Permissive hypercapnia: role in protective lung ventilatory strategies

Martina Ni Chonghaile[a,b], Brendan Higgins[a] and John G. Laffey[a,b]

Purpose of review
Hypercapnia is a central component of current protective ventilatory strategies. This review aims to present and interpret data from recent clinical and experimental studies relating to hypercapnia and its role in protective ventilatory strategies.
Recent findings
Increasing clinical evidence supports the use of permissive hypercapnia, particularly in acute lung injury/acute respiratory distress syndrome, status asthmaticus, and neonatal respiratory failure. However, there are no clinical data examining the contribution of hypercapnia *per se* to protective ventilatory strategies. Recent experimental studies provide further support for the concept of therapeutic hypercapnia, whereby deliberately elevated $PaCO_2$ may attenuate lung and systemic organ injury. CO_2 administration attenuates experimental acute lung injury because of adverse ventilatory strategies, mesenteric ischemia reperfusion, and pulmonary endotoxin instillation. Hypercapnic acidosis attenuates key effectors of the inflammatory response and reduces lung neutrophil infiltration. At the genomic level, hypercapnic acidosis attenuates the activation of nuclear factor-κB, a key regulator of the expression of multiple genes involved in the inflammatory response. The physiologic effects of hypercapnia, both beneficial and potentially deleterious, are increasingly well understood. In addition, reports suggest that humans can tolerate extreme levels of hypercapnia for relatively prolonged periods without adverse effects.
Summary
The potential for hypercapnia to contribute to the beneficial effects of protective lung ventilatory strategies is clear from experimental studies. However, the optimal ventilatory strategy and the precise contribution of hypercapnia to this strategy remain unclear. A clearer understanding of its effects and mechanisms of action is central to determining the safety and therapeutic utility of hypercapnia in protective lung ventilatory strategies.

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

Curr Opin Crit Care 11:56–62. © 2005 Lippincott Williams & Wilkins.

[a]Department of Anaesthesia, Clinical Sciences Institute and National Centre for Biomedical Engineering Sciences, National University of Ireland, Galway, Ireland; and [b]University College Hospital, Galway, Ireland

Supported by grants from the Health Research Board, Ireland, the Irish Lung Foundation, the Yamanouchi European Foundation, and The Association of Anaesthetists of Great Britain and Ireland (J.G.L.) and an Abbott Scholarship awarded by the College of Anaesthetists, Ireland (M.N.C.).

Correspondence to John G. Laffey, Department of Anaesthesia, Clinical Sciences Institute, National University of Ireland, Galway, Ireland
Tel: 353 91 544608; fax: 353 91 544908; e-mail: john.laffey@nuigalway.ie

Current Opinion in Critical Care 2005, 11:56–62

Abbreviations

ALI	acute lung injury
ARDS	acute respiratory distress syndrome
NF-κB	nuclear factor kappa beta
PEEP	positive end-expiratory pressure
TGI	tracheal gas insufflation
VILI	ventilator-induced lung injury

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1070-5295

Introduction

Mechanical ventilatory strategies that use high tidal volumes and transpulmonary pressures directly injure the lung, a phenomenon termed ventilator-induced lung injury (VILI). Developments in our understanding of the pathogenesis of VILI, and clinical outcome data, have increased the use of low lung stretch ventilatory strategies that reduce mechanical trauma and the associated inflammatory effects [1,2]. These strategies generally necessitate hypoventilation and tolerance of hypercapnia to realize the benefits of low lung stretch. This has resulted in a shift in clinical paradigms regarding hypercapnia—from strict avoidance to acceptance, and a realization that even moderate to marked degrees of hypercapnia are well tolerated. Paralleling this paradigm shift, several investigators have demonstrated the potential for induced hypercapnic acidosis to directly attenuate experimental acute lung injury. These findings raise the possibility that hypercapnia may have an active role in the pathogenesis of inflammation and tissue injury. The effects of hypercapnia in acute lung injury states may be independent of, and distinct from, the demonstrated benefits of reduced lung stretch.

This paper reviews the current clinical status of permissive hypercapnia, discusses the 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 acute lung injury. Experimental and clinical studies of special interest, published within the annual period of review, have been highlighted.

Permissive hypercapnia: clinical spectrum

Acute lung injury and acute respiratory distress syndrome

Mechanical ventilation potentiates and may even cause lung damage, and it worsens the outcome in patients with ALI and ARDS [3•,4]. The potential for protective lung ventilatory strategies, with varying degrees of permissive hypercapnia, to improve survival in patients with ALI/ARDS is increasingly clear [3•,4–6]. The direct contribution of hypercapnia *per se* to these protective effects in the clinical context has not been determined. However, the potential for hypercapnia to directly protect against the effects of high stretch mechanical ventilation has recently received strong support in a preliminary communication. Kregenow *et al.* [7] examined mortality as a function of permissive hypercapnia on the day of enrollment of patients to the ARDSnet tidal volume study [6]. Using multivariate logistic regression analysis, and controlling for other comorbidities and severity of lung injury, they reported that permissive hypercapnia reduced mortality in patients randomized to the higher tidal volume [7]. However permissive hypercapnia did not affect outcome in patients randomized to the lower tidal volume.

Of concern, there is clear evidence that many clinicians do not use protective ventilatory strategies in patients with ALI/ARDS, despite convincing outcome data supporting their use [5,6]. Rubenfeld *et al.* [8•] attempted to identify barriers to the implementation of protective ventilatory strategies. Experienced nurses and respiratory therapists, based at hospitals that participated in the ARDS Network trial, were surveyed. Identified barriers to the institution of protective ventilatory strategies included an unwillingness by physicians to relinquish control of ventilator to a set protocol, delays in the diagnosis of ARDS/ALI, and the presence of conditions that were considered by the physicians to be contraindications to a protective lung strategy. Barriers to the continuation of lung protective ventilation included concerns about patient comfort and concerns relating to the potential for hypercapnia, acidosis, and hypoxemia to exert deleterious effects. The therapeutic benefit of protective strategies did not seem to be adequately recognized. This survey has clear limitations and seems to assume that all barriers to the use of protective ventilation are physician-centered. Furthermore, some 'barriers,' such as failure of the physician to relinquish control of the ventilator, may be appropriate, given the therapeutic potential of protective ventilatory strategies. However, these findings deserve careful consideration if the full benefits of lung protective strategies in ALI/ARDS are to be realized.

Status asthmaticus

Although much of the current work regarding ventilatory strategies involving permissive hypercapnia concentrates on its therapeutic potential in ALI/ARDS, its use was first described in patients with status asthmaticus. Permissive hypercapnia continues to play a central role in the ventilatory management of acute severe asthma. Dhuper *et al.* [9], in a study of the factors contributing to the need for tracheal intubation and mechanical ventilation in asthma, report a low incidence of barotrauma and no mortality with a ventilation strategy involving permissive hypercapnia (peak airway pressures maintained <50 cm H_2O irrespective of the $PaCO_2$ level). Gupta *et al.* [10] analyzed the factors contributing to outcome in patients with acute severe asthma admitted to 128 intensive care units in England, Wales, and Northern Ireland participating in the ICNARC (Intensive Care National Audit and Research Center) case-mix database. An analysis of $PaCO_2$ levels in all patients receiving ventilation within 24 hours of admission showed that these patients were treated with a ventilatory strategy that resulted in significant hypercapnia (mean highest $PaCO_2$ of 8.2 KPa) [10].

Neonatal respiratory failure

The benefits of permissive hypercapnia in neonatal respiratory failure are well recognized [11]. In fact, the clearest evidence for the use of permissive hypercapnia is in infants with neonatal respiratory distress syndrome, in which a randomized controlled clinical trial of preterm infants demonstrated a clear benefit with permissive hypercapnia [12]. Kamper *et al.* [13•] conducted a prospective multicenter study of the respiratory treatment of neonates of extremely low gestational age (gestational age <28 weeks) and birthweight (birthweight <1000 g) admitted to neonatal intensive care units across Denmark in 1994 through 1995. They reported that a ventilatory support strategy based on permissive hypercapnia with the early use of nasal continuous positive airway pressure, with surfactant therapy and mechanical ventilation reserved for failure of nasal continuous positive airway pressure, was as effective as strategies involving early mechanical ventilation and seemed to significantly reduce the incidence of chronic lung disease [13•].

Permissive hypercapnia plays an increasing role in the ventilatory treatment of infants with congenital diaphragmatic hernia. This contrasts sharply with traditional management strategies that involved aggressive hyperventilation with the aim of producing systemic alkalinization. However, high levels of barotrauma, poor long-term respiratory outcomes, and poor survival rates have prompted the recognition that the hypoplastic lung is the major pathophysiologic defect. Accordingly, the avoidance of barotrauma has assumed increasing importance, and ventilation strategies involving permissive hypercapnia are increasingly used in this clinical setting. Bagolan *et al.* [14•] conducted a retrospective analysis of the impact of three different treatment protocols on the outcome in high-risk infants with congenital diaphragmatic hernia. They

divided admissions over a 6-year period into three chronologic groups, which were similar in terms of predictive risk factors, based on the treatment protocols used. They reported that a treatment protocol prioritizing permissive hypercapnia produced a substantial increase in survival, decreased barotrauma, and decreased morbidity at 6 months. By contrast, the earlier introduction of high-frequency oscillatory ventilation seemed to have minimal impact. This study has limitations, notably an inability to take account of any impact of other changes in the management of this condition over time, such as delayed surgical intervention. However, the finding of a clear survival benefit with a treatment protocol in which permissive hypercapnia seems to be the sole addition is persuasive [14•].

Tolerance to extreme hypercapnia

Several recent reports emphasize the potential for tolerance to extreme levels of hypercapnia, termed supercarbia, in both adults and children. Mazzeo *et al.* [15] described complete clinical recovery after an episode of prolonged life-threatening status asthmaticus in an 8-year-old boy. Despite maximal medical therapy involving both conventional and "last-resort" bronchodilator therapies, a progressive respiratory acidosis developed, with a nadir pH of 6.77 and $PaCO_2$ of 39 KPa (293 mm Hg) recorded 10 hours after admission. Hemodynamic stability was maintained throughout, and no neurologic or other organ dysfunction was detected after eventual complete resolution of the status asthmaticus. Urwin *et al.* [16] reported survival without adverse sequelae after extreme hypercapnia (PCO_2 31.05 KPa) in an older woman with acute decompensation of chronic obstructive airway disease. These reports serve to allay fears regarding the potential for hypercapnia to exert direct deleterious effects.

Hypercapnia: insights from the laboratory

To our knowledge, no clinical data have directly compared the effects of comparable lung ventilatory strategies in the presence or absence of hypercapnia. At present, it is not feasible to examine the direct effects of hypercapnic acidosis, independent of ventilator strategy, in humans. However, important insights continue to be gained from evaluation of the direct effects of hypercapnia and acidosis in experimental models of lung and systemic organ injury.

Acute lung injury

Recent studies have contributed to a growing body of evidence suggesting that hypercapnia and acidosis exerts biologically important effects in experimental acute lung injury. The potential for hypercapnic acidosis, induced by the administration of inspired CO_2, to attenuate ALI induced by primary (*ie,* lung) ischemia-reperfusion is clear from previous *in vivo* and *ex vivo* studies [17–19]. More recently, hypercapnic acidosis was demonstrated to directly attenuate indices of ALI after secondary (*ie,* mesenteric) ischemia-reperfusion in an *in vivo* rat model [20••]. Lung protection with hypercapnic acidosis occurred despite pulmonary artery pressures that were greater than those observed with normocapnia. Reperfusion increased lipid peroxidation in the bowel, liver, and lung, and it caused histologically apparent bowel injury; however, none of these effects was altered by hypercapnia [20••].

Hypercapnic acidosis protects against VILI in both *ex vivo* and *in vivo* models [21,22]. Recent studies, which used more clinically relevant degrees of tidal stretch, indicate that hypercapnic acidosis exerts more modest protective effects. Strand *et al.* [23•] examined the potential for hypercapnic acidosis to attenuate mild VILI in surfactant-treated preterm lamb lungs. The animals were randomized to receive hypercapnia (mean $PaCO_2$ levels 95 mm Hg) or control conditions. A modest degree of VILI was induced by ventilation with moderate tidal lung stretch (tidal volume 12–15 mL/kg^{-1}) for 30 minutes followed by a conventional tidal volume (6–9 mL/kg^{-1}) for 5.5 hours. Hypercapnic acidosis was well tolerated, and postnatal hemodynamic adaptation seemed to be unaffected. Hypercapnic acidosis attenuated the physiologic indices of ALI and reduced the infiltration of inflammatory cells into the airspaces but not the lung tissue. In addition, there was a consistent but nonsignificant trend to reduced indicators of inflammation in the lung tissue and bronchoalveolar lavage fluid with hypercapnic acidosis [23•]. Laffey *et al.* [24] demonstrated the potential for hypocapnia to worsen and for hypercapnia to attenuate VILI, in the context of a clinically relevant ventilatory strategy in the *in vivo* rabbit. Carbon dioxide modulated key physiologic indices of lung injury; hypocapnia was potentially deleterious, and hypercapnic acidosis was potentially protective. The mechanisms underlying these effects seemed to be independent of alterations in surfactant chemistry [24].

By contrast, Rai *et al.* [25•] reported that hypercapnic acidosis did not attenuate lung injury induced by surfactant depletion, an atelectasis prone model of ALI, which mimics neonatal respiratory distress syndrome. After surfactant depletion, animals were randomized to an injurious (Vt 12 mL/kg; positive end-expiratory pressure [PEEP] 0 cm H_2O) or a protective (Vt 5 mL/kg; PEEP 12.5 cm H_2O) ventilatory strategy and to receive either control conditions or hypercapnic acidosis. Injurious ventilation resulted in significant lung injury, as evidenced by a large alveolar-arterial O_2 gradient, elevated peak airway pressure, increased protein leak, and impaired lung compliance. Hypercapnic acidosis did not attenuate these physiologic indices of ALI. Taken together, these findings suggest that although hypercapnic acidosis substantially attenuates VILI due to excessive stretch, its effects in the context of more clinically relevant lung stretch may be more modest, and it does not attenuate the extent of lung damage due to collapse and reexpansion of atelectatic lung.

The potential for hypercapnic acidosis to exert beneficial effects in the context of a protective lung ventilatory strategy, as distinct from an injurious strategy, remains to be determined.

In the clinical setting, sepsis is the commonest cause of ARDS and is associated with the poorest outcome [26]. The mechanisms that initiate lung injury in sepsis-induced ARDS are quite distinct from those seen in non–sepsis-induced ARDS. Lipopolysaccharide, an endotoxin produced by gram-negative bacteria, is central to the mechanism by which bacteria produce tissue damage. Hypercapnic acidosis attenuated acute lung injury induced by intratracheal endotoxin instillation in the *in vivo* rat [27••]. Hypercapnic acidosis attenuated the physiologic indices of lung injury, including lung compliance and oxygenation, and reduced lung neutrophil infiltration. In addition, stereologic analysis of lung tissue demonstrated that hypercapnic acidosis markedly attenuated the histologic indices of lung damage [27••].

The therapeutic potential of hypercapnic acidosis is underlined by the finding that it seems to be effective even when instituted after the lung injury process begins, in the setting of both mesenteric ischemia-reperfusion and endotoxin-induced ALI models [20••,27••]. This finding contrasts with many other initially promising experimental strategies that demonstrate potential when used before the injury process but lose their effectiveness when used after the development of organ injury, thus minimizing their potential clinical utility. The importance of this finding is underlined by the fact that in the clinical context, the process of acute organ injury is generally well established before a patient comes to a critical care facility for specific therapy.

Mechanistic insights

Nuclear factor kappa beta (NF-κB) is a key regulator of the expression of multiple genes involved in the inflammatory response, and its activation represents a pivotal early step in the activation of this response. Takeshita *et al.* [28••], in a pivotal paper, demonstrated that hypercapnic acidosis significantly inhibits 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 [28••]. Hypercapnic acidosis suppressed 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 [28••]. This represents a key finding, which may constitute the underlying mechanism by which the antiinflammatory effects of hypercapnic acidosis are mediated at a molecular level within the cell [29,30].

Hypercapnia: physiologic insights

Pulmonary

The potential for increasing hypercapnic acidosis to produce a stepwise augmentation of PaO_2 is clear from two recent experimental studies [20••,31•]. A key underlying mechanism is mediated *via* improved matching of ventilation and perfusion in the lung. Brogan *et al.* [32•] demonstrated that most of the beneficial effect of CO_2 on ventilation-perfusion matching could be achieved by limiting CO_2 to late inspiration, which limits the CO_2 to the conducting airways, thereby minimizing the potential for systemic hypercapnic acidosis. Lee *et al.* [33] demonstrated the potential for hypercapnia to increase pulmonary arterial pressures and pulmonary vascular resistance. It is reassuring that the potential for hypercapnic acidosis to alter pulmonary hemodynamics did not seem to be exacerbated in the setting of preexisting pulmonary hypertension.

Regulation of ventilation

Hypercapnia is a potent regulator of ventilation. Crosby *et al.* [34] examined the potential for a 5-day exposure to constant mild elevation of alveolar CO_2 (end tidal PCO_2 elevated by 8 mm Hg) to cause ventilatory adaptation and to alter the chemoreceptor reflex to acute hypoxia and hypercapnia, in 10 healthy human volunteers. They report no major adaptation of ventilation during the exposure to hypercapnia. There was a modest increase in ventilatory chemosensitivity to acute hypoxia but no change in response to acute hypercapnia. A compensatory metabolic alkalosis developed over first 24 to 48 hours and was maintained over the course of the CO_2 exposure.

Tissue oxygenation

Hypercapnic acidosis increases tissue oxygenation, a potentially protective effect in the setting of acute organ ischemia. Hare *et al.* [31•] demonstrated that the mechanism by which hypercapnic acidosis increases cerebral tissue oxygen tension involves a combination of augmentation of PaO_2 and increased regional cerebral blood flow. Ratnaraj *et al.* [35] reported that hypercapnic acidosis increased oxygen tension in both subcutaneous tissues and the intestinal wall. Intestinal wall oxygen tensions were increased to a greater degree in the small intestine than in the large intestine. Inadequate intestinal oxygenation has been implicated as a factor in gut dysfunction, leading to loss of barrier function in critically ill patients.

Neurovascular regulation

The mechanisms underlying hypercapnic acidosis–induced cerebral vasodilation are increasingly well characterized. Nakahata *et al.* [36••] demonstrated that the hypercapnic acidosis–induced cerebral precapillary arteriolar vasodilation is a function of the acidosis rather than the hypercapnia *per se*. Using selective potassium channel

blockers and activators, they demonstrated that the ATP-sensitive K^+ channel, but not the Ca^{2+}-dependent K^+ channel, plays a major role in this vasodilation. Extraluminal normocapnic acidosis, by contrast, induced cerebrovascular vasodilation *via* combined activation of both ATP-sensitive and Ca^{2+}-activated potassium channels in the rat middle cerebral artery [37]. Sato *et al.* [38•] demonstrated that nitric oxide, synthesized by the neuronal isoform of nitric oxide synthase, may mediate the increase in retinal blood flow that occurs with hypercapnic acidosis. Thus, the precise mechanism by which hypercapnic acidosis causes cerebral vasodilation seems to differ depending on the arterial bed and the type of artery studied.

Neuromuscular effects

Recent studies have highlighted the potential for hypercapnia to exert potentially deleterious neuromuscular effects. Shiota *et al.* [39•] demonstrate the potential for hypercapnia to alter the contractile and histologic properties of the diaphragm in rats exposed to prolonged hypercapnia (7.5% CO_2 for 6 weeks,). Hypercapnia depressed diaphragmatic tension development and time to contraction and relaxation, and altered diaphragmatic muscle fiber composition, increasing slow twitch fibers and decreasing fast twitch fibers. Beekley *et al.* [40] demonstrated that short-term exposure to moderate hypercapnia (7% inspired CO_2) may transiently impair neuromuscular function through effects on afferent transmission or synaptic integrity in healthy volunteers. The potential for hypercapnia to alter diaphragmatic structure and function and to affect neuromuscular transmission in the clinical context, which may complicate weaning from ventilation, remains to be determined.

Adjuncts to permissive hypercapnia: dead space gas replacement

At the end of expiration, the ventilator circuit distal to the Y-piece and the anatomic dead space both contain alveolar gas. This CO_2-rich gas then constitutes the first part of the next delivered breath to the distal lung. The contribution of this dead-space gas to ventilation increases with decreased tidal volume, given that this dead-space is relatively fixed. Techniques that aim to replace this dead-space gas with fresh gas have been advocated as an adjunct to protective ventilatory strategies. These techniques may improve the efficiency of ventilation by increasing effective alveolar ventilation, and they may facilitate further reductions in tidal volume, minimizing transpulmonary pressures. Tracheal gas insufflation (TGI) is a technique that delivers fresh gas into the central airways, either continuously or in a phasic fashion during expiration. Experimental studies in animal models of ALI and in lung models have highlighted the potential role of TGI in clinical practice [41]. In a recent experimental study, Zhu *et al.* [42] reported that TGI, either alone or in combination with partial liquid ventilation, attenuates the development of ALI resulting from mechanical ventilation of surfactant depleted lungs.

However, despite extensive investigation, concerns persist about the safety and monitoring of TGI and have impeded its introduction into clinical practice. A significant concern is the risk of tracheal trauma with TGI. In this regard, Dyer *et al.* [43] investigated the distribution of pressures within a model trachea, produced by five different TGI devices. They reported that the Boussignac tracheal tube produced the most even pressure distribution, whereas a reverse-flow catheter produced pressure changes of the smallest magnitude and hence may be safer for clinical use.

Aspiration of dead-space gas (ASPIDS) during expiration and controlled replacement with fresh gas is a related technique designed to minimize dead space. Liu *et al.* [44•] conducted a small preliminary feasibility clinical study of ASPIDS in 8 patients with chronic obstructive pulmonary disease—induced respiratory failure managed with permissive hypercapnia. They demonstrated that ASPIDS results in a similar decrease in $PaCO_2$ but with less intrinsic PEEP, in comparison with comparable levels of TGI in these patients [44•].

Lethvall *et al.* [45•] investigated the potential for a coaxial double-lumen endotracheal tube, which eliminates the contribution to dead space from the ventilator circuit distal to the Y-piece, to improve the efficiency of ventilation in a porcine model of surfactant depletion–induced ALI. Ventilation through the coaxial endotracheal tube improved ventilation efficiency at comparable ventilator settings and tracheal pressures. There were no adverse hemodynamic effects or auto-PEEP detected with the use of the coaxial tube. The reduction in arterial CO_2 levels with the coaxial double-lumen endotracheal tube was inversely proportional to tidal volume, with greater reductions at lower tidal volumes. Evaluations of the initial safety and efficacy of this promising adjunct in patients with ALI are required.

Conclusion

Ventilatory strategies involving hypercapnia are widely used in the setting of acute respiratory failure, with the aim of realizing the benefits of reduced lung stretch. However, the optimal ventilatory strategy and the precise contribution of hypercapnia to this strategy remain unclear. 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. These findings raise the possibility that hypercapnia might be induced for therapeutic effect in this context. However, concerns persist regarding the potential for hypercapnia and/or acidosis to exert deleterious

effects, and the need for caution before extrapolation to the clinical context must be emphasized. A clearer understanding of the effects and mechanisms of action of hypercapnia is central to determining its safety and therapeutic utility.

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