapnia, including pregnancy, are related to hyperventilation (Table 1).[13] Of course, hyperventilation can occur with mechanical ventilation, and artificial clearance of carbon dioxide with the use of extracorporeal techniques (e.g., cardiopulmonary bypass, extracorporeal membrane oxygenation, or devices for the removal of carbon dioxide) is extraordinarily efficient.[6,14,15]

One form of hypocapnic alkalosis that is rarely discussed occurs during critical reduction of pulmonary perfusion (for example, during cardiopulmonary resuscitation). In such cases, there is a dissociation between the condition of central venous blood, with a high partial pressure of arterial carbon dioxide and a low pH, and that of the systemic arterial blood, with a low carbon dioxide tension and an alkalemic pH; this dissociation is due to the combination of low pulmonary perfusion and normal ventilation, and this condition is called pseudorespiratory alkalosis.[16]

TABLE 1. CAUSES OF HYPOCAPNIA.

Hypoxemia	High altitudes, pulmonary disease
Pulmonary disorders	Pneumonia, interstitial pneumonitis, fibrosis, edema, pulmonary embolism, vascular disease, bronchial asthma, pneumothorax
Cardiovascular disorders	Congestive heart failure, hypotension
Metabolic disorders	Acidosis (diabetic, renal, or lactic), hepatic failure
Central nervous system disorders	Psychogenic or anxiety-induced hyperventilation, central nervous system infection, central nervous system tumors
Drugs	Salicylates, methylxanthines, β-adrenergic agonists, progesterone
Miscellaneous	Fever, sepsis, pain, pregnancy

Therapeutic Induction of Hypocapnia

The deliberate induction of hypocapnia for short periods while other definitive treatment measures are being instituted remains a potentially lifesaving therapeutic strategy in situations in which intracranial pressure[17,18] or neonatal pulmonary vascular resistance[19]

From the Department of Physiology, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, and the Department of Anaesthesia and Intensive Care, St. Vincent's University Hospital, Dublin, Ireland (J.G.L.); and the Department of Critical Care Medicine and the Lung Biology Program, the Research Institute, the Hospital for Sick Children, and the Program in Critical Care Medicine, University of Toronto, Toronto (B.P.K.). Address reprint requests to Dr. Kavanagh at the Department of Critical Care Medicine, the Hospital for Sick Children, 555 University Ave., Toronto, ON M5G 1X8, Canada, or at bpk@sickkids.ca.

Downloaded from www.nejm.org at CLEVELAND CLINIC on June 13, 2006 .
Copyright © 2002 Massachusetts Medical Society. All rights reserved.

is critically elevated. There is no evidence to support the therapeutic or prophylactic use of induced hypocapnia in any other context. However, induced hypocapnia has been and may remain a common practice, particularly in patients with brain injury or neonatal respiratory failure, as well as during general anesthesia.

Head Injury

The recognition of the effectiveness of hypocapnic alkalosis in reducing intracranial pressure, together with the identification of elevated intracranial pressure as a pathogenic condition, led to the assumption that hypocapnia should be induced when intracranial pressure was elevated (Fig. 1). Therefore, hyperventilation[20-24] — sometimes resulting in very severe hypocapnia[21-24] — once represented the standard of care for the treatment of patients with head trauma.

Despite expert guidelines recommending against it and evidence of adverse outcomes, deliberate hyperventilation continues to be widely practiced.[25-27] In the United States, 36 percent of board-certified neurosurgeons[25] and almost 50 percent of emergency physicians[26] routinely use prophylactic hyperventilation in patients with severe traumatic brain injury. The suggested indications for its use continue to vary: some suggest using it for suspected,[28] established,[27] or intractable[29] intracranial hypertension, whereas others recommend that it be used only for intracranial hypertension that is accompanied by neurologic deterioration.[30,31] In addition, contemporary textbooks recommend the induction of substantial hypocapnia (partial pressure of arterial carbon dioxide of approximately 25 mm Hg) as a preliminary measure after severe head trauma in both adults[3] and children.[5]

Other Forms of Coma

Because of its effects on intracranial pressure, hyperventilation has been advocated for the management of coma after near-drowning[4] or near-hanging, as well as for the management of cerebral edema in patients with diabetic ketoacidosis.[32] The latter recommendation is of particular concern in the light of the recent recognition of hypocapnia as a key predictor of the development of cerebral edema in children with diabetic ketoacidosis.[33]

Neonatal Care

Neonatal respiratory failure commonly involves pulmonary hypertension, right-to-left shunting, and profound hypoxemia. Hyperventilation to relieve pulmonary hypertension has been advocated for neonates with persistent pulmonary hypertension of the newborn[19,34] or with congenital diaphragmatic hernia.[35] In addition, in the resuscitation of neonates, hyperventilation could rapidly clear excess carbon dioxide resulting from bicarbonate administration and could counteract metabolic acidosis.[36] Previous recommendations included prolonged maintenance of a partial pressure of arterial carbon dioxide below 20 to 30 mm Hg in such infants.[37]

Anesthesia and Surgery

Moderate to severe hypocapnia (partial pressure of arterial carbon dioxide, 20 to 25 mm Hg) has, in the past, been widely advocated as an adjunct to general anesthesia.[38] Its proposed advantages include the minimization of spontaneous respiratory effort and a reduced requirement for sedative, analgesic, and muscle-relaxant medications.[38] The latter advantage may explain the widespread use of intraoperative hyperventilation in the 1960s[39] as a means of reducing the use of anesthetic medications and thus avoiding fetal depression immediately after cesarean section. The use of hypocapnia during general anesthesia remained common for at least the next two decades.[38]

Accidental Induction of Hypocapnia

Hypocapnia can develop as a result of excessive mechanical ventilation.[2,7,35] In addition, cardiopulmonary bypass,[6] high-frequency modes of ventilation,[14] and extracorporeal membrane oxygenation[15] have been associated with the development of unanticipated hypocapnia. The common use of these techniques in neonates, coupled with the potential for hypocapnia-associated intraventricular hemorrhage, suggests that neonates may represent the most vulnerable subgroup of patients (Fig. 2). Because clearance of metabolic acids from the cerebrospinal fluid after hemodialysis takes longer than systemic clearance, hyperventilation may occur, causing hypocapnic alkalosis in patients receiving long-term hemodialysis.[40]

Hypocapnia as a Common Component of Disease

Hypocapnia is also an inherent component of several disease states (Table 1) and is a consistent finding in patients with early asthma,[11] high-altitude pulmonary edema,[12] or acute lung injury.[41] Hypocapnia has long been recognized as the most common acid–base disturbance in critically ill patients,[9] and it is a consistent feature of both septic shock[10] and the systemic inflammatory response syndrome.[8] In fact, hypocapnia is a diagnostic criterion for the latter condition.[8] In addition, it is a prominent feature of diabetic ketoacidosis in children and is a key predictor of cerebral edema in such children.[33]

PATHOBIOLOGY OF HYPOCAPNIA

When it is mild, hypocapnia does not have serious effects in healthy persons. Symptoms and signs include paresthesias, palpitations, myalgic cramps, and seizures.[42] However, extensive data from a spectrum

Downloaded from www.nejm.org at CLEVELAND CLINIC on June 13, 2006 .
Copyright © 2002 Massachusetts Medical Society. All rights reserved.

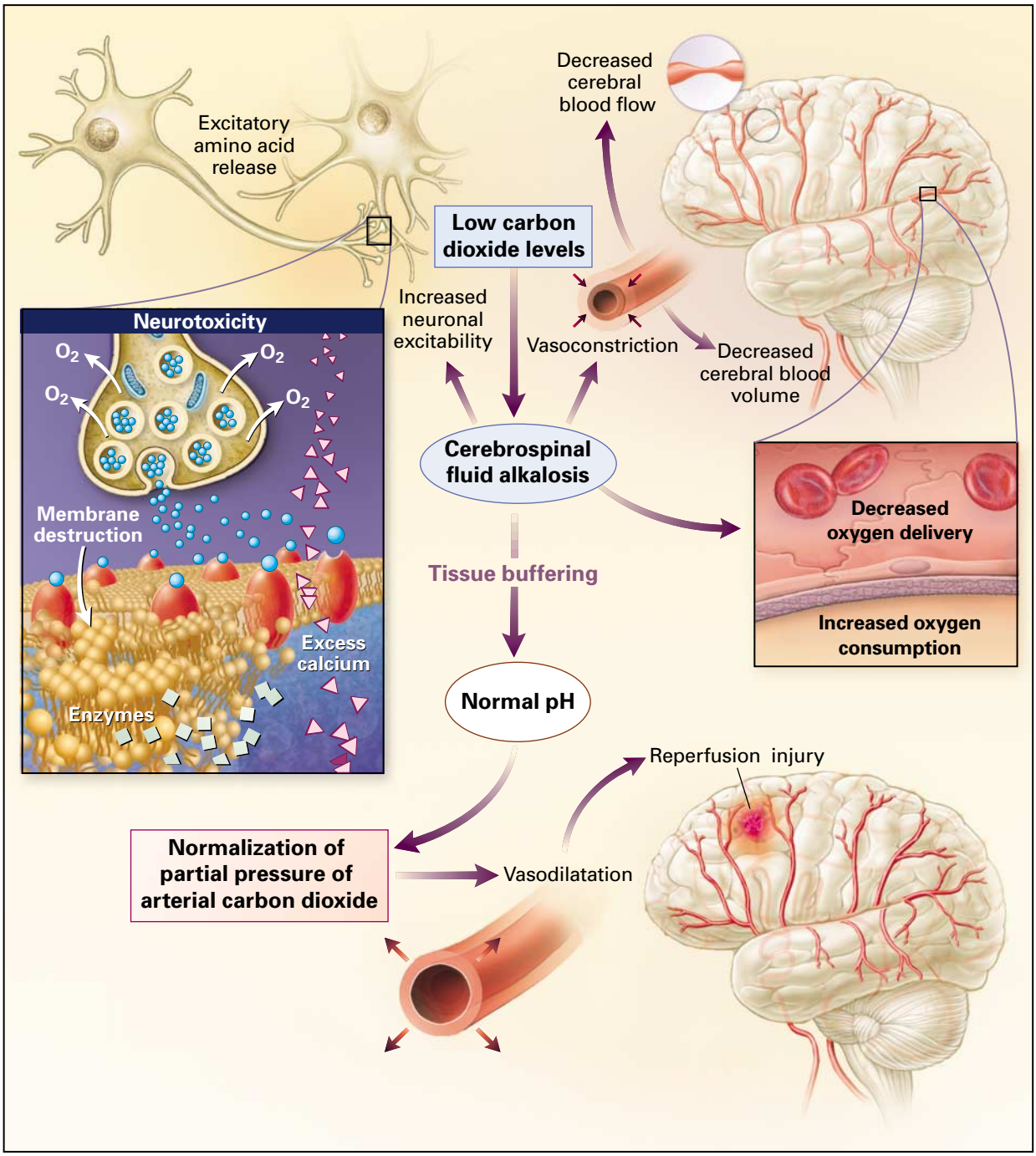

Figure 1. Neurologic Effects of Hypocapnia.

Systemic hypocapnia results in cerebrospinal fluid alkalosis, which decreases cerebral blood flow, cerebral oxygen delivery, and to a lesser extent, cerebral blood volume. The reduction in intracranial pressure may be lifesaving in patients in whom the pressure is severely elevated. However, hypocapnia-induced brain ischemia may occur because of vasoconstriction (impairing cerebral perfusion), reduced oxygen release from hemoglobin, and increased neuronal excitability, with the possible release of excitotoxins such as glutamate. Over time, cerebrospinal fluid pH and, hence, cerebral blood flow gradually return to normal. Subsequent normalization of the partial pressure of arterial carbon dioxide can then result in cerebral hyperemia, causing reperfusion injury to previously ischemic brain regions.

Downloaded from www.nejm.org at CLEVELAND CLINIC on June 13, 2006 .
Copyright © 2002 Massachusetts Medical Society. All rights reserved.

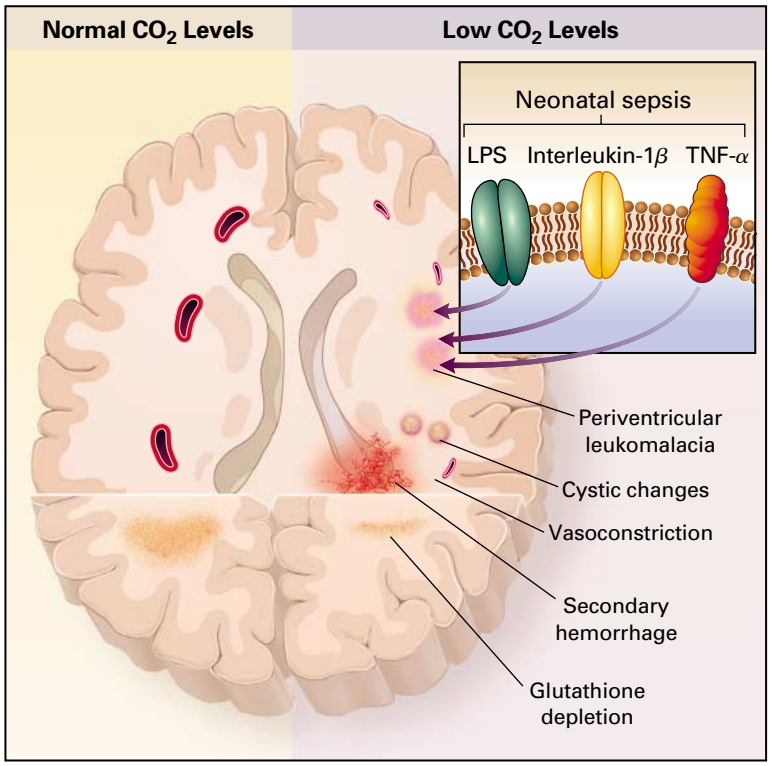

Figure 2. Effects of Hypocapnia on the Brain in Premature Infants.

Hypocapnia has been implicated in the pathogenesis of neonatal white-matter injuries, including periventricular leukomalacia, resulting in intraventricular hemorrhage. At normal carbon dioxide levels (left-hand side of figure), cerebral blood flow is determined by local metabolic demand. Prolonged or severe hypocapnia induces severe cerebral vasoconstriction, resulting in brain ischemia, particularly in poorly perfused areas of the brain such as watershed areas (right-hand side of figure). This ischemia may initiate white-matter destruction in the brain of premature infants. In addition, antioxidant depletion (caused by excitatory amino acids), lipopolysaccharide (LPS), and cytokines produced in response to sepsis, such as interleukin-1β and tumor necrosis factor α (TNF-α), potentiate the process. Finally, restoration of the normal partial pressure of arterial carbon dioxide can result in cerebral vasodilation, which may precipitate or contribute to intraventricular hemorrhage.

of physiological systems indicate that hypocapnia has the potential to propagate or initiate pathological processes. As a common aspect of many acute disorders, hypocapnia may have a pathogenic role in the development of systemic diseases.

Hypocapnia, Hypocapnic Alkalosis, and Acid–Base Status

Hypocapnic alkalosis is synonymous with respiratory alkalosis. Acute hypocapnia results in the immediate development of alkalosis; at any given moment, the extracellular pH may be predicted on the basis of the Henderson–Hasselbach formula:

$$\mathrm{pH} = \mathrm{pKa} + \log\left(\frac{\text{bicarbonate}}{\text{carbon dioxide}}\right).$$

The buffering response to acute hypocapnia is biphasic. First, hypocapnia in the extracellular fluid results in an immediate decrease in the intracellular-fluid carbon dioxide concentration, resulting in the transfer of chloride ions from the intracellular fluid to extracellular-fluid compartments. This chloride-ion egress, accompanied by a decrease in the concentrations of bicarbonate ions in extracellular fluid, is called tissue buffering.[16] Second, the renal response (inhibition of renal tubular reabsorption of bicarbonate ions) can begin within minutes and takes effect over a period of hours to days.[16] With long-term exposure, in the presence of normal renal function, the bicarbonate-ion level begins to fall, and the pH decreases but does not reach the normal value of 7.4 (i.e., a hydrogen ion concentration of 40 nmol per liter).

Downloaded from www.nejm.org at CLEVELAND CLINIC on June 13, 2006 .
Copyright © 2002 Massachusetts Medical Society. All rights reserved.

Respiratory versus Metabolic Alkalosis

The clinical physiology of acid–base disorders focuses on the conditions in the extracellular-fluid compartment. The carbon dioxide molecule is more lipid-soluble than the hydrogen ion, and therefore, acid–base alterations arising from an altered partial pressure of arterial carbon dioxide (respiratory alkalosis or respiratory acidosis) equilibrate across cell membranes (i.e., between extracellular and intracellular fluid) far more rapidly than do primary metabolic acid–base changes. Thus, at a given extracellular pH, the cellular effects are more pronounced when the alkalosis has a respiratory basis than when it has a metabolic basis. Nonetheless, most effects of extracellular hypocapnia result from alkalosis rather than from a low partial pressure of arterial carbon dioxide itself, as has been documented with respect to pulmonary,[43] cerebral,[44] and placental[45] perfusion, as well as myocardial effects.[46] Finally, an additional physiologically-based approach to the analysis of hydrogen-ion homeostasis, called the "strong ion difference" and initially described by Stewart, has been reviewed extensively.[47] According to this approach, the only factors that determine the pH reflect conservation of mass and electrochemical neutrality. These factors can be reduced to the following three groups: the strong ion difference (the sum of the concentrations of sodium, potassium, calcium, and magnesium minus the concentrations of chloride and lactate), the concentration of weak acids (proteins and phosphates), and the partial pressure of arterial carbon dioxide.

Hypocapnia, Cellular Metabolism, and Oxygenation

At the tissue level, an oxygen imbalance occurs when oxygen demand (which reflects the metabolic rate) outstrips oxygen supply. Hypocapnia may cause or aggravate cellular or tissue ischemia by both decreasing the cellular oxygen supply and increasing the cellular oxygen demand (Fig. 3). Although hypocapnia induced by hyperventilation may increase alveolar oxygen tension, multiple important pulmonary effects of hypocapnic alkalosis (e.g., bronchoconstriction,[48] attenuation of hypoxic pulmonary vasoconstriction,[49] and increased intrapulmonary shunting[49]) result in a net decrease in the partial pressure of arterial oxygen. Because both hypocapnia and alkalosis cause a leftward shift of the oxyhemoglobin dissociation curve, off-loading of oxygen at the tissue level is restricted.[50] In addition, hypocapnia causes systemic arterial vasoconstriction, decreasing the global and regional oxygen supply and compounding the reduction in the delivery of oxygen to tissue.[51]

Hypocapnia may increase the metabolic demand of tissue through cellular excitation or contraction (Fig. 3). Finally, alkalosis — especially respiratory alkalosis — inhibits the usual negative feedback by which a low pH limits the production of endogenous organic acids (such as lactate).[52]

Dose–Response Relation and Duration of Hypocapnia

Although mild hypocapnia results in few or no serious effects, marked hypocapnia may cause serious adverse effects.[30,50,53-55] However, data are limited, and extrapolation to all organ systems or disease entities might not be justified. If hypocapnia is prolonged, buffering (by decreasing the level of bicarbonate ions in extracellular fluid) results in a gradual return of the extracellular fluid pH toward normal. In the brain, because local pH determines the degree of cerebral vasoconstriction, such buffering normalizes cerebral blood flow,[44] decreasing the effectiveness of the reduction in intracranial pressure[56] and possibly attenuating the neuronal ischemia. This scenario in the central nervous system is complicated, because the restoration of the partial pressure of arterial carbon dioxide to normal after buffering may result in cerebral hyperperfusion[56,57] that can cause a rebound increase in intracranial pressure, aggravate reperfusion injury (Fig. 1), or precipitate hemorrhage (Fig. 2).

HYPOCAPNIA AND THE BRAIN

The mechanisms underlying the adverse neurologic consequences of hypocapnia are similar to those seen in other tissues when there is reperfusion injury and an imbalance between oxygen supply and demand. The control of acid–base homeostasis in the cerebrospinal fluid has been reviewed extensively,[58] with special attention to important specific issues in the regulation of the cerebral circulation.

Intracranial Hypertension

The cranial cavity has a fixed volume, and when the mass of any of its contents increases (as it may, for example, in patients with cerebral edema, hematoma after a head injury, or a brain tumor), a critical elevation of intracranial pressure may occur. This elevation in pressure may result in impaired cerebral perfusion, a risk of brain-stem herniation, and possibly, adverse outcomes from direct pressure on neuronal cells (Fig. 1). In order to reduce intracranial pressure, the volume of the cranial contents must be reduced. Hypocapnic alkalosis decreases the cerebral blood volume by means of potent cerebral vasoconstriction, thereby lowering intracranial pressure (Fig. 1).

Mechanisms of Deleterious Central Nervous System Effects

The beneficial effects of hypocapnia on intracranial pressure, however, may be outweighed by the effects of a reduced oxygen supply. If the reduction in cerebral blood flow is disproportionately greater than that of the intracranial blood volume,[59] cerebral ischemia can result.[60] In experimental cerebral ischemia,

Downloaded from www.nejm.org at CLEVELAND CLINIC on June 13, 2006 .
Copyright © 2002 Massachusetts Medical Society. All rights reserved.

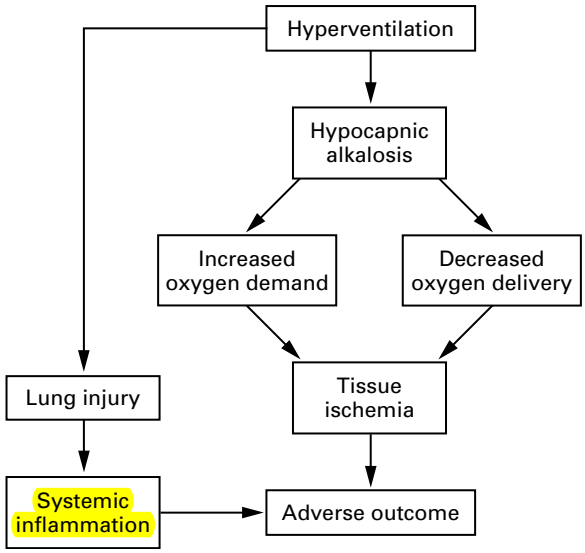

Figure 3. Effects of Hypocapnia on Global Oxygen Supply and Demand.

Hypocapnic alkalosis adversely alters the balance between global oxygen delivery and oxygen consumption. It decreases global and regional oxygen delivery through a combination of decreased systemic oxygen tension, tissue perfusion, and oxygen unloading at the tissue level. Conversely, hypocapnic alkalosis may increase the metabolic requirement for oxygen at the cellular level through physiological increases in cell excitation or contraction. It may also directly contribute to the pathogenesis of acute lung injury and systemic inflammation. These interrelated actions of hypocapnic alkalosis may critically compromise cellular survival and contribute to adverse outcomes.

hypocapnia increases the lactate production associated with ischemia,[61] although this may be explained in part by an inhibition of brain phosphofructokinase activity that is unrelated to ischemia.[62] In the past, hypocapnia was thought to increase regional perfusion to ischemic parts of the brain at the expense of uninjured brain tissue; this phenomenon, termed "inverse steal," does not actually occur.[63] In fact, hypocapnia increases cerebral oxygen demand. Hypocapnia increases neuronal excitability, seizure activity,[64] and anaerobic metabolism.[61] Finally, the presence of hypocapnia during cardiopulmonary resuscitation may worsen brain injury.[65] Hypocapnic potentiation of seizure activity, in addition to increasing oxygen demand, augments production of the cytotoxic excitatory amino acids associated with seizures.[66] Hypocapnia may also induce increases in neuronal dopamine,[67] which may increase the risk of convulsions.

Deleterious Central Nervous System Effects in Clinical Context

Neonatal Brain Injury

Hypocapnia appears to be particularly injurious to the brain in premature infants (Fig. 2). In preterm infants who are exposed to severe hypocapnia (a partial pressure of arterial carbon dioxide of less than 15 mm Hg [<2 kPa]), even of relatively short duration, considerable long-term neurologic abnormalities may develop[68]; such abnormalities are associated with many forms of pathologic neonatal brain conditions (Table 2). Neurovascular factors that may predispose the immature brain to such injury include poorly developed vascular supply to vulnerable areas,[69] antioxidant depletion by excitatory amino acids,[70] and the lipopolysaccharide[71] and cytokine[72] effects that potentiate destruction of white matter (Fig. 2).

Data from neonates clearly suggest that severe hypocapnia after hyperventilation,[68] high-frequency ventilation,[14] and extracorporeal membrane oxygenation[15] contribute to adverse neurologic outcomes. In addition, abrupt termination of hyperventilation results in reactive cerebral hyperemia,[57] which may cause intracranial hemorrhage in premature neonates.[57] Because hypocapnia, induced by accident or design, is common in such neonates, awareness of these associations is extremely important.

Traumatic Brain Injury

In patients with traumatic brain injury, prophylactic hyperventilation is actually associated with worse outcomes,[1] which may be explained in part by reduced cerebral oxygenation.[55] Thus, although intracranial pressure may decrease transiently, it may do so at the expense of cerebral perfusion.[59] In addition, hypocapnia may exacerbate secondary brain injury, because increased cerebral vascular reactivity and vasoconstriction can result in decreases in regional cerebral blood flow.[60] Therefore, hypocapnia may result in a disproportionate (regional) decrease in cerebral blood flow, without a further decrease in intracranial pressure.[18] Because of these possibilities, a panel of experts has recommended against the prophylactic use of hyperventilation.[30]

Acute Stroke

Hyperventilation has classically been advocated as a therapy for patients with acute stroke, intended to reduce intracranial pressure (Fig. 1), to induce inverse steal in ischemic areas of the brain, and to correct acidosis in the zones around ischemic tissue. Despite the theoretical physiological benefits, as described earlier, positive outcomes have not been realized; rather, patients do poorly.[73]

Postoperative Psychomotor Dysfunction

Cognitive impairment after general anesthesia is a cause for concern, because the growing trend toward ambulatory (same-day) anesthesia and surgery (and away from overnight stays in hospitals after surgery) results in the discharge of patients at an earlier

Downloaded from www.nejm.org at CLEVELAND CLINIC on June 13, 2006 .
Copyright © 2002 Massachusetts Medical Society. All rights reserved.

stage of their recovery. Postoperative cognitive dysfunction is of particular concern in the elderly, who are more susceptible to it and more vulnerable to its consequences. Acute hypocapnia is common during general anesthesia, and otherwise healthy patients who are subjected to hypocapnia during general anesthesia have been found to have impaired psychomotor function (Table 2) for up to six days.[74] Such effects are especially pronounced in older patients.[75] The causative role of hypocapnia in postoperative cognitive dysfunction is underscored by the finding that exposure to an elevated partial pressure of arterial carbon dioxide during anesthesia appears to enhance postoperative neuropsychologic performance.[75] Reassuringly, according to studies of postoperative cognition in otherwise healthy patients, the adverse effects of hypocapnia, although often prolonged, appear to be reversible.[74,75]

Panic Disorder

The exact role of hypocapnia in panic disorder is unclear. However, metabolic alkalosis induces panic in a substantial proportion of patients with panic disorder,[76] and the central nervous system signs seen during panic attacks (e.g., dizziness, lightheadedness, confusion, and syncope) are consistent with the presence of hypocapnia-induced cerebral hypoxia.[77]

Hypocapnia may be an important underlying mechanistic link between panic disorder and other diseases. For example, patients with asthma and panic disorder may be at increased risk for other illnesses.[78] A majority of patients with recurrent chest pain but no angiographic evidence of coronary artery disease meet the diagnostic criteria for panic disorder. Because hypocapnia is common in both of these groups, the possibility of underlying organic disease should always be considered in patients with hypocapnia.

TABLE 2. ADVERSE NEUROLOGIC AND MYOCARDIAL EFFECTS OF HYPOCAPNIA.

Brain injury in neonates
Multicystic encephalomalacia
Cystic periventricular leukomalacia
Pontosubicular necrosis
Cerebral infarction
Reactive hyperemia and hemorrhage
Impairment of cerebral function in adults
Increased time to regain consciousness, increased reaction times
Poorer psychomotor performance, diminished higher intellectual functions
Personality changes
Myocardial effects
Decreased myocardial oxygen supply
Reduced coronary flow and collateral flow
Increased coronary vascular resistance, increased risk of coronary-artery spasm
Increased coronary microvascular leakage
Increases in platelet count and aggregation
Increased myocardial oxygen demand
Increased oxygen extraction
Increased (and later decreased) contractility
Increased intracellular calcium concentration
Increased systemic vascular resistance
Myocardial ischemia
Reperfusion injury

Altitude Sickness

Sudden exposure to very high altitude can result in long-term neurologic impairment. However, the central nervous system impairment seen in previously healthy mountaineers after exposure to extremely high altitudes has been demonstrated to be most closely correlated with the degree of hypocapnia — not the level of hypoxia — attained.[79] The cause of acute central nervous system symptoms at high altitudes appears to be alkalosis due to increased minute ventilation; such alkalosis can be prevented by pretreatment with acetazolamide, which ameliorates the symptoms of high-altitude pulmonary edema.[80]

HYPOCAPNIA AND THE LUNG

Adverse pulmonary consequences of experimentally induced hypocapnia have been described in terms of effects on airways, alveolar-capillary permeability, lung compliance, and pulmonary vasculature, as well as the overall effect on lung injury.

Hypocapnia and the Tracheobronchial Tree

Airway hypocapnia increases airway resistance[81] by inducing bronchospasm and increasing airway-microvasculature permeability (Fig. 4).[82] Bronchoconstriction induced by hypocapnia may have adverse consequences.[11,82] Although hypocapnia is a consistent feature of asthma, it is not clear whether it has a clinically important pathogenic role. More than 30 years ago, it was hypothesized that hypocapnia resulting from hyperventilation during an asthma attack may perpetuate the bronchospasm and culminate in a cycle of progressive hypocapnia and increasing bronchospasm (Fig. 4).[83] This theory is seldom discussed now, but considerable experimental evidence supports it.[11,48,81,82] Furthermore, clinical data indicate that hypocapnia may contribute to increased airway resistance in patients with asthma.[11] In addition, alveolar hypocapnia occurs during cardiopulmonary bypass, resulting in bronchoconstriction, increased airway resistance, and reduced lung compliance.[84] These changes are reversed by the addition of inspired carbon dioxide.[84]

Acute Lung Injury

Pathophysiology

Aside from changes in airway resistance, hypocapnia causes increased pulmonary-capillary permeability,[53] parenchymal injury,[85] and depletion of lamellar

Downloaded from www.nejm.org at CLEVELAND CLINIC on June 13, 2006 .
Copyright © 2002 Massachusetts Medical Society. All rights reserved.

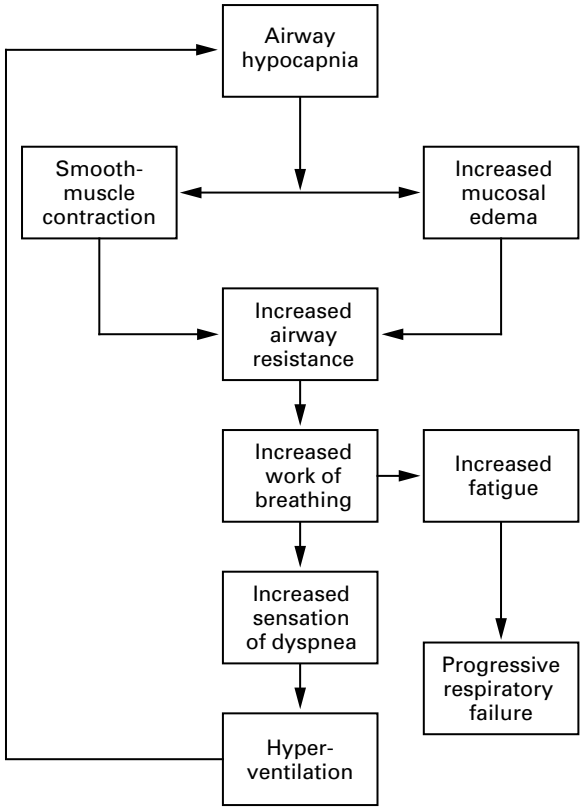

Figure 4. Potential Role of Hypocapnia in Asthma.

Hypocapnia increases airway resistance by causing bronchospasm and increased microvascular permeability. These effects, in turn, increase the work of breathing and may potentiate the sensation of dyspnea, leading to further hyperventilation, progressive hypocapnia, and increasing bronchospasm, culminating in a cycle of fatigue and respiratory failure.

bodies.[86] These negative effects are all ameliorated by supplemental carbon dioxide.[53,85,86] Hypocapnia decreases overall lung compliance in humans,[87] perhaps because of effects on surfactant function. Finally, alveolar hypocapnia attenuates hypoxic pulmonary vasoconstriction, worsening intrapulmonary shunt and systemic oxygenation.[49]

Clinical Consequences

Hyperventilation and hypocapnic alkalosis frequently coexist in patients with lung injury[88]; moreover, hyperventilation can cause acute lung injury. Although it is difficult to separate hyperventilation from hypocapnic alkalosis, the association of hyperventilation, hypocapnia, and worsened lung injury is increasingly well documented.[2,7,35] Such lung injury and related outcomes are conventionally considered to be due to excessive mechanical lung stretch. Thus, hypocapnia is conventionally thought to play a passive — not a pathogenic — part in lung injury. However, the concept that hypocapnia might have a pathogenic role in the acute respiratory distress syndrome was first proposed in 1971 by Trimble and colleagues.[41] They reported that, in a small study of patients with post-traumatic lung injury, hypocapnia was associated with worsened pulmonary function that was reversed by supplemental inspired carbon dioxide.[41]

Neonatal Lung Dysfunction

Both hyperventilation and hypocapnia have been identified as independent determinants of long-term pulmonary dysfunction in survivors of neonatal intensive care units.[35] As noted above, hypocapnia is common in critically ill neonates and can potentiate many pathogenic lung processes; it is possible that hypocapnia may have a causative role in the development of bronchopulmonary dysplasia.[35]

HYPOCAPNIA AND THE CARDIOVASCULAR SYSTEM

Cardiovascular effects of hypocapnic alkalosis include alterations in myocardial oxygenation and cardiac rhythm (Table 2). In addition, hypocapnia may have a causal role in digital-artery spasm in peripheral vascular disorders (e.g., Raynaud's disease), possibly, at least in part, because hypocapnic alkalosis causes or worsens vasoconstriction and enhances platelet aggregation.[89]

Myocardial Ischemia

Acute hypocapnia decreases myocardial oxygen delivery while increasing oxygen demand (Table 2).[90] Oxygen demand is increased through increases in myocardial contractility[91] and systemic vascular resistance.[92] In addition, hypocapnia may precipitate thrombosis[93] through increased platelet levels or platelet aggregation. These effects may contribute to the variant angina that characteristically occurs with hyperventilation. Thus, hypocapnia may contribute to clinically relevant acute coronary syndromes.

Cardiac Dysrhythmias

Hypocapnia has been clearly linked to the development of arrhythmias, both in critically ill patients[9] and in patients with panic disorder.[77] Such effects may be secondary to ischemia, but specific direct myocardial effects may occur. Conversely, hypocapnic alkalosis may be therapeutically effective in arrhythmias induced by local anesthetics[46] or tricyclic antidepressants[94]; in these cases, the alkalosis is the determinant of efficacy.

Downloaded from www.nejm.org at CLEVELAND CLINIC on June 13, 2006 .
Copyright © 2002 Massachusetts Medical Society. All rights reserved.

HYPOCAPNIA AND HEART–LUNG INTERACTIONS

Central sleep apnea results in hypoxemia, increased sympathetic nervous system activity, and daytime somnolence; when it occurs in patients with congestive heart failure, it increases the risk of death. An enhanced ventilatory response to carbon dioxide may contribute to the development of central sleep apnea in some patients with congestive heart failure,[95] and hypocapnia triggers periodic respirations in these patients.[96] One of the mechanisms by which application of noninvasive positive airway pressure reduces central sleep apnea is by increasing hemoglobin oxygen saturation and increasing the partial pressure of arterial carbon dioxide toward or above the apneic threshold.[96] In fact, central sleep apnea is predicted by the presence of hypocapnia during waking hours.[97] Thus, hypocapnia is a common finding in patients with sleep apnea and may be pathogenic.

HYPOCAPNIA AND HUMAN DEVELOPMENT

In pregnant women, the partial pressure of arterial carbon dioxide is maintained at approximately 10 mm Hg lower than in nonpregnant women (Table 1). This physiologic state is associated with lowered serum bicarbonate-ion concentrations, which revert to normal values shortly after delivery. However, further lowering of the partial pressure of arterial carbon dioxide — even for a short duration, such as during anesthesia for cesarean section — may have serious adverse affects on the fetus (such as decreased fetal oxygen tension, increased base deficit, lower Apgar scores, and delayed onset of rhythmic neonatal breathing).[98] These effects may be prevented by administering inspired carbon dioxide.[98] Alkalosis associated with hypocapnia decreases placental perfusion, reduces umbilical-vein oxygen tension,[99] and causes reflex spasm of the umbilical vein.[45] Because carbon dioxide increases fetal respiration, which may cause increased stretch and distention of the lung,[100] fetal hypocapnia may impair pulmonary maturation.

SUMMARY

Hypocapnia is neither a benign clinical entity nor an epiphenomenon. On the contrary, increasing evidence suggests that hypocapnia appears to induce substantial adverse physiological and medical effects. Thus, the decision to institute hypocapnia for therapeutic purposes should be undertaken only after careful consideration of the risks and benefits and should in general be limited to emergency management of life-threatening increases in intracranial pressure or pulmonary-vascular resistance. The risk of accidental hypocapnia should be recognized and measures taken to prevent it. Prophylactic induction of hypocapnia currently has no clinical role.

Supported by the Canadian Institutes of Health Research. Dr. Kavanagh is the recipient of a Premier's Research Excellence award from the Ontario Ministry of Energy, Science, and Technology, and Dr. Laffey is the recipient of a Training Fellowship from the Health Research Board, Ireland.

We are indebted to Drs. D. Bohn, A.C. Bryan, K. Killian, E. Phillipson, and A.K. Tanswell for their critical review of the manuscript; and to Theresa and Bill Sakno for assistance with the figures.

REFERENCES

1. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg 1991;75:731-9.
2. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. Pediatrics 1985;76:488-94.
3. Andrews BT. General management and intensive care of the neurosurgical patient. In: Grossman RG, Loftus CM, eds. Principles of neurosurgery. 2nd ed. Philadelphia: Lippincott–Raven, 1999:3-14.
4. Rowin ME, Christensen D, Allen EM. Pediatric drowning and near-drowning. In: Rogers MC, Helfaer MA, eds. Handbook of pediatric intensive care. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1999:445-58.
5. Rosman PN. Nervous system. In: Burg FD, Wald ER, Ingelfinger JR, Polin RA, eds. Gellis & Kagan's current pediatric therapy 16. Philadelphia: W.B. Saunders, 1999:431-6.
6. Nevin M, Colchester AC, Adams S, Pepper JR. Evidence for involvement of hypocapnia and hypoperfusion in aetiology of neurological deficit after cardiopulmonary bypass. Lancet 1987;2:1493-5.
7. Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338:347-54.
8. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644-55.
9. Mazzara JT, Ayres SM, Grace WJ. Extreme hypocapnia in the critically ill patient. Am J Med 1974;56:450-6.
10. Blair E. Hypocapnia and gram-negative bacteremic shock. Am J Surg 1970;119:433-9.
11. van den Elshout FJ, van Herwaarden CL, Folgering HT. Effects of hypercapnia and hypocapnia on respiratory resistance in normal and asthmatic subjects. Thorax 1991;46:28-32.
12. Horrobin D. High altitude pulmonary oedema: pathophysiology and recommendations for prevention and treatment. East Afr Med J 1972;49:327-31.
13. Phillipson EA. Disorders of ventilation. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL, eds. Harrison's principles of internal medicine. 13th ed. New York: McGraw-Hill, 1994:1234-40.
14. Riphagen S, Bohn D. High frequency oscillatory ventilation. Intensive Care Med 1999;25:1459-62.
15. Graziani LJ, Gringlas M, Baumgart S. Cerebrovascular complications and neurodevelopmental sequelae of neonatal ECMO. Clin Perinatol 1997; 24:655-75.
16. Adrogué HJ, Madias NE. Management of life-threatening acid–base disorders. N Engl J Med 1998;338:107-11.
17. Darby JM, Yonas H, Marion DW, Latchaw RE. Local "inverse steal" induced by hyperventilation in head injury. Neurosurgery 1988;23:84-8.
18. Marion DW, Firlik A, McLaughlin MR. Hyperventilation therapy for severe traumatic brain injury. New Horiz 1995;3:439-47.
19. Drummond WH, Gregory GA, Heymann MA, Phibbs RA. The independent effects of hyperventilation, tolazoline, and dopamine on infants with persistent pulmonary hypertension. J Pediatr 1981;98:603-11.
20. Miller JD. Medical management of acute head injury. In: Swash M, Oxbury J, eds. Clinical neurology. Edinburgh, Scotland: Churchill Livingstone, 1991:694-7.
21. Ruben BH, Greenberg J. Neurologic injury: prevention and initial care. In: Civetta JM, Taylor RW, Kirby RR, eds. Critical care. 2nd ed. Philadelphia: J.B. Lippincott, 1992:725-45.
22. Brown M. ICU — critical care. In: Barash PG, Cullen BF, Stoelting RK, eds. Clinical anesthesia. Philadelphia: J.B. Lippincott, 1989:1455-76.
23. Hayek DA, Veremakis C. Physiologic concerns during brain resuscita-

Downloaded from www.nejm.org at CLEVELAND CLINIC on June 13, 2006 .
Copyright © 2002 Massachusetts Medical Society. All rights reserved.

tion. In: Civetta JM, Taylor RW, Kirby RR, eds. Critical care. 2nd ed. Philadelphia: J.B. Lippincott, 1992:1449-66.
24. Heffner JE, Sahn SA. Controlled hyperventilation in patients with intracranial hypertension: application and management. Arch Intern Med 1983;143:765-9.
25. Marion DW, Spiegel TP. Changes in the management of severe traumatic brain injury: 1991-1997. Crit Care Med 2000;28:16-8.
26. Huizenga JE, Zink B, Maio R, Hill E. The penetrance of head injury management guidelines into the practice patterns of Michigan emergency physicians. Acad Emerg Med 2000;7:1171.
27. Himmelseher S, Pfenninger E. Neuroprotektion in der Neuroanästhesie: die gegenwärtige praxis in Deutschland. Anaesthesist 2000;49:412-9.
28. Yundt KD, Diringer MN. The use of hyperventilation and its impact on cerebral ischemia in the treatment of traumatic brain injury. Crit Care Clin 1997;13:163-84.
29. Allen CH, Ward JD. An evidence-based approach to management of increased intracranial pressure. Crit Care Clin 1998;14:485-95.
30. Bullock RM, Chesnut RM, Clifton GL, et al. Initial management. J Neurotrauma 2000;17:463-9.
31. Brain Trauma Foundation. The use of hyperventilation in the acute management of severe traumatic brain injury. J Neurotrauma 1996;13:699-703.
32. Edge JA. Management of diabetic ketoacidosis in childhood. Br J Hosp Med 1996;55:508-12.
33. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med 2001;344:264-9.
34. Cyanosis and congenital heart disease. In: Black JA, Whitfield MF. Neonatal emergencies: early detection and management. 2nd ed. London: Butterworth-Heinemann, 1991:166-77.
35. Garland JS, Buck RK, Allred EN, Leviton A. Hypocarbia before surfactant therapy appears to increase bronchopulmonary dysplasia risk in infants with respiratory distress syndrome. Arch Pediatr Adolesc Med 1995;149:617-22.
36. Peckham GJ. Resuscitation of the newborn. In: Holbrook PR, ed. Textbook of pediatric critical care. Philadelphia: W.B. Saunders, 1993:61-70.
37. Respiratory distress. In: Harper RG, Yoon JJ. Handbook of neonatology. 2nd ed. Chicago: Year Book Medical, 1987:167-257.
38. Acid-base and electrolyte balance. In: Atkinson RS, Rushman GB, Lee JA. A synopsis of anaesthesia. Bristol, England: IOP Publishing, 1987:75-84.
39. Cohen EN. Thiopental-curare-nitrous oxide anesthesia for cesarean section: 1950 to 1960. Anesth Analg 1962;41:122-7.
40. Rosenbaum BJ, Coburn JW, Shinaberger JH, Massry SG. Acid-base status during the interdialytic period in patients maintained with chronic hemodialysis. Ann Intern Med 1969;71:1105-11.
41. Trimble C, Smith DE, Rosenthal MH, Fosburg RG. Pathophysiologic role of hypocarbia in post-traumatic pulmonary insufficiency. Am J Surg 1971;122:633-8.
42. Gluck SL. Acid-base. Lancet 1998;352:474-9.
43. Schreiber MD, Heymann MA, Soifer SJ. Increased arterial pH, not decreased $PaCO_2$, attenuates hypoxia-induced pulmonary vasoconstriction in newborn lambs. Pediatr Res 1986;20:113-7.
44. Fencl V, Vale JR, Broch JR. Cerebral blood flow and pulmonary ventilation in metabolic acidosis and alkalosis. Scand J Clin Lab Invest 1968;22:Suppl 102:VIII-B.
45. Motoyama EK, Rivard G, Acheson F, Cook CD. The effect of changes in maternal pH and P-CO_2 on the P-O_2 of fetal lambs. Anesthesiology 1967;28:891-903.
46. Porter JM, Markos F, Snow HM, Shorten GD. Effects of respiratory and metabolic pH changes and hypoxia on ropivacaine-induced cardiotoxicity in dogs. Br J Anaesth 2000;84:92-4.
47. Fencl V, Leith DE. Stewart's quantitative acid-base chemistry: applications in biology and medicine. Respir Physiol 1993;91:1-16.
48. O'Cain CF, Hensley MJ, McFadden ER Jr, Ingram RH Jr. Pattern and mechanism of airway response to hypocapnia in normal subjects. J Appl Physiol 1979;47:8-12.
49. Domino KB, Lu Y, Eisenstein BL, Hlastala MP. Hypocapnia worsens arterial blood oxygenation and increases VA/Q heterogeneity in canine pulmonary edema. Anesthesiology 1993;78:91-9.
50. Nunn JF. Applied respiratory physiology. 3rd ed. London: Butterworths, 1987.
51. Guzman JA, Kruse JA. Gut mucosal-arterial PCO_2 gradient as an indicator of splanchnic perfusion during systemic hypo- and hypercapnia. Crit Care Med 1999;27:2760-5.
52. Hood VL, Tannen RL. Protection of acid–base balance by pH regulation of acid production. N Engl J Med 1998;339:819-26.
53. Laffey JG, Engelberts D, Kavanagh BP. Injurious effects of hypocapnic alkalosis in the isolated lung. Am J Respir Crit Care Med 2000;162:399-405.
54. Shepard JW Jr, Dolan GF, Yu SY. Factors regulating lamellar body volume density of type II pneumocytes in excised dog lungs. J Appl Physiol 1982;53:555-62.
55. Skippen P, Seear M, Poskitt K, et al. Effect of hyperventilation on regional cerebral blood flow in head-injured children. Crit Care Med 1997;25:1402-9.
56. Raichle ME, Posner JB, Plum F. Cerebral blood flow during and after hyperventilation. Arch Neurol 1970;23:394-403.
57. Gleason CA, Short BL, Jones MD Jr. Cerebral blood flow and metabolism during and after prolonged hypocapnia in newborn lambs. J Pediatr 1989;115:309-14.
58. Kazemi H, Johnson DC. Regulation of cerebrospinal fluid acid-base balance. Physiol Rev 1986;66:953-1037.
59. Fortune JB, Feustel PJ, deLuna C, Graca L, Hasselbarth J, Kupinski AM. Cerebral blood flow and blood volume in response to O_2 and CO_2 changes in normal humans. J Trauma 1995;39:463-71.
60. Weckesser M, Posse S, Olthoff U, Kemna L, Dager S, Muller-Gartner HW. Functional imaging of the visual cortex with bold-contrast MRI: hyperventilation decreases signal response. Magn Reson Med 1999;41:213-6.
61. Vannucci RC, Brucklacher RM, Vannucci SJ. Effect of carbon dioxide on cerebral metabolism during hypoxia-ischemia in the immature rat. Pediatr Res 1997;42:24-9.
62. Norberg K, Siesjo BK. Cerebral metabolism in hypoxic hypoxia. I. Pattern of activation of glycolysis: a re-evaluation. Brain Res 1975;86:31-44.
63. Ruta TS, Drummond JC, Cole DJ. The effect of acute hypocapnia on local cerebral blood flow during middle cerebral artery occlusion in isoflurane anesthetized rats. Anesthesiology 1993;78:134-40.
64. Huttunen J, Tolvanen H, Heinonen E, et al. Effects of voluntary hyperventilation on cortical sensory responses: electroencephalographic and magnetoencephalographic studies. Exp Brain Res 1999;125:248-54.
65. Safar P, Xiao F, Radovsky A, et al. Improved cerebral resuscitation from cardiac arrest in dogs with mild hypothermia plus blood flow promotion. Stroke 1996;27:105-13.
66. Graham EM, Apostolou M, Mishra OP, Delivoria-Papadopoulos M. Modification of the N-methyl-D-aspartate (NMDA) receptor in the brain of newborn piglets following hyperventilation induced ischemia. Neurosci Lett 1996;218:29-32.
67. Pastuszko P, Wilson DF. Activation of tyrosine hydroxylase in striatum of newborn piglets in response to hypocapnic ischemia and recovery. Adv Exp Med Biol 1997;411:65-73.
68. Greisen G, Munck H, Lou H. Severe hypocarbia in preterm infants and neurodevelopmental deficit. Acta Paediatr Scand 1987;76:401-4.
69. De Reuck J. Cerebral angioarchitecture and perinatal brain lesions in premature and full-term infants. Acta Neurol Scand 1984;70:391-5.
70. Oka A, Belliveau MJ, Rosenberg PA, Volpe JJ. Vulnerability of oligodendroglia to glutamate: pharmacology, mechanisms, and prevention. J Neurosci 1993;13:1441-53.
71. Gilles FH, Leviton A, Kerr CS. Endotoxin leucoencephalopathy in the telencephalon of the newborn kitten. J Neurol Sci 1976;27:183-91.
72. Yoon BH, Romero R, Kim CJ, et al. High expression of tumour necrosis factor-α and interleukin 6 in periventricular leukomalacia. Am J Obstet Gynecol 1997;177:406-11.
73. Plum F. Hyperpnea, hyperventilation, and brain dysfunction. Ann Intern Med 1972;76:328.
74. Wollman SB, Orkin LR. Postoperative human reaction time and hypocarbia during anaesthesia. Br J Anaesth 1968;40:920-6.
75. Hovorka J. Carbon dioxide homeostasis and recovery after general anaesthesia. Acta Anaesthesiol Scand 1982;26:498-504.
76. Coplan JD, Goetz R, Klein DF, et al. Plasma cortisol concentrations preceding lactate-induced panic: psychological, biochemical, and physiological correlates. Arch Gen Psychiatry 1998;55:130-6.
77. Hanashiro PK. Hyperventilation: benign symptom or harbinger of catastrophe? Postgrad Med 1990;88:191-3, 196.
78. Lehrer PM. Emotionally triggered asthma: a review of research literature and some hypotheses for self-regulation therapies. Appl Psychophysiol Biofeedback 1998;23:13-41.
79. Hornbein TF, Townes BD, Schoene RB, Sutton JR, Houston CS. The cost to the central nervous system of climbing to extremely high altitude. N Engl J Med 1989;321:1714-9.
80. Hackett PH, Roach RC. High-altitude illness. N Engl J Med 2001;345:107-14.
81. Jamison JP, Glover PJ, Wallace WF. Comparison of the effects of inhaled ipratropium bromide and salbutamol on the bronchoconstrictor re-

Downloaded from www.nejm.org at CLEVELAND CLINIC on June 13, 2006 .
Copyright © 2002 Massachusetts Medical Society. All rights reserved.

sponse to hypocapnic hyperventilation in normal subjects. Thorax 1987; 42:809-14.
82. Reynolds AM, McEvoy RD. Tachykinins mediate hypocapnia-induced bronchoconstriction in guinea pigs. J Appl Physiol 1989;67:2454-60.
83. Hypoxemia and hypocapnia in asthma. N Engl J Med 1968;278:1068.
84. Bayindir O, Akpinar B, Ozbek U, et al. The hazardous effects of alveolar hypocapnia on lung mechanics during weaning from cardiopulmonary bypass. Perfusion 2000;15:27-31.
85. Kolobow T, Moretti MP, Fumagalli R, et al. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation: an experimental study. Am Rev Respir Dis 1987;135:312-5.
86. Shepard JW Jr, Hauer D, Miyai K, Moser KM. Lamellar body depletion in dogs undergoing pulmonary artery occlusion. J Clin Invest 1980; 66:36-42.
87. Cutillo A, Omboni E, Perondi R, Tana F. Effect of hypocapnia on pulmonary mechanics in normal subjects and in patients with chronic obstructive lung disease. Am Rev Respir Dis 1974;110:25-33.
88. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill — too little of a good thing? Lancet 1999;354:1283-6.
89. Williams H, Freeman LJ, Nixon PG. Hyperventilation and Raynaud's disease. Postgrad Med J 1987;63:377-9.
90. Kazmaier S, Weyland A, Buhre W, et al. Effects of respiratory alkalosis and acidosis on myocardial blood flow and metabolism in patients with coronary artery disease. Anesthesiology 1998;89:831-7.
91. Boix JH, Marin J, Enrique E, Monferrer J, Bataller A, Servera E. Modifications of tissular oxygenation and systemic hemodynamics after the correction of hypocapnia induced by mechanical ventilation. Rev Esp Fisiol 1994;50:19-26.
92. Richardson DW, Kontos HA, Raper AJ, Patterson JL Jr. Systemic circulatory responses to hypocapnia in man. Am J Physiol 1972;223:1308-12.
93. Staubli M, Vogel F, Bartsch P, Fluckiger G, Ziegler WH. Hyperventilation-induced changes of blood cell counts depend on hypocapnia. Eur J Appl Physiol Occup Physiol 1994;69:402-7.
94. Dziukas LJ, Vohra J. Tricyclic antidepressant poisoning. Med J Aust 1991;154:344-50.
95. Javaheri S. A mechanism of central sleep apnea in patients with heart failure. N Engl J Med 1999;341:949-54.
96. Naughton MT, Benard DC, Rutherford R, Bradley TD. Effect of continuous positive airway pressure on central sleep apnea and nocturnal PCO_2 in heart failure. Am J Respir Crit Care Med 1994;150:1598-604.
97. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999;160:1101-6.
98. Peng AT, Blancato LS, Motoyama EK. Effect of maternal hypocapnia v. eucapnia on the foetus during caesarean section. Br J Anaesth 1972;44: 1173-8.
99. Cook PT. The influence on foetal outcome of maternal carbon dioxide tension at caesarean section under general anaesthesia. Anaesth Intensive Care 1984;12:296-302.
100. Nagai A, Thurlbeck WM, Deboeck C, Ioffe S, Chernick V. The effect of maternal CO_2 breathing on lung development of fetuses in the rabbit: morphologic and morphometric studies. Am Rev Respir Dis 1987;135: 130-6.

Copyright © 2002 Massachusetts Medical Society.

POSTING PRESENTATIONS AT MEDICAL MEETINGS ON THE INTERNET

Posting an audio recording of an oral presentation at a medical meeting on the Internet, with selected slides from the presentation, will not be considered prior publication. This will allow students and physicians who are unable to attend the meeting to hear the presentation and view the slides. If there are any questions about this policy, authors should feel free to call the *Journal*'s Editorial Offices.

Downloaded from www.nejm.org at CLEVELAND CLINIC on June 13, 2006 .
Copyright © 2002 Massachusetts Medical Society. All rights reserved.