CRITICAL CARE

Bench-to-bedside review: Carbon dioxide

Gerard Curley[1,2], John G Laffey[1,2] and Brian P Kavanagh*[3]

Abstract

Carbon dioxide is a waste product of aerobic cellular respiration in all aerobic life forms. $PaCO_2$ represents the balance between the carbon dioxide produced and that eliminated. Hypocapnia remains a common – and generally underappreciated – component of many disease states, including early asthma, high-altitude pulmonary edema, and acute lung injury. Induction of hypocapnia remains a common, if controversial, practice in both adults and children with acute brain injury. In contrast, hypercapnia has traditionally been avoided in order to keep parameters normal. More recently, advances in our understanding of the role of excessive tidal volume has prompted clinicians to use ventilation strategies that result in hypercapnia. Consequently, hypercapnia has become increasingly prevalent in the critically ill patient. Hypercapnia may play a beneficial role in the pathogenesis of inflammation and tissue injury, but may hinder the host response to sepsis and reduce repair. In contrast, hypocapnia may be a pathogenic entity in the setting of critical illness. The present paper reviews the current clinical status of low and high $PaCO_2$ in the critically ill patient, discusses the insights gained to date from studies of carbon dioxide, identifies key concerns regarding hypocapnia and hypercapnia, and considers the potential clinical implications for the management of patients with acute lung injury.

Introduction

The partial pressure of CO_2 in the blood ($PaCO_2$) represents the balance between CO_2 produced, CO_2 eliminated, and CO_2 (rarely) inspired:

$$PaCO_2 \propto \frac{CO_2 \text{ production}}{CO_2 \text{ elimination}} + \text{inspired } [CO_2]$$

*Correspondence: brian.kavanagh@sickkids.ca
[3]Departments of Critical Care Medicine and Anesthesia and the Program in Physiology and Experimental Medicine, The Hospital for Sick Children, University of Toronto, 555 university Avenue, Toronto, ON M5G 1X8, Canada
Full list of author information is available at the end of the article

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For practical purposes, $PaCO_2$ reflects the rate of CO_2 elimination.

Prevalence and causes of altered CO_2 tension

There are no common physiological causes of hypercapnia. Historically, uses of CO_2 included elimination of carbon monoxide poisoning, augmentation of cerebral perfusion during carotid endarterectomy, hastening emergence from general anesthesia, and as treatment for retinal artery occlusion.

The commonest reason for hypercapnia in ventilated patients is a reduced tidal volume (V_T); this situation is termed permissive hypercapnia. Accidental hypercapnia occurs with problems such as circuit misconnections that permit rebreathing. Increased CO_2 production is uncommon, but occurs with hyperpyrexia, shivering, neuroleptic malignant syndrome, heat stroke, thyrotoxicosis or pheochromocytoma.

Indirect calorimetry utilizes whole-body CO_2 production, together with O_2 consumption, to reflect the amount of energy released from substrate oxidation (that is, the oxidation of carbohydrates, lipids and proteins), although it is more accurate at assessing resting energy expenditure. As such, massive carbohydrate oxygenation may contribute to hypercapnia in patients with impaired pulmonary diffusion [1].

Hypocapnia may be physiologic, accidental, or induced (Table 1). In the critically ill patient, hypocapnia can develop with excessive mechanical ventilation or with cardiopulmonary bypass, high-frequency ventilation, or extracorporeal membrane oxygenation. It may be deliberately induced when intracranial pressure [2] – or neonatal pulmonary artery pressure [3] – is elevated.

Importance of altered CO_2 tension in critical illness
Hypercapnia

High V_T causes, or potentiates, lung injury [4]. Smaller V_T often leads to elevated $PaCO_2$, termed permissive hypercapnia, and is associated with better survival [5,6]. These low-V_T strategies are not confined to patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS); they were first reported successful in severe asthma [7], and attest to the overall safety of hypercapnia. Indeed, hypercapnia in the presence of higher V_T may independently improve survival [8].

Table 1. Causes of hypocapnia

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

Hypocapnia

Hypocapnia is common in several diseases (Table 1; for example, early asthma, high-altitude pulmonary edema, lung injury), is a common acid–base disturbance and a criterion for systemic inflammatory response syndrome [9], and is a prognostic marker of adverse outcome in diabetic ketoacidosis [10]. Hypocapnia – often prolonged – remains common in the management of adult [11] and pediatric [12] acute brain injury.

Carbon dioxide transport, sensing and molecular response

CO_2 is carried in the blood as HCO_3^-, in combination with hemoglobin and plasma proteins, and in solution. Inside the cell, CO_2 interacts with H_2O to produce carbonic acid (H_2CO_3), which is in equilibrium with H^+ and HCO_3^-, a reaction catalyzed by carbonic anhydrase. CO_2 transport into cells is complex, and passive diffusion, specific transporters and rhesus proteins may all be involved.

CO_2 is sensed in central and peripheral neurons. Changes in CO_2 and H^+ are sensed in chemosensitive neurons in the carotid body and in the hindbrain [13,14]. Whether CO_2 or the pH are preferentially sensed is unclear, but the ventilatory response to hypercapnic acidosis (HCA) exceeds that of an equivalent degree of metabolic acidosis [15], suggesting specific CO_2 sensing. Bicarbonate directly activates adenylate cyclase [16], increasing cAMP and activating protein kinase A, opening Ca^{2+} channels and permitting influx of Ca^{2+} [14]. In the glomus cells of the carotid nucleus, increased CO_2 levels activate Ca^{2+} channels independent of the pH [17].

A key molecular mechanism by which hypercapnia may exert its effects, both beneficial and deleterious, is through the NF-κB transcription factor. NF-κB is a major transcription factor that regulates genes responsible for immunity and inflammation, including proinflammatory cytokines. An *in vitro* study has demonstrated that elevated CO_2 levels suppress expression of TNF and other cytokines by pulmonary artery endothelial cells via suppression of NF-κB activation [18]. Furthermore, hypercapnia inhibits pulmonary epithelial wound repair, also via an NF-κB mechanism [19].

Physiologic effects of CO_2

The physiologic effects of CO_2 are diverse and incompletely understood, with direct effects often counterbalanced by indirect effects. In addition, the net effect of hypocapnia or hypercapnia may occur as a function of the pH or CO_2 *per se.*

Respiratory system

CO_2 is important in matching regional lung ventilation to perfusion. Alveolar CO_2 increases local alveolar ventilation [20] via inhibition of conducting airway tone. Hypercapnia increases pulmonary vascular tone, potentiating hypoxic pulmonary vasoconstriction and further augmenting V/Q matching, but in some cases exacerbating pulmonary hypertension.

Hypocapnia can worsen ventilation–perfusion matching and gas exchange in the lung via a number of mechanisms, including bronchoconstriction [21], reduction in collateral ventilation [22], reduction in parenchymal compliance [23], and attenuation of hypoxic pulmonary vasoconstriction and increased intrapulmonary shunting [24].

Central nervous system

CO_2 stimulates ventilation (see above). Peripheral chemoreceptors respond more rapidly than the central neurons, but central chemosensors make a larger contribution to stimulating ventilation. CO_2 increases cerebral blood flow (CBF) by 1 to 2 ml/100 g/minute per 1 mmHg in $PaCO_2$ [25], an effect mediated by pH rather than by the partial pressure of CO_2. Hypercapnia elevates both the partial pressure of O_2 in the blood and CBF, and reducing $PaCO_2$ to 20 to 25 mmHg decreases CBF by 40 to 50% [26]. The effect of CO_2 on CBF is far larger than its effect on the cerebral blood volume. During sustained hypocapnia, CBF recovers to within 10% baseline by 4 hours; and because lowered HCO_3^- returns the pH towards normal, abrupt normalization of CO_2 results in (net) alkalemia and risks rebound hyperemia.

Hypocapnia increases both neuronal excitability and excitatory (glutamatergic) synaptic transmission, and suppresses GABA-A-mediated inhibition, resulting in increased O_2 consumption and uncoupling of metabolism to CBF [27].

Cardiovascular system

Hypercapnia directly inhibits cardiac and vascular muscle contractility, effects that are counterbalanced by sympathoadrenal increases in heart rate and contractility, increasing the cardiac output overall [28]. The partial pressure of O_2 in the blood is increased because increased cardiac output coupled with reduced intrapulmonary shunt increases O_2 delivery, and tissue release of O_2 is augmented because hypercapnia and acidemia shift the hemoglobin–O_2 curve rightward. In addition, HCA increases the O_2 tension in both subcutaneous tissues and in the intestinal wall [29].

Indeed, a large body of evidence now attests to the ability of hypercapnia to increase peripheral tissue oxygenation, independently of its effects on cardiac output [30,31]. In experimental polymicrobial sepsis in female sheep, HCA improved tissue oxygenation and reduced lung edema formation more than dobutamine administration [32]. A study in white rabbits ascertained that 150 mmHg was the permissive upper limit of acute hypercapnia with respect to improvement of tissue perfusion and oxygenation [33]. Finally, a further positive effect of HCA on bioenergetics is evident in the form of a reduction in cellular O_2 consumption [34] and hypercapnia induced mitigation of the fall in gut ATP during endotoxemia in rats, pointing to improvement in energy metabolism in this setting. The net impact is thus increased O_2 supply and less demand. In contrast, hypocapnia does the opposite.

Carbon dioxide – insights from the bench

Experimental studies provide important preclinical information on the effects and mechanisms of action of CO_2.

Acute lung injury

HCA is protective in many models of ALI. Although hypercapnia reduces the severity of overwhelming experimental ventilator-induced lung injury [35], its effects in milder injury are modest [36] and it may not protect in extensive atelectasis [37]. Hypercapnia inhibits hypoxia-induced chronic pulmonary hypertension in adult and newborn rodents [38,39], and protects against chronic neonatal lung injury [40]. The beneficial effects of HCA in such models are increasingly well understood, and include attenuation of lung neutrophil recruitment, pulmonary and systemic cytokine concentrations, cell apoptosis, and O_2-derived and nitrogen-derived free radical injury.

Concern has been raised regarding the potential for the anti-inflammatory effects of HCA to impair the host response to infection. In early pulmonary infection, this potential impairment does not appear to occur, with HCA reducing the severity of acute-severe *Escherichia coli* pneumonia-induced ALI [41]. In the setting of more established *E. coli* pneumonia, HCA is also protective [42]. Of concern, HCA worsens the severity of prolonged bacterial pneumonia by a mechanism involving reduced bacterial killing [43]. In contrast, HCA reduces the severity of lung injury and hemodynamic compromise caused by cecal ligation and puncture-induced polymicrobial systemic sepsis [44,45]. The effects of HCA in sepsis therefore appear to depend on the duration of infection and on the site of infection. Other potential adverse effects of hypercapnia may include impairment of alveolar epithelial function, leading to reduced edema clearance [46]. Lastly, HCA may delay cellular repair and wound healing [19], slowing recovery and healing following ALI/ARDS.

Hypocapnia increases microvascular permeability and impairs alveolar fluid reabsorption in the isolated rat lung, due to an associated decrease in Na/K-ATPase activity [47]. These effects may be important in the pathogenesis of pulmonary edema. Experimental hypocapnia causes profound acute parenchymal lung injury that may be ameliorated by normalization of alveolar CO_2 by adding inspired CO_2 [48]; it also worsens ischemia–reperfusion-induced lung injury [49].

Myocardial and vascular injury

HCA protects the heart following ischemia–reperfusion injury. Reperfusion with a hypercapnia acidotic perfusate enhances recovery of myocardial function following prolonged ischemia *ex vivo* as well as *in vivo* [50]. In experimental polymicrobial sepsis in female sheep, HCA improved tissue oxygenation and reduced lung edema formation more than dobutamine administration [32]. Hypocapnia worsens ischemic injury in the neonatal lamb myocardium [51] and abolishes the protective effects of preconditioning.

Central nervous system

Hypercapnia attenuates hypoxic-ischemic brain injury in the immature rat [52] and protects the porcine brain from reoxygenation injury by attenuation of free radical action. Hypercapnia increases the size of the region at risk of infarction in experimental acute focal ischemia; in hypoxic-ischemic injury in the immature rat brain, hypocapnia worsens the histologic magnitude of stroke [52] and is associated with a decrease in CBF to the hypoxia-injured brain as well as disturbance of glucose utilization and phosphate reserves. Hypocapnia during resuscitation increases functional and histologic evidence of brain injury following experimental cardiac arrest in dogs [53]. Hypocapnia further exacerbates the cerebral O_2 supply:demand imbalance by increasing neuronal excitability, increasing excitatory synaptic transmission, and via a direct effect on the neuronal membrane itself

[54]. Severe hypocapnia increases *N*-methyl-D-aspartic acid receptor-mediated neurotoxicity in the newborn piglet and increases neuronal dopamine, particularly in the striatum, which may worsen reperfusion injury, especially in the immature brain [55]. Indeed, hypocapnia may be directly neurotoxic, through increased incorporation of choline into membrane phospholipids [56].

Clinical profile of hypocapnia in the critically ill patient

Potential benefits
There are some potential benefits of acute hypocapnic alkalosis in specific critically ill patients [57]. For patients who have life-threatening elevations in intracranial pressure, rapid induction of hypocapnia for short durations may prevent brainstem herniation, allowing definitive diagnosis and therapy to be instituted. Hypocapnia may also be indicated in neonates with pulmonary hypertensive crises. The knowledge of the dramatic deleterious effects of hypocapnia on the neonatal brain, together with the known adverse effects of excessive lung stretch, however, have led to the use of alternative measures in this regard. There are very few other situations where hypocapnia is of benefit.

Potential risks
Hypocapnia may be a pathogenic entity in the setting of critical illness, particularly in ARDS patients. Edmunds and Holm demonstrated more than 30 years ago that alveolar hypocapnia produces hemorrhagic consolidation in the lung, and that attenuation of such adverse effects could be achieved by addition of inhaled CO_2 [48]. In the clinical context, Trimble and colleagues in 1971 demonstrated that hypocapnia increased airway resistance, increased work of breathing, worsened ventilation/perfusion matching, increased the alveolar–arterial O_2 gradient and decreased the partial pressure of O_2 in the blood in ARDS patients, and that administration of CO_2 (that is, therapeutic hypercapnia) improved systemic oxygenation and reduced the shunt fraction [58]. Both hyperventilation and hypocapnia have been identified as *independent* determinants of long-term pulmonary dysfunction in patients with bronchopulmonary dysplasia, as well as being implicated in the pathogenesis of asthma.

In traumatic brain injury, sustained hypocapnia may exacerbate cerebral hypoperfusion. Hypocapnia-induced cerebral vasoconstriction may worsen cerebral vasospasm in these patients, and has been demonstrated to exacerbate pre-existing impairment of CBF and metabolism in patients with traumatic brain injury. Coles and colleagues demonstrated that moderate hypocapnia (<34 mmHg) can significantly reduce global CBF and result in significant increases in the volume of critically

hypoperfused tissue in the injured brain [27]. Prophylactic hyperventilation of head-injured patients, formerly employed in order to reduce intracranial pressure, *worsens* outcome [59]. In children with severe head injury, hypocapnia-induced critical cerebral ischemia has also been demonstrated. In the setting of resuscitation following cardiac arrest, hypocapnia induces cerebral ischemia in the post-resuscitation period [60]. Hypocapnic akalosis has also been associated with poor prognosis in patients with acute cerebrovascular accidents.

In the critically ill patient, hypocapnia has been clearly linked to the development of arrhythmias, adversely affects the myocardial supply:demand balance [61], increases the risk of coronary vasospasm [62], and may worsen the progression of acute coronary syndromes.

Clinical profile of hypercapnia in the critically ill patient
Potential benefits
There are no clinical studies of hypercapnia independent of V_T in mechanical ventilation strategies. Indirect evidence exists in humans, however, for a protective effect of HCA independent of V_T. Kregenow and colleagues examined mortality as a function of permissive hypercapnia in patients enrolled in the ARDS Network V_T study [4,8]. Using multivariate logistic regression analysis, and controlling for other co-morbidities and severity of lung injury, they demonstrated that permissive hypercapnia reduced mortality in patients randomized to the higher V_T (12 ml/kg) [8]. There was, however, no additional protective effect of permissive hypercapnia in patients randomized to receive the lower V_T (6 ml/kg) [8].

In children with congenital heart disease undergoing cardiopulmonary bypass, blood gas management with a pH-stat strategy, which results in higher $PaCO_2$ levels, reduces postoperative morbidity [63].

Potential risks
Rapid induction of hypercapnia in the critically ill patient may have adverse effects. Acute hypercapnia impairs myocardial function. HCA may induce vasoconstriction of the pulmonary vascular bed, leading to right ventricular systolic overload; and in patients with ARDS, HCA may exacerbate hypoxic vasoconstriction. In patients with severe ARDS, HCA – induced by V_T reduction and increases in positive end-expiratory pressure – impaired right ventricular function and hemodynamics despite positive effects on oxygenation and alveolar recruitment [64]. An adverse effect of hypercapnia on skeletal muscle function, and diaphragmatic function in particular, is a concern.

Hypercapnia-induced increases in CBF and cerebral blood volume may adversely impact on intracranial

pressure in patients with traumatic brain injury. An association between intraventricular hemorrhage and severe, but not mild, hypercapnia has been reported in retrospective studies.

Defining a safe and efficacious threshold of hypercapnia remains an elusive goal. Although beneficial effects, including tissue oxygenation, may have a ceiling level in animals [33], similar findings have not been reported in humans. Evidence of a temporal limit to beneficial effects undermines this concept further – timing (that is, adaptation) may be as important as the degree of severity. Attempts to specify such a value are problematic outside the clinical context. Clinicians must be mindful of the tradeoff between the beneficial and deleterious effects of hypercapnia as outlined, and must tailor treatment in each individual case; for example, in the case of combined lung and head injury, regional monitors of cerebral oxygenation and intracranial pressure may be used to guide therapy.

Therapeutic hypercapnia in the critically ill patient

Despite extensive effort over the past decade, particularly in the experimental setting, the ideal target population for trials of therapeutic hypercapnia (that is, administration of CO_2 to the ventilator breathing circuit) remains somewhat ill-defined. Given the immuno-suppressive effects of HCA, and its potential to retard reparative processes, HCA may ultimately prove its utility as a temporary and brief measure, designed to limit predictable and transient organ injury. In that respect, therapeutic hypercapnia during or immediately post cardiopulmonary bypass would appear to hold some promise. HCA is protective in numerous experimental models of organ ischemia–reperfusion, and recent clinical studies have shown improved systemic oxygenation with the use of therapeutic hypercapnia after bidirectional superior cavopulmonary anastomosis in children [65].

Hypercapnia in the critically ill patient – role of buffering

In patients managed with protective ventilation strate-gies, buffering of the acidosis induced by hypercapnia remains a common – albeit controversial – clinical practice. Buffering with sodium bicarbonate was permitted in the ARDS Network V_T study [4]. The need to consider the effects of buffering HCA is emphasized by the fact that both hypercapnia and acidosis *per se* may exert distinct biologic effects. There is no evidence to support buffering, however, and a number of specific concerns exist regarding this practice. The protective effects of HCA in experimental lung injury are a function of the acidosis, rather than the elevated CO_2 *per se* [66], and therefore buffering may simply ablate any protective effects. In experimental lung injury induced by *E. coli* or endotoxin, renal buffering of hypercapnia significantly worsened physiological and histological measurements of injury [67].

Specific concerns exist regarding sodium bicarbonate, the buffer used most frequently in the clinical setting. The effectiveness of bicarbonate infusion as a buffer is dependent on the ability to excrete CO_2, rendering it less effective in buffering HCA. In fact, bicarbonate may further raise $PaCO_2$ where alveolar ventilation is limited, such as in ARDS. While bicarbonate may correct the arterial pH, it may worsen an intracellular acidosis because the CO_2 produced when bicarbonate reacts with metabolic acids diffuses readily across cell membranes, whereas bicarbonate cannot.

There may be a role for alternative buffers, such as the amino alcohol tromethamine (*tris*-hydroxymethyl amino-methane (THAM)). THAM penetrates cells easily and can buffer pH changes and simultaneously reduce the partial pressure of CO_2 [68]. Unlike bicarbonate, which requires an open system for CO_2 elimination in order to exert its buffering effect, THAM is effective in a closed or semi-closed system [68]. THAM rapidly restores pH and acid–base regulation in acidemia caused by CO_2 retention [68]. In ARDS patients, THAM attenuates the hemodynamic consequences of a rapidly induced HCA.

In summary, if a clinician elects to buffer HCA, the rationale for this practice should be clear – for example, to ameliorate potentially deleterious hemodynamic consequences of acidosis – and THAM should be considered rather than bicarbonate.

Summary and conclusions

The importance and complexity of inter-relationships between alterations in systemic CO_2 tension and critical illness states is increasingly appreciated. Ventilator strategies involving hypercapnia are widely utilized in the critically ill adult and child, with the aim of realizing the benefits of reduced lung stretch. The potential for hypercapnia to directly contribute to the beneficial effects of protective lung ventilatory strategies is clear from experimental studies demonstrating protective effects in models of acute lung and systemic organ injury. Concerns persist, however, regarding the potential for hypercapnia and/or acidosis to exert deleterious effects, and the need for caution prior to extrapolation to the clinical context must be emphasized.

Hypocapnia is an underappreciated phenomenon in the critically ill patient, and is potentially deleterious, particularly when severe or prolonged. Hypocapnia should be avoided except in specific clinical situations; when induced, hypercapnic acidosis should be for specific indications while definitive measures are undertaken.

A clearer understanding of the effects and mechanisms of action of CO_2 is central to determining its safety and

therapeutic utility in the critically ill patient. In the coming years, research efforts should focus on determining the potential mechanisms by which alterations in CO_2 tension contribute to the pathogenesis of acute organ injury states. Such insights should advance our understanding of the situations in which hypercapnia or hypocapnia may be helpful or dangerous, and should guide clinicians with regard to the rational use of CO_2 in the critically ill patient.

Abbreviations

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CBF, cerebral blood flow; CO_2, carbon dioxide; HCA, hypercapnic acidosis; NF, nuclear factor; O_2, oxygen; $PaCO_2$, partial pressure of carbon dioxide in the blood; THAM, *tris*-hydroxymethyl aminomethane; TNF, tumor necrosis factor; V_T, tidal volume.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Anaesthesia, Clinical Sciences Institute, National University of Ireland, Galway, Ireland. [2]Lung Biology Group, National Centre of Biomedical Engineering Sciences, National University of Ireland, Galway, Ireland. [3]Departments of Critical Care Medicine and Anesthesia and the Program in Physiology and Experimental Medicine, The Hospital for Sick Children, University of Toronto, 555 university Avenue, Toronto, ON M5G 1X8, Canada.

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