Review

Bench-to-bedside review: Permissive hypercapnia

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Abstract

Current protective lung ventilation strategies commonly involve hypercapnia. This approach has resulted in an increase in the clinical acceptability of elevated carbon dioxide tension, with hypoventilation and hypercapnia 'permitted' in order to avoid the deleterious effects of high lung stretch. Advances in our understanding of the biology of hypercapnia have prompted consideration of the potential for hypercapnia to play an active role in the pathogenesis of inflammation and tissue injury. In fact, hypercapnia may protect against lung and systemic organ injury independently of ventilator strategy. However, there are no clinical data evaluating the direct effects of hypercapnia *per se* in acute lung injury. This article reviews the current clinical status of permissive hypercapnia, discusses insights gained to date from basic scientific studies of hypercapnia and acidosis, identifies key unresolved concerns regarding hypercapnia, and considers the potential clinical implications for the management of patients with acute lung injury.

Keywords acidosis, acute lung injury, acute respiratory distress syndrome, buffering, hypercapnia, mechanical ventilation, ventilation induced lung injury, sepsis

Introduction

Current protective lung ventilation strategies generally involve some degree of hypercapnia. This has resulted in a shift in clinical paradigms regarding hypercapnia from avoidance to tolerance, with hypercapnia increasingly permitted in order to realize the benefits of low lung stretch. Insights from laboratory models of acute lung injury (ALI) have suggested that hypercapnia may play an active role in the pathogenesis of inflammation and tissue injury. This raises the possibility that hypercapnia *per se* may exert direct protective effects in ALI states, distinct from the demonstrated benefits of reduced lung stretch. However, there are no clinical data evaluating the efficacy of hypercapnia *per se*, independent of ventilator strategy, in ALI states. Furthermore, it is unlikely that a clinical trial of 'permissive hypercapnia' will be carried out, at least in the medium term.

This article reviews the current clinical status of permissive hypercapnia, discusses insights gained to date from basic scientific studies of hypercapnia and acidosis, and considers the potential clinical implications of these findings for the management of patients with ALI.

Permissive hypercapnia: current paradigms

The potential for mechanical ventilation to potentiate or even cause lung injury and worsen outcome in acute respiratory distress syndrome (ARDS) patients is clear [1–3]. Ventilator-associated lung injury (VALI) may occur via several mechanisms. Mechanotrauma results from repetitive over-stretching and damage to lung tissue, and cyclic alveolar recruitment and derecruitment [4–9]. Increased mechanical stress may directly activate the cellular and humoral immune response in the lung [8–11], although the exact role played

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; IκB = inhibitory protein κB; NF-κB = nuclear factor κB; $Paco_2$ = arterial carbon dioxide tension; THAM = tris-hydroxymethyl aminomethane; VALI = ventilator-associated lung injury.

by this mechanism in the pathogenesis of lung and systemic organ injury has been disputed [12,13]. In any case, the potential for intrapulmonary prostaglandins [14], cytokines [15], endotoxin [16] and bacteria [17] to cross an impaired alveolar–capillary barrier following high stretch mechanical ventilation is clear.

VALI may be limited by instituting protective lung ventilation strategies in order to reduce mechanical trauma and the resulting inflammatory effects. These strategies invariably involve a reduction in the tidal volume and/or transalveolar pressure, which generally leads to an elevation in arterial carbon dioxide tension ($PaCO_2$), an approach that has been termed 'permissive hypercapnia'. These protective lung ventilation strategies have been demonstrated to improve survival in patients with ARDS [1,18,19]. The reported levels of $PaCO_2$ and pH (mean maximum $PaCO_2$ 67 mmHg, mean pH 7.2) in the study conducted Hickling and coworkers [18] reflect typical levels observed with institution of this technique. Accordingly, there has been a shift toward greater clinical acceptability of hypercapnia in ALI and ARDS. Current paradigms attribute the protective effect of these ventilatory strategies solely to reductions in lung stretch, with hypercapnia permitted in order to achieve this goal. However, the potential exists for hypercapnia to modulate the pathogenesis of VALI.

'Bedside-to-bench': rationale for laboratory studies

Protective ventilatory strategies that involve hypoventilation result in both limitation of tidal volume and elevation in systemic carbon dioxide tension. Lung stretch is distinct from elevated carbon dioxide tension, and by manipulation of respiratory parameters (frequency, tidal volume, dead-space, inspired carbon dioxide) it can, at least to some extent, be separately controlled. The ARDSnet investigators reported a 25% reduction in mortality with a complex ventilation strategy [20] involving limitation of mean tidal volume to 6 ml/kg, as compared with a more traditional tidal volume of 12 ml/kg [2]. That study minimized the potential for hypercapnia in the low tidal volume group, and instead permitted increased respiratory rates (respiratory frequency of 29 breaths/min). In fact, the need to reduce tidal volumes substantially to improve outcome in ARDS patients was recently questioned [21,22], and it is increasingly clear that most clinicians seldom use very low tidal volumes in practice [23]. These findings raise questions regarding the need for – and indeed the clinical acceptability of – permissive hypercapnia.

These issues underscore the need to determine the effects of hypercapnia in isolation. If hypercapnia were proven to have independent benefit, then deliberately elevating $PaCO_2$ could confer an additional advantage over reducing lung stretch. Conversely, in patients managed with conventional permissive hypercapnia, adverse effects of elevated $PaCO_2$ might be concealed by the benefits of lessened lung stretch.

Because outcome in the intensive care unit might be related to systemic injury – as opposed to simply lung injury – it is necessary to determine the effects of hypercapnia on pathophysiological function in the heart and brain as well as the lung. These issues are further underlined by the fact that hypercapnia has potentially severe adverse effects in some clinical settings, such as critically elevated intracranial pressure or pulmonary vascular resistance.

It is not currently practicable or feasible to examine the direct effects of hypercapnic acidosis, independent of ventilator strategy, in humans. This has necessitated a return to the laboratory bench, and an examination of the potential for induced hypercapnia to modulate the severity of ALI and systemic organ injury in animal models.

Hypercapnia and acidosis: insights from the bench

There is a growing body of evidence suggesting that hypercapnia and acidosis exert biologically important beneficial effects in experimental ALI and systemic organ injury. The mechanisms that underlie these protective effects of hypercapnia are increasingly well characterized.

Acute lung injury

Direct administration of inspired carbon dioxide has been demonstrated to attenuate ALI in several *ex vivo* and *in vivo* laboratory models. In the isolated perfused rabbit lung, hypercapnic acidosis was demonstrated to attenuate the increases in lung permeability seen following free radical [24], ischaemia/reperfusion [24,25] and ventilator-induced [26] ALI. Hypercapnic acidosis directly attenuates indices of ALI such as oxygenation, lung mechanics and lung permeability, following *in vivo* pulmonary [27] and mesenteric [28] ischaemia/reperfusion. Hypercapnic acidosis also directly protects against endotoxin-induced lung injury, a model of sterile sepsis-induced ARDS [29]. Hypercapnic acidosis attenuates pulmonary apoptosis, a mechanism of programmed cell death, following pulmonary ischaemia/reperfusion [27].

In most clinical scenarios, therapeutic intervention is only possible after initiation of the injury process. The therapeutic potential of hypercapnic acidosis is underlined by the finding that it was effective when instituted after initiation of the lung injury process, in the settings of both mesenteric ischaemia/reperfusion and endotoxin-induced ALI models [28,29]. This contrasts with many other initially promising experimental strategies, which demonstrate potential when used before the injury process but lose their effectiveness when utilized after the development of organ injury.

The ability of hypercapnic acidosis to attenuate VALI directly was examined in *in vivo* laboratory studies. Hypercapnic acidosis has been demonstrated to attenuate physiological and histological indices of lung injury induced by very high

levels of lung stretch [30]. Hypercapnic acidosis exhibits more modest protective effects in the context of more clinically relevant tidal stretch [31]. However, hypercapnic acidosis did not attenuate lung injury induced by surfactant depletion, an atelectasis-prone model of ALI [32]. Taken together, these findings suggest that, in VALI, hypercapnic acidosis may attenuate the component of injury that is due to lung stretch but not that due to collapse and re-expansion of atelectatic lung.

Systemic organ injury

Patients with ARDS tend not to die from respiratory failure *per se* but rather because of the development of multiorgan failure [33]. Hence, any consideration of the potential effects of hypercapnic acidosis in critical illness must include its effects in extrapulmonary organs.

Hypercapnic acidosis appears to exert protective effects on the myocardium. In the isolated heart, reperfusion with a hypercapnic acidotic perfusate for a short period potentiates recovery of myocardial function following prolonged cold cardioplegic ischaemia [34]. Metabolic acidosis to an equivalent pH also appears to exert protective effects in *ex vivo* models [35], although this is disputed [34]. Kitakaze and coworkers [36] found that reperfusions with both hypercapnic and metabolic acidotic reperfusates were equally effective in reducing infarct size in an *in vivo* canine model of left anterior descending coronary artery ischaemia.

In the brain, hypercapnic acidosis attenuates hypoxic/ischaemic brain injury in the immature rat [37,38]. Hypercapnic acidosis protects the porcine brain from hypoxia/reoxygenation-induced injury [39] and attenuates neuronal apoptosis [40]. Cortical brain homogenates develop fewer free radicals and less lipid peroxidation when pH is lowered by carbon dioxide than when it is lowered by hydrochloric acid [41]. In isolated hepatocytes exposed to anoxia [42] and chemical hypoxia [43], acidosis markedly delays the onset of cell death. Correction of the pH actually accelerated cell death. This phenomenon may represent a protective adaptation against hypoxic and ischaemic stress. Isolated renal cortical tubules exposed to anoxia have improved ATP levels on reoxygenation at a pH of 6.9 when compared with tubules incubated at a pH of 7.5 [42].

Dose–response issues

There is experimental evidence that the beneficial effects of moderate hypercapnia may be counterbalanced by a potential for adverse effects at higher levels. This is supported by experimental evidence demonstrating that protection from the adverse effects of brain ischaemia was better when the inspired carbon dioxide was set at 6% rather than at 9% [37]. Of concern, severe hypercapnia produced by 15% carbon dioxide was more recently demonstrated to worsen neurological injury in this context [44]. In isolated hepatocytes, the degree of protection from anoxic injury conferred by a metabolic acidosis was greater at a pH of 6.9 than at a pH of 6.6 [42].

Hypercapnia and acidosis: mechanisms of action

A clear understanding of the cellular and biochemical mechanisms that underlie the protective effects of hypercapnic acidosis is essential for several reasons. It constitutes a prerequisite if translation of the laboratory findings to the bedside is to be accomplished, because it allows us to define more clearly the potential therapeutic utility of hypercapnic acidosis in ALI. Of particular importance, a greater understanding of the mechanisms of action of hypercapnic acidosis facilitates prediction of its potential side effects in the clinical context. This may result in the identification of patient groups for which hypercapnia may have deleterious effects and should be avoided. Furthermore, it facilitates extrapolation of these insights to a variety of other disease states. In this regard, the finding that the protective effects of hypercapnic acidosis in stretch-induced lung injury appear independent of effects on surfactant [31] may have implications for surfactant-deficient disease states such as infant respiratory distress syndrome. Finally, a greater understanding of the protective actions of hypercapnic acidosis in ALI may lead to the discovery of other promising therapeutic modalities for this devastating disease process.

Acidosis versus hypercapnia

The protective effects of hypercapnic acidosis may be a function of the acidosis or the hypercapnia *per se,* or a combination of both. Acidosis is common in critical illness and is often a poor prognostic sign. However, this effect is associative rather than causative, and prognosis depends on the underlying condition rather than on the acidosis *per se*. This issue is of particular relevance when considering the appropriateness of buffering in the clinical context. If any protective effects of hypercapnic acidosis were found to result from the acidosis, then efforts to buffer a hypercapnic acidosis would lessen such protection and should be discouraged. Conversely, if hypercapnia *per se* (and not the acidaemia) were found to be protective, then further research efforts should be directed to finding better buffering strategies in order to maximize the benefits of hypercapnia.

The protective effects of hypercapnic acidosis in experimental lung and systemic organ injury appear to be primarily a function of the acidosis generated [25,45]. The myocardial protective effects of hypercapnic acidosis are also seen with metabolic acidosis both in *ex vivo* [35] and *in vivo* [36,46] models. In the liver, acidosis delays the onset of cell death in isolated anoxic hepatocytes [42,43,47]. However, the type of acidosis (i.e. hypercapnic versus metabolic) does appear to be of importance. Although normocapnic (i.e. metabolic) acidosis attenuates primary ischaemia/reperfusion-induced ALI in an *ex vivo* model, it is less effective than hypercapnic acidosis [25]. In addition, there are reports of lung [48] and

intestinal [49] injury following induction of metabolic acidosis by hydrochloric acid infusion in whole animal models. However, it is important to recognize that infusion of hyperosmolar solutions of strong acids into whole animal preparations may produce toxic effects that are unrelated to any change in pH [50].

Conversely, in the isolated lung the protective effects of hypercapnic acidosis in ischaemia/reperfusion-induced ALI are greatly attenuated if the pH is buffered toward normal [25]. Of concern, hypercapnia at normal pH may cause injury to alveolar epithelial cell monolayers [45] and decrease surfactant protein A function *in vitro* [51].

Anti-inflammatory effects

Several key components of the inflammatory response, which contribute substantially to tissue injury and damage in ARDS patients, appear to be attenuated by hypercapnic acidosis. Hypercapnic acidosis appears to interfere with the coordination of the immune response by reducing cytokine signalling [52–54]. Hypercapnic acidosis inhibits the release of tumour necrosis factor-α and interleukin-1 from stimulated macrophages *in vitro* [52]. The potential for hypercapnic acidosis to attenuate pulmonary and systemic levels of key cytokines *in vivo* is clear from the finding that it decreased tumour necrosis factor-α levels in bronchoalveolar lavage fluid following pulmonary ischaemia/reperfusion [27].

The cellular and molecular mechanisms that underlie the inhibitory effects of hypercapnic acidosis in the neutrophil are increasingly well understood. Hypercapnic acidosis modulates neutrophil expression of selectins and intercellular adhesion molecules, which are necessary for neutrophil binding to the vascular surface during inflammation [55]. Hypercapnia and acidosis may impair neutrophil intracellular pH regulation. Intracellular pH decreases when neutrophils are activated by immune stimuli [56–59]. If milieu pH is normal, then there tends to be a recovery in neutrophil intracellular pH back toward normal levels. Hypercapnia decreases extracellular and intracellular pH in the local milieu, resulting in a rapid fall in neutrophil cytosolic pH [54,60,61], potentially overwhelming the capacity of neutrophils, and in particular activated neutrophils [62], to regulate cytosolic pH. Failure to restore neutrophil cytosolic pH has been demonstrated to impair functions such as chemotaxis [63,64]. The potential for hypercapnic acidosis to attenuate neutrophil activity *in vivo* is clear from the finding that it attenuates lung neutrophil recruitment after both ventilator induced [30] and endotoxin induced [29] ALI.

Effects on free radical generation and activity

Hypercapnic acidosis appears to attenuate free radical production and modulate free radical induced tissue damage. In common with most biological enzymes, the enzymes that produce these oxidizing agents function optimally at neutral physiological pH levels. Oxidant generation by both basal and stimulated neutrophils appears to be regulated by ambient carbon dioxide levels, with oxidant generation reduced by hypercapnia and increased by hypocapnia [54]. The production of superoxide by stimulated neutrophils *in vitro* is decreased at acidic pH [65–67]. In the brain, hypercapnic acidosis attenuates glutathione depletion and lipid peroxidation, which are indices of oxidant stress [39]. In the lung, hypercapnic acidosis has been demonstrated to reduce free radical tissue injury following pulmonary ischaemia/reperfusion [27]. Hypercapnic acidosis appears to attenuate the production of higher oxides of nitric oxide, such as nitrite and nitrate, following both ventilator-induced [26] and endotoxin-induced [29] ALI. Hypercapnic acidosis inhibits ALI mediated by xanthine oxidase, a complex enzyme system produced in increased amounts during periods of tissue injury, which is a potent source of free radicals [68] in the isolated lung [24]. In *in vitro* studies the enzymatic activity of xanthine oxidase was potently decreased by acidosis, particularly hypercapnic acidosis [24,25].

Concerns exist regarding the potential for hypercapnia to potentiate tissue nitration by peroxynitrite, a potent free radical. Peroxynitrite is produced *in vivo* largely by the reaction of nitric oxide with superoxide radical, and causes tissue damage by oxidizing a variety of biomolecules and by nitrating phenolic amino acid residues in proteins [69–73]. The potential for hypercapnia to promote the formation of nitration products from peroxynitrite has been clearly demonstrated in recent *in vitro* experiments [45,51]. However, the potential for hypercapnia to promote nitration of lung tissue *in vivo* appears to depend on the injury process. Hypercapnic acidosis decreased tissue nitration following pulmonary ischaemia/reperfusion-induced ALI [27], but it increased nitration following endotoxin-induced lung injury [29].

Regulation of gene expression

Hypercapnic acidosis has been demonstrated to regulate the expression of genes that are central to the inflammatory response. Nuclear factor-κB (NF-κB) is a key regulator of the expression of multiple genes that are involved in the inflammatory response, and its activation represents a pivotal early step in the activation of the inflammatory response [74]. NF-κB is found in the cytoplasm in an inactive form bound to inhibitory proteins called inhibitory protein-κB (IκB), of which the important isoforms are IκB-α and IκB-β. IκB proteins are phosphorylated by the IκB kinase complex and subsequently degraded, thus allowing NF-κB to translocate into the nucleus, bind to specific promoter sites and activate target genes [74]. Hypercapnic acidosis has been demonstrated to inhibit significantly endotoxin-induced NF-κB activation and DNA binding activity in human pulmonary endothelial cells via a mechanism mediated through a decrease in IκB-α degradation [75]. Hypercapnic acidosis was demonstrated to suppress endothelial cell production of intercellular adhesion molecule-1 and interleukin-8 mRNA and protein, which are

thought to be mainly regulated by the NF-κB-related pathway, and suppressed indices of cell injury [75].

'Bench-to-bedside': clinical implications

Permissive hypercapnia has become a central component of protective lung ventilatory strategies, and is increasingly accepted in the clinical context. Hypercapnia results in the generation of an acidosis, the extent of which depends on the degree of hypercapnia and whether buffering is practiced. Although the presence of an acidosis, whether hypercapnic or metabolic, indicates loss of physiological homeostasis and the presence of disease and/or organ dysfunction, it represents an association rather than a cause–effect relationship, and it does not indicate that acidosis is directly harmful. As discussed earlier, considerable experimental evidence suggests the potential for hypercapnia and acidosis to exert protective effects in the setting of ALI and systemic organ injury. The mechanisms that underlie the effects of hypercapnia are increasingly well delineated. However, there are concerns that these mechanisms of action may result in deleterious effects in specific clinical contexts.

Hypercapnia and protective lung ventilation

There is an increasing body of evidence in the critical care literature attesting to the safety of hypercapnic acidosis in patients undergoing permissive hypercapnia [18,19,76–81]. Furthermore, the potential for hypercapnia to protect against the deleterious effects of mechanical ventilation is clear. The potential for hypercapnia to attenuate to the deleterious effects of high stretch mechanical ventilation in the clinical context has recently received strong support in a preliminary report from Kregenow and coworkers [82], in which those investigators examined mortality as a function of permissive hypercapnia in patients enrolled in the ARDSnet tidal volume study [2]. Using multivariate logistic regression analysis, and controlling for other comorbidities and severity of lung injury, they reported that, in the high tidal volume arm of the study, permissive hypercapnia was an independent predictor of survival. However, there was no additional protective effect of permissive hypercapnia in patients randomly assigned to receive the lower tidal volume (6 ml/kg) [82].

At present, there are insufficient clinical data to suggest that hypercapnia *per se* should be independently induced, outside the context of a protective ventilatory strategy. Ventilatory strategies that involve hypercapnia are clinically acceptable only provided that the clinician is primarily targeting reduced tidal stretch. In fact, the recent questioning of the real benefit of low (versus moderate) tidal volume ventilation for adults with ARDS may result in hypercapnia becoming less acceptable in the ventilatory management of ARDS, in the absence of proven beneficial effects in this context.

Hypercapnia and haemodynamic stability

The potential for hypercapnic acidosis to exert significant haemodynamic effects in patients with ARDS is clear [83]. However, the potential for hypercapnic acidosis to exert detrimental effects on myocardial function [84] and on the peripheral circulation [85] may be overstated. Hypercapnic acidosis, even when rapidly induced, has been demonstrated not to produce significant haemodynamic disturbances [83,85]. Hypercapnic acidosis has repeatedly been demonstrated to increase cardiac output in ARDS patients [80,83]. In a small but carefully conducted clinical study, the rapid induction of a hypercapnic acidosis ($Paco_2$ 80 mmHg, pH 7.2) did impair myocardial contractility, as evaluated with echocardiography [83]. However, cardiac output was significantly increased despite impairment in contractility, presumably as a result of a proportionately greater fall in systemic vascular resistance. These findings are supported by a study that evaluated the haemodynamic effects of the apnoea test for brain-stem function [85]. A 10-min apnoea test for brain death, which resulted in a mean pH of 7.17 ± 0.02 and mean $Paco_2$ of 78 ± 3 mmHg, produced minimal haemodynamic effects in these patients. The safety of hypercapnic acidosis is further supported by reports that individuals, both adults [86] and children [87] have survived exposure to extreme levels.

Nevertheless, at higher levels of hypercapnia and acidosis, haemodynamic instability may become a limiting factor. This is supported by experimental evidence demonstrating that animal survival following mesenteric ischaemia/reperfusion was better when the inspired carbon dioxide was set at 5% rather than at 10% or 20% [28]. Mortality in these animals resulted from severe haemodynamic instability after mesenteric reperfusion at higher inspired carbon dioxide levels.

Hypercapnia in sepsis

Significant concerns have been raised regarding the safety of hypercapnia in the context of sepsis [29,88,89]. The importance of these concerns is clear given the prevalence of sepsis as a cause of admission to the intensive care unit [90], the frequency of nosocomial infection in the critically ill [91] and the fact that severe sepsis associated with multiorgan failure remains a leading cause of death in these patients [32]. Laboratory studies of hypercapnic acidosis to date have been in sterile, nonsepsis models of ALI and systemic organ injury [89]. Although hypercapnic acidosis has been shown to be protective against endotoxin-induced lung injury [29], this pathway is only one of several mechanisms by which live proliferating bacteria cause lung injury.

Hypercapnia and/or acidosis may modulate the interaction between host and bacterial pathogen via several mechanisms, as discussed above. The potent anti-inflammatory properties of hypercapnic acidosis may impair the host response to live bacterial sepsis. The potential for hypercapnia to alter intracellular pH regulation may inhibit neutrophil microbicidal [63,64] and chemotactic activity [92]. The production of free radicals such as the superoxide radical, hydrogen peroxide and hypochlorous acid are central

to the bactericidal activity of neutrophils and macrophages. The potential for hypercapnic acidosis to attenuate free radical production is clear. This is of importance given that the phagocytic activity and bactericidal capacity of neutrophils and macrophages is central to an effective host response to invading bacteria. Acidosis may render some antibiotics less effective [93]. In addition, acidosis may alter the mechanism of neutrophil cell death from apoptosis to necrosis, which may result in increased tissue destruction [54,94]. Conversely, hypercapnia may retard pathogen growth, and thereby decrease the overall septic insult [95,96]. At the cellular level, mitochondrial dysfunction and cellular dysoxia are central to the pathogenesis of sepsis [97,98]. Hypercapnia might favourably modulate cellular supply–demand balance in favour of cellular survival, given its effects in other contexts [99]. However, the potential interactions between hypercapnia and sepsis at the cellular level remain to be elucidated.

The overall effect of the degree of hypercapnia seen with protective lung ventilation on the host response to sepsis remains unclear. Many *in vitro* studies examining the effects of carbon dioxide on indices of immune function utilize levels well beyond that seen in the clinical context. Nevertheless, the potential for hypercapnia to exert deleterious effects in the context of sepsis, and to result in significant adverse consequences, is clear.

Buffering of permissive hypercapnia

Buffering of the acidosis induced by hypercapnia in ARDS patients remains a common albeit controversial clinical practice [100,101] and was permitted in the ARDSnet study [2]. However, there are no long-term clinical outcome data (e.g. survival, duration of hospital stay) to support the buffering of a hypercapnic acidosis, and several concerns exist regarding this practice. There is evidence that the protective effects of hypercapnic acidosis in ALI are a function of the acidosis rather than of elevated carbon dioxide *per se* [25,45]. Specific concerns exist regarding the use of bicarbonate to buffer the acidosis produced by hypercapnia. The effectiveness of bicarbonate infusion as a buffer is dependent on the ability to excrete carbon dioxide, rendering it less effective in buffering a hypercapnic acidosis. In fact, bicarbonate may further raise systemic carbon dioxide levels under conditions of reduced alveolar ventilation, such as ARDS [102]. Furthermore, although bicarbonate may correct arterial pH, it may worsen an intracellular acidosis because the carbon dioxide produced when bicarbonate reacts with metabolic acids diffuses readily across cell membranes, whereas bicarbonate cannot [103]. Taken together, these issues suggest that, in the absence of a correction to the primary problem, buffering a hypercapnic acidosis with bicarbonate is not likely to be of benefit.

These concerns do not exclude a role for the use of other buffers, such as the amino alcohol tromethamine (tris-hydroxymethyl aminomethane [THAM]), in specific situations in which the physiological effects of hypercapnic acidosis are of concern. THAM penetrates cells easily and can buffer pH changes and simultaneously reduce carbon dioxide tension [104], making it effective in situations where carbon dioxide excretion is limited, such as ARDS [83]. In clinical studies THAM has been demonstrated to improve arterial pH and base deficit, and did not increase $PaCO_2$ tension [83,105]. THAM administration ameliorated the haemodynamic consequences and rapidly induced hypercapnic acidosis in a small but carefully performed clinical study in ARDS patients [83].

Conclusion

Permissive hypercapnia is a central component of current protective lung ventilatory strategies in the clinical context. Furthermore, induced hypercapnic acidosis appears to demonstrate considerable protective effects in several laboratory models of ALI and systemic organ injury. However, there are concerns regarding the potential for hypercapnia and/or acidosis to exert deleterious effects, particularly in the setting of sepsis, that suggest the need for caution and further investigation into the effects of hypercapnia in the clinical context. Furthermore, the acceptability of permissive hypercapnia may be questioned in the future, given concerns regarding the real benefit of low (versus moderate) tidal volume ventilation for adults with ARDS. A clearer understanding of the effects and mechanisms of action of hypercapnia and acidosis is essential to facilitate identification of the optimum response to, and tolerance of, hypercapnia in the setting of protective ventilator strategies, and to define more clearly the safety and potential therapeutic utility of hypercapnia in ARDS.

Competing interests

The author(s) declare that they have no competing interests.

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