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Perioperative control of CO₂

CO₂, a waste gas, accumulates in the presence of respiratory failure and has characteristically been thought of as a gas to be excreted. Like other waste products, many practitioners thought the less present the better.¹ Perhaps because end-tidal CO₂ monitoring is now mandatory, anesthesiologists are now continuously aware on a second-to-second basis, of some measure of CO₂ flux in their patients. This monitoring imperative, coupled with new insights into oxygenation and carbon dioxide exchange, in addition to the increasing knowledge of the importance of ventilatory technique, means that the anesthesiologist is faced with contemplating "carbon dioxide" issues on a continuous basis.

Control of PaCO₂ during anesthesia

The level of arterial CO₂ under normal circumstances is tightly controlled in the region of 40 mmHg. Changes in PaCO₂ result from altered production or altered elimination. Hypercapnia results from either increased production, decreased elimination, or direct administration of CO₂. Increased production characteristically can occur from hyperpyrexia, increased muscle activity and sepsis. In the context of anesthesia, some of the more important causes of increased production include emergence from anesthesia, direct addition of CO₂ (e.g., laparoscopy), tourniquet release, and intraoperative catastrophes such as malignant hyperthermia, neuroleptic malignant syndrome or thyroid crisis. Clearance of CO₂ is a function of the adequacy of alveolar ventilation with respect to pulmonary perfusion. Alveolar ventilation is reduced with decreased minute ventilation or when the physiologic deadspace is increased. Increases in deadspace in the context of anesthesia can of course occur from inappropriate circuit connection, as well as bronchospasm or impaired pulmonary perfusion. Reduced minute ventilation results from inadequate tidal volume or respiratory rate.

Traditional indications for direct administration of CO₂ containing gas mixtures have included the speeding of recovery from anesthesia or to directly produce cerebral vasodilatation. In the modern era this has been

replaced by laparoscopy which increases CO₂ through direct peritoneal injection of CO₂; the respiratory effects are complicated by impairment of abdominal compliance causing reduced minute ventilation, as well as reducing venous return and potentially increasing physiologic deadspace through reduced pulmonary perfusion. Finally, most anesthetics involve some degree of rebreathing, involving a requirement for CO₂ scavenging. Depletion of scavenging efficiency or bypass of scavenging systems results in an increased FiCO₂ which will elevate PaCO₂ directly. Finally, an increasingly commonly recognized cause of hypercapnia in critically ill patients includes overfeeding, particularly with excessive carbohydrates.

Measurement of CO₂ in the operating room

End-tidal CO₂ reflects that proportion of arterial CO₂ that is delivered to the pulmonary vascular bed and then detected in the proximal airway. The anesthesiologist frequently uses end-tidal CO₂ as a surrogate for arterial CO₂ but there are important differences. In the context of increased deadspace, the gradient will be increased and the end-tidal CO₂ will be significantly lower (as opposed to just moderately lower) than the arterial CO₂ tension. The end-tidal CO₂ has additional uses also. First, it can be used to confirm tracheal (as opposed to esophageal) intubation in the presence of intraoperative anesthesia or sedation. In the setting of resuscitation, end-tidal CO₂ tension reflects the degree of lung perfusion and hence cardiac output, provided that the endotracheal tube is definitely placed in the trachea. Of course, unless end-tidal CO₂ is detected, in the setting of resuscitation, the absence of end-tidal CO₂ cannot be used to distinguish between the misplacement of an endotracheal tube and absence of pulmonary perfusion. Finally, the shape of the end-tidal CO₂ trace can indicate the cause of increased deadspace where bronchospasm results in a upwardly sloping expiratory curve because of inhomogeneous emptying of alveolar lung units. Aside from physiology, alterations in end-tidal CO₂ give valuable warnings to the anesthesiologist. An increase

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in end-tidal CO_2 always means an increase in arterial CO_2 , affecting either increased production or diminished minute ventilation. A reduction in end-tidal CO_2 however can mean reduced CO_2 production, increased clearance or increased gradient. Importantly, for the anesthesiologist, a reduced end-tidal CO_2 may reflect inadequate pulmonary perfusion and cardiac output, and an abrupt drop in end-tidal CO_2 may be the first sign of a pulmonary embolism (thromboembolic or venous air embolism).

An additional series of gradients exist that are becoming increasingly important to the anesthesiologist. Although traditionally, anesthesiologists have measured arterial and/or end-tidal CO_2 , direct assessment of tissue CO_2 is increasingly recognized as a marker of tissue ischemia. The best described methods include gastric tonometry, where a tonometer (sampling line) lies in the stomach in direct connection with the gastric mucosa, and the contents of the tonometric line reach equilibrium with the gastric mucosal cells.² A decrease in cellular gastric intramucosal pH is thought to reflect adverse mucosal oxygen supply/demand balance, reflected in either reduced gastric intramucosal pH or increased gastric intramucosal CO_2 . In order to correct for arterial levels of CO_2 tension, this is perhaps best corrected for PaCO_2 , and expressed as the intramucosal to arterial CO_2 gradient.

A final measure of CO_2 of potential interest to anesthesiologists is global mixed venous to arterial CO_2 gradient. Elevation of this gradient reflects inadequate oxygen delivery and excess accumulation of CO_2 in the mixed venous blood. This is a marker of reduced global delivery of oxygen and cardiac output.

Hypocapnia – perioperative causes

The usual cause of perioperative hypocapnia is excessive mechanical ventilation.³ This is usually inadvertent or in many cases simply ignored. In the vast majority of situations it is without adverse effect. Additional causes of low PaCO_2 aside from increased alveolar ventilation, include reduced production, most commonly secondary to a hypothermia-induced low metabolic rate.

Hypocapnia – potential benefits

There are some good reasons for inducing acute hypocapnic alkalosis.³ For patients who have life-threatening elevations in intracranial pressure and who are in danger of coning (brainstem herniation), rapid induction of hypocapnia through hyperventilation is mandatory, in conjunction with adjunct therapies (mannitol, hypertonic saline) while definitive diagnosis or therapy is attempted. Similarly, neonatal patients

with severe pulmonary hypertensive crisis can be dramatically improved by induction of hypocapnia. However, there are very few other situations where hypocapnia is of benefit.

Hypocapnia – experimental evidence of risks

Hypocapnia may adversely affect global organ oxygen supply/demand balance by decreasing systemic oxygenation,^{4,5} decreasing oxygen unloading at the tissue level, and concurrently increasing organ metabolic demand.

Neurologic

Hypocapnia reduces cerebral oxygen supply by decreasing cerebral blood flow, and severe hypocapnia may result in global and regional cerebral ischemia. Furthermore, in experimental acute focal ischemia, hypocapnia increases the size of the region at risk of ischemia, and in combined global and ischemic injury in the immature brain, hypocapnia worsens the histologic magnitude of stroke.⁶ Hypocapnia further exacerbates the cerebral oxygen supply/demand imbalance by increasing neuronal excitability,⁷ *via* a direct effect on the neuronal membrane. In the clinical context hypocapnia induced critical cerebral ischemia has been demonstrated following cardiac arrest, and in children with head injury.⁸ Hypocapnia during resuscitation increases functional and histologic evidence of brain injury following experimental cardiac arrest in dogs.⁹

Pulmonary

Adverse pulmonary consequences of experimentally induced hypocapnia have been described in terms of effects on airways, alveolar-capillary permeability, lung compliance, pulmonary vasculature, as well as overall impact on lung injury. Hypocapnia causes and potentiates bronchoconstriction.¹⁰ At a localized level, this may reduce excessive ventilation, and would be beneficial in the context of localized pulmonary perfusion deficits (e.g., pulmonary emboli). However, generalized bronchoconstriction in response to hypocapnia may have deleterious consequences, particularly in patients with asthma. Hypocapnia increases microvascular permeability, in both tracheal mucosa, and the alveolar-capillary barrier.¹¹ This may be important in the pathogenesis of pulmonary edema. Hypocapnia decreases lung compliance in healthy volunteers and in patients with chronic obstructive lung disease probably as a result of altered surfactant production. Alveolar hypocapnia attenuates hypoxic pulmonary vasoconstriction, worsening intrapulmonary shunt and systemic oxygenation.⁵ Experimental hypocapnia

causes profound acute parenchymal lung injury,¹² that may be ameliorated by normalization of alveolar PCO₂ with increasing FiCO₂, and worsens ischemia-reperfusion induced lung injury.¹¹

Myocardial

Hypocapnia adversely impacts on myocardial O₂ supply/demand balance and may increase the risk of myocardial ischemia. Experimental hypocapnia increases coronary vascular resistance, reduces coronary blood flow and myocardial O₂ delivery and left ventricular performance and reduces collateral flow in experimental myocardial ischemia.¹³ Hypocapnia also increases O₂ demand by increasing myocardial contractility. Finally, myocardial oxygenation may be additionally compromised at the microvascular level, because alkalosis increases myocardial capillary permeability. These findings may explain the mechanism of hypercapnia-induced accentuation of ischemic injury in the neonatal lamb myocardium.¹⁴

Hypocapnia – clinical evidence of risks

There is an increasing body of physiological – and outcome – data from clinical studies indicating adverse consequences of hypocapnia in clinical contexts of direct relevance to anesthesiologists.

Neurologic

Hypocapnia may cause prolonged neurologic dysfunction in patients undergoing general anesthesia. Indices of psychomotor function following emergence from general anesthesia indicate that otherwise healthy patients subjected to hypocapnia are significantly impaired for up to 48 hr.¹⁵ Hypocapnic ventilation resulted in worse postanesthetic neuropsychological performance compared with normocapnic ventilation, in terms of increased time to regain consciousness, prolonged reaction times, poorer flicker-fusion and digit span scores, as well as longer track tracing times and counting-down times.¹⁵ Similar findings have been reported in other studies,¹⁶ and the effects appear to be especially pronounced in older patients.¹⁵ The role of CO₂ in these studies is underscored by the finding that exposure to hypercapnia in anesthetized patients appears to enhance postoperative neuropsychological performance.¹⁵ The effects of hypocapnia in these studies of essentially healthy patients, while often prolonged, were reversible. However the potential clearly exists for hypocapnia to cause permanent psychomotor changes in susceptible patients.

Hypocapnia has also been implicated in the pathogenesis of adverse outcome in patients undergoing cardiopulmonary bypass. In one report, severe

hypocapnia has been implicated in the pathogenesis of neurologic damage postcardiopulmonary bypass.¹⁷ Alpha-stat management of blood gases during cardiopulmonary bypass, resulting in lower systemic CO₂ levels, has been demonstrated to worsen cerebrovascular status.¹⁸

These concerns are compounded by evidence of prolonged adverse neurological outcome following severe hypocapnia induced by hyperventilation or extracorporeal membrane oxygenation (ECMO).¹⁹ Hypocapnia pre-ECMO has been associated with an increased incidence of sensorineural hearing loss in school age children.¹⁹ Finally, prophylactic hyperventilation of head injured patients, formerly employed in order to reduce intracranial pressure, has been clearly associated with *worsened* outcome.²⁰

Pulmonary

The association of hyperventilation, hypocapnia and worsened acute lung injury is increasingly well documented. In fact, hypocapnia has long been implicated in the pathogenesis of adult respiratory distress syndrome (ARDS).²¹ In 1971, Trimble *et al.* demonstrated that hypocapnia increased airway resistance, increased work of breathing, worsened ventilation/perfusion (V/Q) matching, increased alveolar-arterial O₂ gradient and decreased PaO₂ in patients diagnosed with what was then termed post-traumatic pulmonary insufficiency.²¹ Both hyperventilation *and* hypocapnia have been identified as *independent* determinants of long term pulmonary dysfunction in patients with bronchopulmonary dysplasia. Clinical data confirms that hypocapnia may contribute to airway obstruction and bronchospasm in asthmatic patients.²²

Myocardial

Hypocapnia may contribute to the development of clinical relevant acute coronary syndromes in patients with coronary disease undergoing anesthesia. Hypocapnia reduces cardiac performance in these patients, primarily through increasing systemic vascular resistance. In the critically ill, hypocapnia has been clearly linked to the development of arrhythmias.²³

Hypercapnia – perioperative causes

The causes of intraoperative hypercapnia have been reviewed earlier and several are of particular interest to the anesthesiologist, including laparoscopy, and anesthesia associated catastrophes including malignant hypothermia. In addition, shivering on awakening is associated with elevated production of CO₂. It is not clear whether elevated CO₂ is harmful or beneficial in the context but it certainly marks disordered physiology.

Hypercapnia – potential benefits

Hypercapnia has been progressively accepted in critical care in perioperative medicine for patients with lung injury or asthma. This is called permissive hypercapnia and in principle reflects the growing acceptance that excessive tidal stretch is harmful and that with reduced tidal stretch, there is an obligatory elevation in arterial CO_2 . This is reflected in the results of almost all the major trials of ventilatory strategy in ARDS where minute ventilation and tidal volume have been reduced, resulting in this hypercapnic state. For ARDS the idea was first proposed by Hickling *et al.*^{24,25} but was initially demonstrated in neonatal respiratory failure by Wung *et al.* from Columbia University, New York.²⁶ Thus, permissive hypercapnia can benefit a patient with lung injury or asthma because the lung stretch, which is likely injurious, is reduced. In this setting the hypercapnia is tolerated and intensivists and anesthesiologists have become “used” to the hypercapnia and, as their practice evolves, see it as less of a threat to the patient. Potential downsides from permissive hypercapnia have been reviewed in detail,²⁷ and they include elevated intracranial pressure, pulmonary vascular resistance or potentially increased sympathetic or mimetic activity.

Hypercapnia may result in beneficial effects at a cellular level through augmentation of O_2 supply and demand, inhibition of free radical activity, and inhibition of cellular enzyme systems. At an organ level, hypercapnia may be protective to the central nervous system (CNS), lungs, or heart. The initial indication that hypercapnia had benefits in brain ischemia came from the work of Vannucci *et al.*,⁶ who showed in a neonatal animal model of hypoxia ischemia model that supplemental CO_2 added to inspired gas resulted in less overall histological brain injury. In addition, neuronal cells in culture have been shown to be far less susceptible to free radical injury, an important component of ischemia reperfusion in the setting of acidosis. More recently pulmonary investigation of hypercapnia focused on models of ischemia reperfusion or stretch induced lung injury. *Ex vivo* reperfusion models have demonstrated that hypercapnic acidosis is extremely protective against reperfusion injury, and this protection was associated with inhibition of the xanthine oxidase.²⁸ Subsequent work using this model confirmed that the protection afforded by hypercapnic acidosis is superior to that afforded by the equivalent acidemia induced by metabolic acidosis.²⁹ Finally, a stretch induced injury has been shown to be attenuated by hypercapnic acidosis in *ex vivo*³⁰ and *in vivo*³¹ models. Although these effects are dramatic, they have only been reproduced in short term experimental

models and the mechanisms are unclear.

Myocardial ischemia reperfusion injury is significantly inhibited by hypercapnic acidosis.¹⁴ This has direct application to perioperative care, especially for the anesthetic care of patients undergoing cardiopulmonary bypass. A prospective randomized control trial evaluated postoperative cardiac and CNS status in the blood gas management during cardiopulmonary bypass in children undergoing repair of congenital heart disease.¹⁸ The blood gas management was with either pH-stat (more CO_2 is added) or with alpha-stat approaches. The outcome demonstrated improved cardiovascular function, reduced requirement for hemodynamic support and potentially improved cerebrovascular status in the children managed with the pH-stat approach, suggesting a beneficial role for CO_2 in perioperative protection.

Systemic oxygenation

There is increasing evidence that hypercapnia improves oxygenation, although this is not predicted by the classical alveolar gas equation, which would suggest that at a given FiO_2 and minute ventilation, increasing the FiCO_2 would reduce arterial O_2 . However, the effects appear to be mediated through improved V/Q matching, increased cardiac output and increased mixed venous oxygenation. Whereas beneficial effects in oxygenation are seen in multiple experimental models, these have not been mirrored in severely ill patients with ARDS. In this context, while hypercapnia *per se* may have effects on increasing V/Q matching and cardiac output, the effects of reduced tidal volume required to achieve hypercapnia may be counterproductive. Thus, there may be significant differences in oxygenation resulting from hypercapnia depending on how the hypercapnia is induced.

Hypercapnia – experimental evidence of risks

Hypercapnia, traditionally thought of as the accumulation of a waste gas, is now being progressively more tolerated by clinicians. However, despite the above-mentioned data indicating protective effects of hypercapnia, there are significant concerns. The biggest concern might be the propensity for CO_2 to augment the process of protein nitration whereby peroxynitrate (a derivative of nitric oxide and superoxide ions) may react with - and ‘nitrate’ - proteins, particularly tyrosine amino acids. The evidence for this has come from predominantly *in vitro* cell culture preparations of pulmonary epithelial cells^{32,33} wherein hypercapnia increases nitration of tyrosine residues. In the case of surfactant protein A, this increased nitration is associated with functional impairment of the surfactant protein,

which may have serious consequences in perioperative care or ARDS. Additional evidence that nitration might be an adverse phenomenon comes from the experience showing that plasma proteins of patients with ARDS have a high degree of nitration and this is associated with functional impairment of these proteins.

Role of buffering in hypercapnia

The use of buffering has been driven by the clinician's quest to maintain physiology, in this case acid base balance, in as normal a range as possible in very ill patients. Buffering metabolic acidosis with bicarbonate results in an increased production of CO_2 . Thus, buffering is an important consideration in hypercapnia because CO_2 can be directly elevated as a result. An additional important issue is the effect of CO_2 on the development and resolution of primary metabolic acidosis. Acidosis may perform an important function during acute illness whereby acidemia, resulting in a negative feedback loop, inhibits the ongoing generation of organic acids.³⁴ In hypercapnia this has been demonstrated also and the effect of lactate inhibition resulting from global hypoxia may be stronger with hypercapnic acidosis *vs* the infusion of metabolic acid.³⁵ Finally, buffering of hypercapnic acidosis in the setting of lung reperfusion injury results in a worsening of injury compared with the unbuffered state.²⁹

Conclusion

The importance and complexity of inter-relationships between alterations in systemic CO_2 tension in acute illness states is increasingly appreciated by the intensivist and anesthesiologist. 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 why.

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