

## 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.<sup>1,2</sup> Despite concern about adverse effects, the induction of hypocapnia has commonly been recommended for diverse disease states.<sup>3-5</sup> Thus, hypocapnia, whether produced deliberately<sup>3-5</sup> or accidentally,<sup>6,7</sup> remains prevalent in clinical practice (Table 1). In addition, hypocapnia is a common component of many acute illnesses, although its importance is often underestimated.<sup>8-12</sup> 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<sub>2</sub>) reflects the balance between the production and elimination of carbon dioxide (CO<sub>2</sub>), as described by the following formula:

$$\text{PaCO}_2 \text{ is proportional to } \frac{\text{CO}_2 \text{ production}}{\text{CO}_2 \text{ elimination}} + \text{inspired CO}_2.$$

The volume of inspired carbon dioxide is usually negligible, whereas reduced carbon dioxide produc-

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.

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, $\beta$ -adrenergic agonists, progesterone
Miscellaneous
Fever, sepsis, pain, pregnancy

tion 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).<sup>13</sup> 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.<sup>6,14,15</sup>

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.<sup>16</sup>

## 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<sup>17,18</sup> or neonatal pulmonary vascular resistance<sup>19</sup>

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<sup>20-24</sup> — sometimes resulting in very severe hypocapnia<sup>21-24</sup> — 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.<sup>25-27</sup> In the United States, 36 percent of board-certified neurosurgeons<sup>25</sup> and almost 50 percent of emergency physicians<sup>26</sup> 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,<sup>28</sup> established,<sup>27</sup> or intractable<sup>29</sup> intracranial hypertension, whereas others recommend that it be used only for intracranial hypertension that is accompanied by neurologic deterioration.<sup>30,31</sup> 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<sup>3</sup> and children.<sup>5</sup>

#### **Other Forms of Coma**

Because of its effects on intracranial pressure, hyperventilation has been advocated for the management of coma after near-drowning<sup>4</sup> or near-hanging, as well as for the management of cerebral edema in patients with diabetic ketoacidosis.<sup>32</sup> 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.<sup>33</sup>

#### **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<sup>19,34</sup> or with congenital diaphragmatic hernia.<sup>35</sup> In addition, in the resuscitation of neonates, hyperventilation could rapidly clear excess carbon

dioxide resulting from bicarbonate administration and could counteract metabolic acidosis.<sup>36</sup> Previous recommendations included prolonged maintenance of a partial pressure of arterial carbon dioxide below 20 to 30 mm Hg in such infants.<sup>37</sup>

#### **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.<sup>38</sup> Its proposed advantages include the minimization of spontaneous respiratory effort and a reduced requirement for sedative, analgesic, and muscle-relaxant medications.<sup>38</sup> The latter advantage may explain the widespread use of intraoperative hyperventilation in the 1960s<sup>39</sup> 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.<sup>38</sup>

#### **Accidental Induction of Hypocapnia**

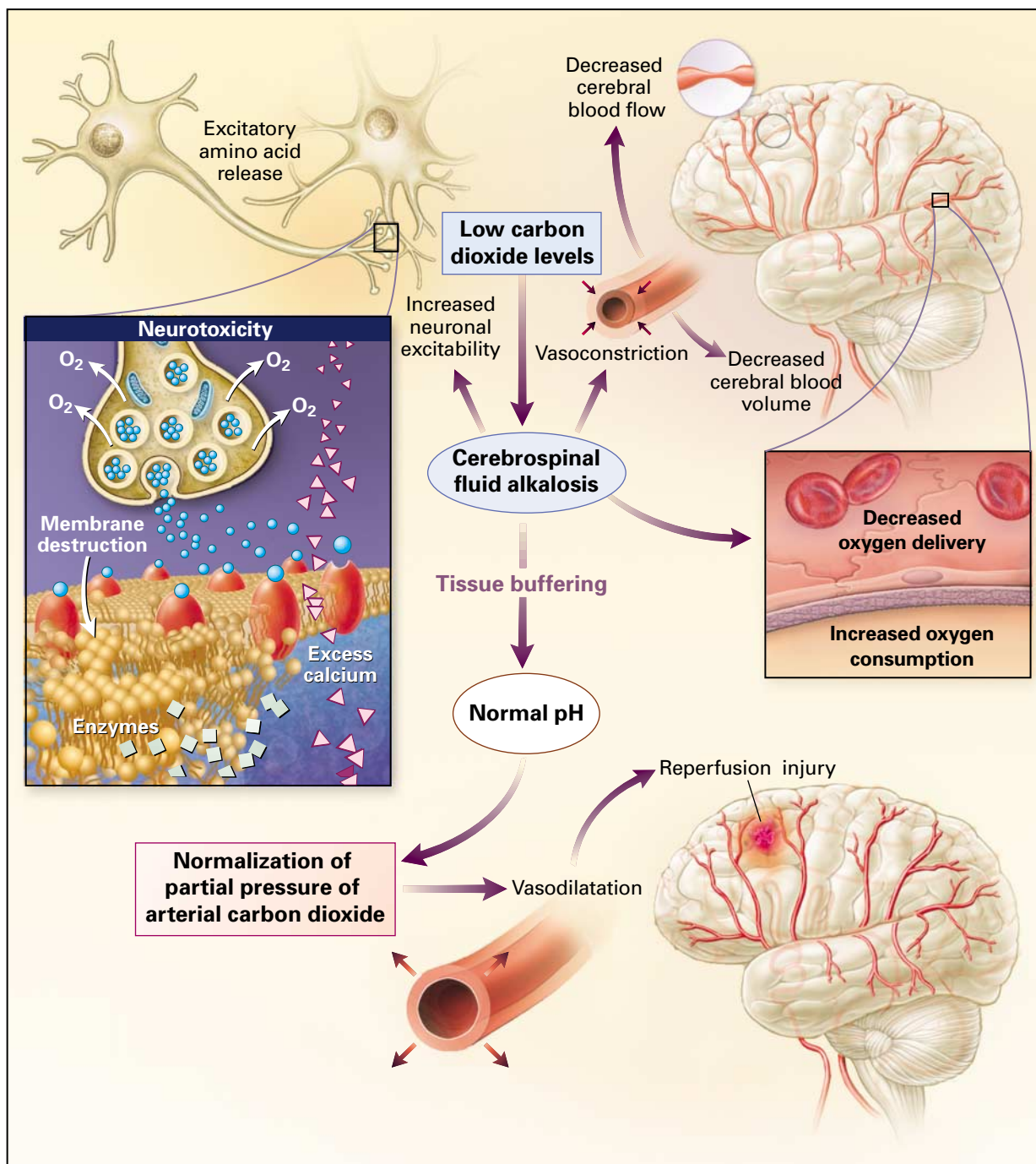
Hypocapnia can develop as a result of excessive mechanical ventilation.<sup>2,7,35</sup> In addition, cardiopulmonary bypass,<sup>6</sup> high-frequency modes of ventilation,<sup>14</sup> and extracorporeal membrane oxygenation<sup>15</sup> have been associated with the development of unanticipated hypocapnia. 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.<sup>40</sup>

#### **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,<sup>11</sup> high-altitude pulmonary edema,<sup>12</sup> or acute lung injury.<sup>41</sup> Hypocapnia has long been recognized as the most common acid-base disturbance in critically ill patients,<sup>9</sup> and it is a consistent feature of both septic shock<sup>10</sup> and the systemic inflammatory response syndrome.<sup>8</sup> In fact, hypocapnia is a diagnostic criterion for the latter condition.<sup>8</sup> In addition, it is a prominent feature of diabetic ketoacidosis in children and is a key predictor of cerebral edema in such children.<sup>33</sup>

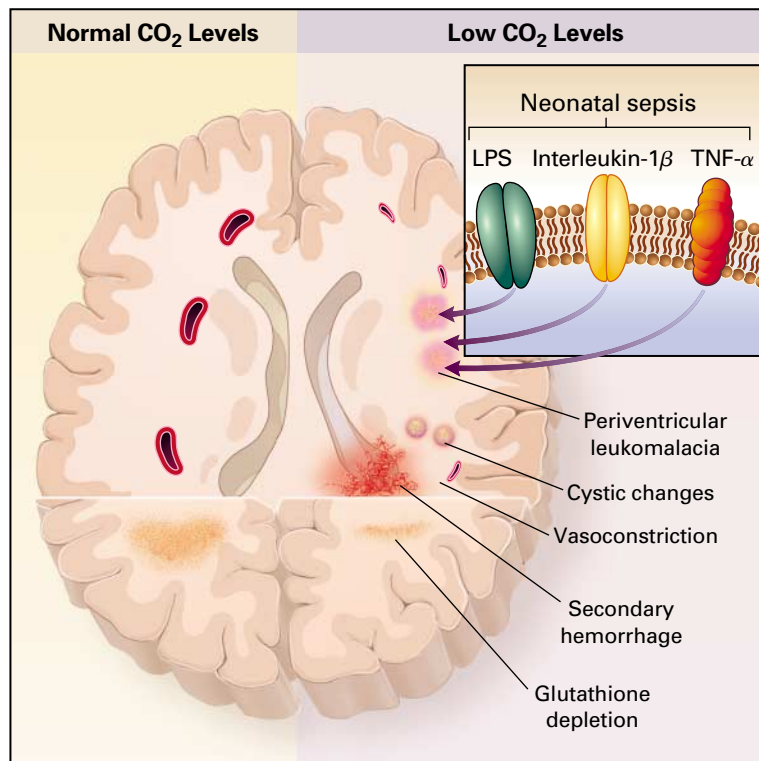
#### **PATHOBIOLOGY OF HYPOCAPNIA**

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



**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.



**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-1 $\beta$  and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), 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:

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

The buffering response to acute hypocapnia is bi-

phasic. 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.<sup>16</sup> 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.<sup>16</sup> 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).

### **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,<sup>43</sup> cerebral,<sup>44</sup> and placental<sup>45</sup> perfusion, as well as myocardial effects.<sup>46</sup> 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.<sup>47</sup> 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,<sup>48</sup> attenuation of hypoxic pulmonary vasoconstriction,<sup>49</sup> and increased intrapulmonary shunting<sup>49</sup>) 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.<sup>50</sup> 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.<sup>51</sup>

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).<sup>52</sup>

### **Dose–Response Relation and Duration of Hypocapnia**

Although mild hypocapnia results in few or no serious effects, marked hypocapnia may cause serious adverse effects.<sup>30,50,53–55</sup> 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,<sup>44</sup> decreasing the effectiveness of the reduction in intracranial pressure<sup>56</sup> 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<sup>56,57</sup> that can cause a rebound increase in intracranial pressure, aggravate reperfusion injury (Fig. 1), or precipitate hemorrhage (Fig. 2).

### **HYPOCAPNIA AND THE BRAIN**

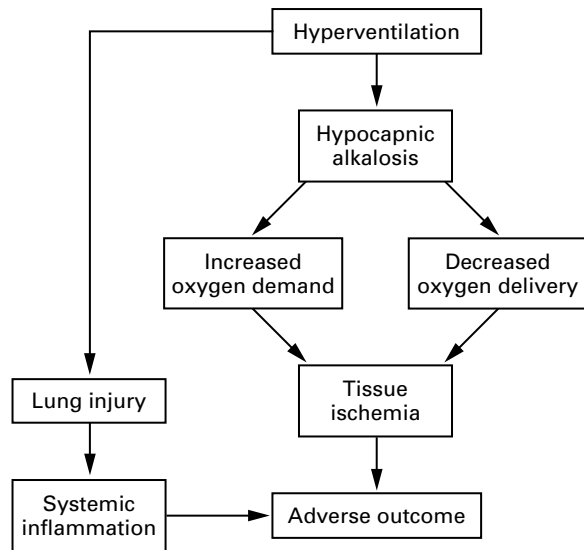
The mechanisms underlying the adverse neurologic consequences of hypocapnia are similar to those seen in other tissues when there is reperfusion injury and an imbalance between oxygen supply and demand. The control of acid–base homeostasis in the cerebrospinal fluid has been reviewed extensively,<sup>58</sup> 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,<sup>59</sup> cerebral ischemia can result.<sup>60</sup> In experimental cerebral ischemia,



**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,<sup>61</sup> although this may be explained in part by an inhibition of brain phosphofructokinase activity that is unrelated to ischemia.<sup>62</sup> 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.<sup>63</sup> In fact, hypocapnia increases cerebral oxygen demand. Hypocapnia increases neuronal excitability, seizure activity,<sup>64</sup> and anaerobic metabolism.<sup>61</sup> Finally, the presence of hypocapnia during cardiopulmonary resuscitation may worsen brain injury.<sup>65</sup> Hypocapnic potentiation of seizure activity, in addition to increasing oxygen demand, augments production of the cytotoxic excitatory amino acids associated with seizures.<sup>66</sup> Hypocapnia may also induce increases in neuronal dopamine,<sup>67</sup> 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<sup>68</sup>; 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,<sup>69</sup> antioxidant depletion by excitatory amino acids,<sup>70</sup> and the lipopolysaccharide<sup>71</sup> and cytokine<sup>72</sup> effects that potentiate destruction of white matter (Fig. 2).

Data from neonates clearly suggest that severe hypocapnia after hyperventilation,<sup>68</sup> high-frequency ventilation,<sup>14</sup> and extracorporeal membrane oxygenation<sup>15</sup> contribute to adverse neurologic outcomes. In addition, abrupt termination of hyperventilation results in reactive cerebral hyperemia,<sup>57</sup> which may cause intracranial hemorrhage in premature neonates.<sup>57</sup> 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,<sup>1</sup> which may be explained in part by reduced cerebral oxygenation.<sup>55</sup> Thus, although intracranial pressure may decrease transiently, it may do so at the expense of cerebral perfusion.<sup>59</sup> In addition, hypocapnia may exacerbate secondary brain injury, because increased cerebral vascular reactivity and vasoconstriction can result in decreases in regional cerebral blood flow.<sup>60</sup> Therefore, hypocapnia may result in a disproportionate (regional) decrease in cerebral blood flow, without a further decrease in intracranial pressure.<sup>18</sup> Because of these possibilities, a panel of experts has recommended against the prophylactic use of hyperventilation.<sup>30</sup>

##### 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.<sup>73</sup>

##### 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

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.<sup>74</sup> Such effects are especially pronounced in older patients.<sup>75</sup> 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.<sup>75</sup> Reassuringly, according to studies of postoperative cognition in otherwise healthy patients, the adverse effects of hypocapnia, although often prolonged, appear to be reversible.<sup>74,75</sup>

**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,<sup>76</sup> 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.<sup>77</sup>

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.<sup>78</sup> 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.

**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.<sup>79</sup> 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.<sup>80</sup>

**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<sup>81</sup> by inducing bronchospasm and increasing airway-microvasculature permeability (Fig. 4).<sup>82</sup> Bronchoconstriction induced by hypocapnia may have adverse consequences.<sup>11,82</sup> 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).<sup>83</sup> This theory is seldom discussed now, but considerable experimental evidence supports it.<sup>11,48,81,82</sup> Furthermore, clinical data indicate that hypocapnia may contribute to increased airway resistance in patients with asthma.<sup>11</sup> In addition, alveolar hypocapnia occurs during cardiopulmonary bypass, resulting in bronchoconstriction, increased airway resistance, and reduced lung compliance.<sup>84</sup> These changes are reversed by the addition of inspired carbon dioxide.<sup>84</sup>

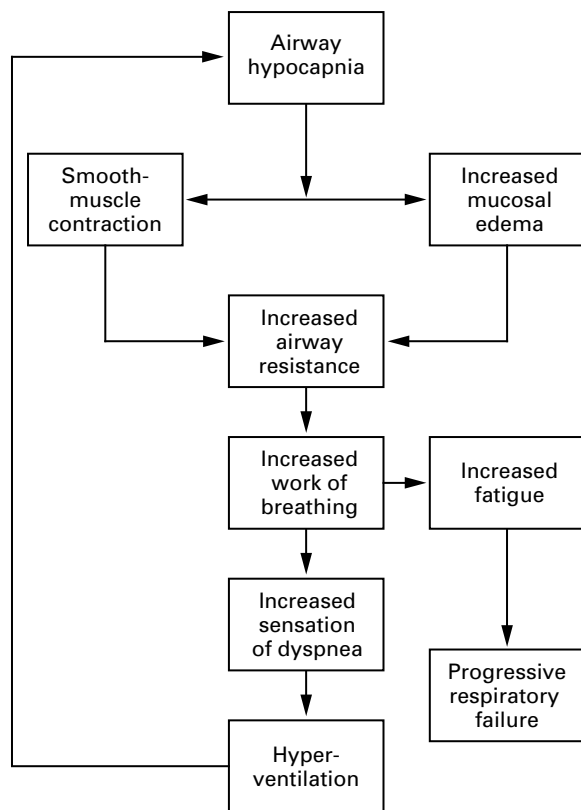
**Acute Lung Injury**

**Pathophysiology**

Aside from changes in airway resistance, hypocapnia causes increased pulmonary-capillary permeability,<sup>53</sup> parenchymal injury,<sup>85</sup> and depletion of lamellar

**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



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

#### **Clinical Consequences**

Hyperventilation and hypocapnic alkalosis frequently coexist in patients with lung injury<sup>88</sup>; 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 in-

creasingly well documented.<sup>2,7,35</sup> 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.<sup>41</sup> 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.<sup>41</sup>

#### **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.<sup>35</sup> 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.<sup>35</sup>

#### **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.<sup>89</sup>

#### **Myocardial Ischemia**

Acute hypocapnia decreases myocardial oxygen delivery while increasing oxygen demand (Table 2).<sup>90</sup> Oxygen demand is increased through increases in myocardial contractility<sup>91</sup> and systemic vascular resistance.<sup>92</sup> In addition, hypocapnia may precipitate thrombosis<sup>93</sup> 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<sup>9</sup> and in patients with panic disorder.<sup>77</sup> 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<sup>46</sup> or tricyclic antidepressants<sup>94</sup>; in these cases, the alkalosis is the determinant of efficacy.



## 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,<sup>95</sup> and hypocapnia triggers periodic respirations in these patients.<sup>96</sup> 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.<sup>96</sup> In fact, central sleep apnea is predicted by the presence of hypocapnia during waking hours.<sup>97</sup> 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 effects on the fetus (such as decreased fetal oxygen tension, increased base deficit, lower Apgar scores, and delayed onset of rhythmic neonatal breathing).<sup>98</sup> These effects may be prevented by administering inspired carbon dioxide.<sup>98</sup> Alkalosis associated with hypocapnia decreases placental perfusion, reduces umbilical-vein oxygen tension,<sup>99</sup> and causes reflex spasm of the umbilical vein.<sup>45</sup> Because carbon dioxide increases fetal respiration, which may cause increased stretch and distention of the lung,<sup>100</sup> 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 tak-

en 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. Bohm, A.C. Bryan, K. Killian, E. Philipson, and A.K. Tanswell for their critical review of the manuscript; and to Theresa and Bill Sakno for assistance with the figures.*

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