Permissive hypercapnia: what to remember

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Purpose of review
Hypercapnia is a central component of diverse respiratory disorders, while 'permissive hypercapnia' is frequently used in ventilatory strategies for patients with severe respiratory failure. This review will present data from recent studies relating to hypercapnia, focusing on issues that are of importance to anesthesiologists caring for the surgical and/or critically ill patient.

Recent findings
Protective ventilatory strategies involving permissive hypercapnia are widely used in patients with severe respiratory failure, particularly in acute respiratory distress syndrome, status asthmaticus, chronic obstructive pulmonary disease and neonatal respiratory failure. The physiologic effects of hypercapnia are increasingly well understood, and important recent insights have emerged regarding the cellular and molecular mechanisms of action of hypercapnia and acidosis. Acute hypercapnic acidosis is protective in multiple models of nonseptic lung injury. These effects are mediated in part through inhibition of the NF-κB pathway. Hypercapnia-mediated NF-κB inhibition may also explain several deleterious effects, including delayed epithelial wound healing and decreased bacterial killing, which has been demonstrated to cause worse lung injury in prolonged untreated pneumonia models.

Summary
The mechanisms of action of hypercapnia and acidosis continue to be elucidated, and this knowledge is central to determining the safety and therapeutic utility of hypercapnia in protective lung ventilatory strategies.

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

INTRODUCTION

Permissive hypercapnia (PHC) results from lung protective mechanical ventilation approaches, whereby elevated arterial CO_2 is accepted to minimize ventilator-induced lung injury (VILI). These approaches have been demonstrated to improve the outcome from acute respiratory distress syndrome (ARDS) [1,2]. Ventilation strategies incorporating PHC are also well described in other diseases leading to acute respiratory failure in adults and children, including severe asthma and chronic obstructive pulmonary disease (COPD). Paralleling these developments is a growing body of knowledge regarding the mechanisms of action – both beneficial and deleterious – of hypercapnia and its associated acidosis, and extensive clinical experience attesting to the benign clinical profile of moderate hypercapnia, can be used to help guide the rational use of PHC at the bedside in the patient with severe respiratory failure.

This study reviews the physiology of 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 patients with acute lung injury. The experimental and clinical studies of special interest, published within the annual period of review, have been highlighted.

PHYSIOLOGY OF HYPERCAPNIA

Hypercapnia exerts multiple physiologic effects on different organs, particularly the pulmonary, cardiovascular and cerebrovascular systems.

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KEY POINTS

- Protective ventilatory strategies, which reduce lung stretch, require tolerance of 'permissive' hypercapnia and have improved outcome from ARDS. Evidence also supports the use of permissive hypercapnia strategies in acute severe asthma and chronic obstructive airways disease.
- The physiologic effects of hypercapnia are increasingly well understood, while important recent insights have emerged regarding the cellular and molecular mechanisms of action of hypercapnia and acidosis.
- The protective effects of acute hypercapnic acidosis in diverse preclinical models are mediated through potent effects on the host immune system, with key effects mediated through inhibition of the NF-κB pathway. Hypercapnia-mediated NF-κB inhibition may also explain several deleterious effects, including delayed epithelial wound healing and decreased bacterial killing.
- A clear understanding of the effects and mechanisms of action of hypercapnia is central to determining its safety and therapeutic utility. When using permissive hypercapnia the clinician must decide for each specific patient what the appropriate trade-off is between the benefits of avoiding higher tidal volumes and the cost – and benefits – of the associated hypercapnia.
- The potential for extracorporeal CO_2 removal technologies to facilitate even greater reductions in tidal and minute ventilation is clear, but awaits definitive studies.

Pulmonary

Moderate hypercapnia improves arterial oxygenation in both normal [3–5] and diseased lungs [6,7] by reducing ventilation–perfusion heterogeneity. An important recent experimental study suggests that CO_2 directly affects lung compliance by modulating actin–myosin interactions [8▪▪]. Moderate hypercapnia increases, whereas hypocapnia reduces lung parenchymal compliance, directing ventilation to underventilated lung regions (low ventilation–perfusion) with higher alveolar pCO_2, resulting in better ventilation–perfusion matching. Hypercapnia may also increase lung compliance through increased alveolar surfactant secretion and more effective surface tension-lowering properties of surfactants under acidic conditions [9].

CO_2 tensions – both alveolar and systemic – appear to modulate airway resistance. Hypocapnia causes bronchoconstriction [10▪▪], whereas hypercapnia has been shown to increase [11,12], decrease [13] or have little net effect [14] on lung resistance. These variable responses appear to result from contrasting effects of alveolar hypercapnia, which directly relaxes small bronchi, and systemic hypercapnia that indirectly can cause vagal nerve-mediated central airway constriction [10▪▪,12].

The effects of hypercapnia on the diaphragm are complex. Older studies suggest that hypercapnic acidosis (HCA) impairs diaphragmatic contractility and worsens diaphragmatic fatigue in spontaneously breathing individuals [15]. In recent studies, in which minute ventilation is controlled, HCA preserved diaphragmatic contractility and prevented prolonged ventilation-induced diaphragmatic dysfunction [16▪▪] by reducing diaphragmatic myosin loss and inflammation [17▪▪]. The clinical impact of hypercapnia on diaphragmatic function, especially with regard to weaning from mechanical ventilation, has yet to be elucidated.

Systemic hemodynamics and tissue oxygenation

HCA enhances tissue perfusion and oxygenation, through multiple mechanisms. HCA increases cardiac output (CO), improves lung mechanics and ventilation–perfusion matching, increases peripheral perfusion and enhances peripheral tissue hemoglobin oxygen unloading (Bohr effect). Hypercapnia increases CO through increased sympathoadrenal activity despite directly decreasing myocardial contractility [18]. Indeed, CO_2 increases cardiac index by 10–15% by each 10 mmHg of $PaCO_2$ increase [19,20], subcutaneous and muscle tissue oxygen tension in both animals and humans [19–24]. In contrast, even a short period of hypocapnic alkalosis significantly reduces CO [20,25], portal blood flow, gut perfusion and splanchnic oxygen delivery [25]. Hypoventilation-induced HCA preserves hemodynamics in uncompensated experimental hemorrhagic shock [26].

Much attention has focused recently on the potential for hypercapnia-mediated enhanced tissue perfusion to reduce postoperative wound infection. Fleischmann *et al.* [22] have shown in a small study that intraoperative hypercapnia was associated with significantly higher colon tissue oxygenation. Similar observations have been reported in morbidly obese surgical patients [23]. However, a recent multicenter randomized controlled trial (RCT), including 1206 patients undergoing colon surgery, failed to demonstrate clear benefits of intraoperative hypercapnia in surgical site infection (SSI) compared with normocapnia [27▪▪].

Cerebrovascular regulation

Carbon dioxide is a key regulator of cerebrovascular tone. For each 1 mmHg change in $PaCO_2$, there is a 1 to 2 ml/100 g/min change in global cerebral blood

flow [28]. Indeed, decreases in the reactivity of the cerebral vasculature to CO_2 may be a useful predictor of stroke risk [29▪▪]. These effects are mediated by extracellular pH rather than by direct changes in $PaCO_2$ [30]. Mechanisms leading to cerebral vasodilatation or relaxation differ between adults and neonates. In adults, hypercapnia-induced vasodilatation is mediated, in part, by nitric oxide, whereas in neonates, the main mediators are prostaglandins [28]. These mediators then activate K-ATP and K-Ca channels through intracellular second messengers (cGMP/cAMP) resulting in decreased intracellular-Ca^{2+} and vasodilation [31].

HCA-mediated increases in cerebral blood flow are a clear concern in the setting of reduced intracranial compliance. Indeed, traditional management of traumatic brain injury frequently included sustained hypocapnia to reduce cerebral blood volume and control raised intracranial pressure [32]. However, accumulating evidence has challenged this concept [33]. Sustained hypocapnia reduces cerebral O_2 supply [34] and increases brain ischemia [35], increases vasospasm risk [36,37] and worsens neuronal excitability [38], thereby potentiating seizures [39]. More recent studies have shown that prehospital severe hypocapnia in traumatic brain injury patients worsens the outcome [40–42].

HYPERCAPNIA IN PRECLINICAL DISEASE MODELS

Key insights into the effects of hypercapnia and acidosis – potentially beneficial and harmful – have emerged from preclinical models, in which it is possible to independently alter CO_2 tension and ventilation.

Ventilation-induced lung injury and repair

Substantial evidence demonstrates that moderate hypercapnia directly reduces VILI (Table 1) [43–50, 51▪▪,52–55,56▪▪,57▪▪,58]. Studies using clinically more relevant (V_t) have further underlined the potential for hypercapnia to protect against mechanical stretch [46–49]. The biologic response to cyclic stretch occurs through mechanosensors that transmit signals from the deformed extracellular matrix to the interior of the cell [49,50]. A recent study has demonstrated that HCA prevents the stretch-induced activation of p44/42 MAP-kinase [51▪▪,59,60] (Fig. 1). Furthermore, hypercapnia markedly reduced apoptosis, oxidative stress and inflammation by inhibiting the downward activation of the signal-regulating kinase 1JNK/p38 MAP-kinase pathway in alveolar epithelial cells [50]. HCA also reduces stretch-induced lung inflammation and improves lung mechanics by inhibiting IκB-α degradation and nuclear p65 translocation [49] (Fig. 1). The question whether the protective effect of HCA is mediated through CO_2 directly or pH in the context of VILI is still unknown. A recent study comparing the effect of HCA with normocapnic metabolic acidosis found that metabolic acidosis exerted similar protection against VILI as HCA [48].

Of potential concern, hypercapnia may retard lung epithelial and cellular repair following stretch-induced injury. Doerr *et al.* [52] demonstrated first that HCA impairs plasma membrane resealing in VILI. HCA also delays epithelial wound closure in multiple pulmonary cell lines by reducing NF-κB-dependent epithelial cell migration [53].

Lung ischemia–reperfusion injury

Lung ischemia–reperfusion is a key mechanism of injury in diverse clinical situations, including lung transplantation, pulmonary embolism and ARDS. HCA has been demonstrated to attenuate ischemia–reperfusion-induced lung injury [54] by preserving endothelial capillary barrier function and reducing lipid peroxidation, peroxynitrite production and apoptosis in lung tissue [55,58,61] (Table 1). The dose–response characteristic of hypercapnia and its efficacy in pulmonary as well as systemic ischemia–reperfusion-induced lung injury is well described [55,58,61]. Recent insights into the protective mechanisms of HCA include the demonstration that hypercapnia suppressed T-cell function in post-lung transplantation [56▪▪]. Hypercapnia also attenuated ischemia–reperfusion-induced NF-κB pathway activation and reduced lung inflammation and apoptosis [62], through mechanisms involving NF-κB inhibition and upregulation of the potent antioxidant enzyme, hemeoxygenase-1 [57▪▪].

Sepsis

The potential for HCA to impair the host immune response in the setting of sepsis has raised serious concerns (Table 2) [63–67,68▪▪,69–75]. Accumulating data suggest that hypercapnia may result in net benefit or harm depending on the site and duration of bacterial infection, the use of antibiotic therapy and whether the acidosis induced by hypercapnia is buffered or not. In pneumonia models, HCA is protective in early [64] and more established infections [65]. In contrast, hypercapnia may be harmful in prolonged, untreated pneumonia, likely by reducing neutrophil-mediated and macrophage-mediated bacterial killing. This effect is completely

Table 1. Summary of key publications on the effect and potential mechanisms of hypercapnia and/or acidosis in nonseptic acute lung injury models

Study	Experimental model	Injury	Applied CO_2 concentration	Effect
Broccard *et al.*, 2001 [43]	*Ex vivo* (rabbit)	VILI	Targeted $PaCO_2$: 70–100 mmHg	HCA reduced microvascular permeability, lung edema formation and BAL protein content in ex-vivo VILI.
Sinclair *et al.*, 2002 [44]	*In vivo* (rabbit)	VILI	~12%	HCA attenuated edema formation and histological injury in VILI.
Laffey *et al.*, 2003 [45]	*In vivo* (rabbit)	VILI	12%	HCA attenuated VILI in a clinically more relevant V_t ventilation (12 ml/kg). HCA improved oxygenation and lung mechanics.
Halbertsma *et al.*, 2008 [46]	*In vivo* (mouse)	VILI	2, 4%	HCA reduced BAL neutrophil count and cytokines (IL-β, TNF-α, IL-6, KC)
Peltekova *et al.*, 2010 [47]	*In vivo* (mouse)	VILI	Dose response curve (0, 5, 12, 25%)	HCA improved lung mechanics and permeability, reduced BAL TNF-α, *COX2* gene expression. HCA also increased nitrotyrosine formation.
Kapetanakis *et al.*, 2011 [48]	*Ex vivo* (rabbit)	VILI	Targeted pCO_2: 100–130 mmHg	Normocapnic metabolic acidosis prevented lung edema formation to the same extent as HCA.
Contreras *et al.*, 2012 [49]	In-vivo (rat), in-vitro pulmonary epithelial cells	VILI	5%	HCA reduced VILI, and BAL cytokines (IL-6, TNF-α, CINC-1). Moderate VILI prevented cytoplasmic IκB degradation and nuclear p65 translocation. This was confirmed in in-vitro stretch injury.
Yang *et al.*, 2013 [50]	In-vivo (rat) and in-vitro alveolar epithelial cells	VILI	Targeted $paCO_2$ 80–100 mmHg	HCA attenuated microvascular leak, oxidative stress and inflammation. HCA reduced caspase-3 activation (apoptosis), MPO, MDA, enhanced SOD levels via ASK-1-JNK/p38 pathway inhibition.
Otulakowski *et al.*, 2014 [51▪▪]	Ex-vivo (mouse), and in-vitro alveolar epithelial cells	VILI	12%	Hypercapnia prevented activation of EGFR and p44/42 MAPK pathway *in vitro*. TNFR shedding (an ADAM-17 targeted ligand induced by stretch injury) was reduced *in vivo*.
Doerr *et al.*, 2005 [52]	Ex-vivo (rat) and in-vitro alveolar epithelial cell	VILI/plasma membrane resealing	12%, in-vitro pCO_2: 119 mmHg	HCA reduced lung edema formation *in vivo* and plasma membrane resealing *in vivo* and *in vitro*.
O'Toole *et al.*, 2009 [53]	*In vitro*	Scratch wound	10,15%	CO_2 rather than pH reduced the rate of wound closure (cell migration) in a dose-dependent manner via NF-κB pathway inhibition.
Shibata *et al.*, 1998 [54]	*In vivo* (rat)	Free radical	25%	HCA attenuated free radical-induced injury via inhibition of endogenous xanthine oxidase and improved lung permeability.
Laffey *et al.*, 2000 [55]	*Ex vivo* (rabbit)	Pulmonary IR	12%	HCA attenuated IR-induced lung and systemic injury. Reduced BAL inflammation (TNF-α), 8-isoprostane and nitrotyrosine generation in lung tissue. HCA reduced apoptosis.
Gao *et al.*, 2014 [56▪▪]	In-vivo (rat) and in-vitro T cells	Pulmonary IR lung transplant	5%	Hypercapnia decreased $CD3^+/CD4^+$ T cell ratio, proinflammatory cytokines and increased anti-inflammatory cytokines *in vivo*. CO_2 inhibited CD28 and CD2, key molecules of T-cell activation and acidosis reduced T-cell cytokine production *in vitro*.
Wu *et al.*, 2013 [57▪▪]	Ex-vivo (rat) and in-vitro alveolar epithelial cells	Pulmonary IR	5%	HCA reduced lung permeability and inflammation. HCA also increased HO-1 activity via inhibition of the IKK-NF-κB pathway.
Laffey *et al.*, 2003 [58]	*In vivo* (rat)	Mesenteric IR	Dose response curve (0, 2.5, 5, 10, 20%),	HCA attenuated IR-induced microvascular leak, improved lung mechanics and oxygenations. CO_2 higher than 5% did not provided added benefit.

ADAM-17, ADAM metallopeptidase 17; ASK-1, apoptosis signal-regulating kinase-1; CINC-1, cytokine-induced neutrophil chemoattractant-1; COX2, cyclooxygenase 2; EGRF, epidermal growth factor receptor; HO-1, heme oxygense-1; IκB, inhibitory kappa B; IL-β, interleukin β; IL-6, interleukin-6; IR, ischemia–reperfusion; JNK, c-Jun N-terminal kinase; KC, keratocyte-derived chemokine; MDA, malondialdehyde; MPO, myeloperoxidase; NF-κB, nuclear factor kappa B; p44/42 MAPKp44/p42 mitogen-activated protein kinase; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; TNFR, tumor necrosis factor receptor; VILI, ventilator-induced lung injury.

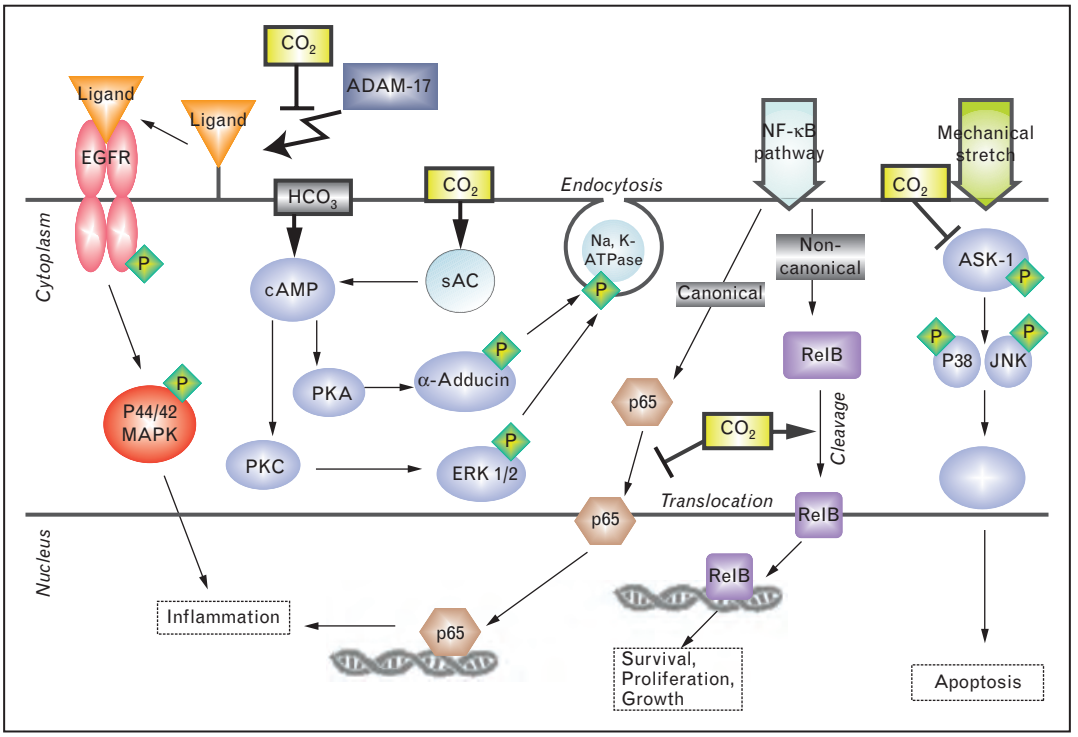

FIGURE 1. Key intra-cellular signalling pathways modulated by CO_2. Phosphorylation of P44/42 induced by stretch injury is decreased with HCA by inhibition of ADAM-17, thereby reducing inflammation in alveolar epithelial cells. Clearance of lung edema is decreased following the HCA-induced endocytosis of the Na,K-ATPase transporter. The translocation of anti-inflammatory RelB is increased by HCA and HCA also can impair the translocation of the NF-kB protein p65. Apoptotic signaling through the ASK1-JNK/p38 MAPK pathway is impaired by HCA, as shown by decreased levels of activated ASK-1, p38 and JNK and decreased levels of cleaved caspase 3. ADAM-17, ADAM metallopeptidase 17; ASK-1, apoptosis signal-regulating kinase-1; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; PKA, protein kinase A.

attenuated with antibiotic therapy [66]. These observations have recently been confirmed by Gates *et al.* [68▪▪]. Hypercapnia impaired neutrophil phagocytosis and bacterial killing capacity without affecting neutrophil recruitment [68▪▪]. Importantly, hypercapnia increased bacterial load in lung, spleen and liver, indicating significant level of systemic dissemination of bacterial sepsis [68▪▪]. Physiologic buffering has also been shown to be deleterious in *Escherichia coli*-induced pneumonia [67].

In systemic sepsis, HCA has a more favorable profile, protecting against early [70,71] and more established [69] cecal ligation and puncture (CLP)-induced septic shock. In prolonged CLP sepsis, the protective effect of hypercapnia on lung injury was less marked [71]. Importantly, HCA did not alter BAL and peritoneal bacterial load in these studies. The potential for localized hypercapnia to exert protective effects in the setting of experimental abdominal sepsis has been demonstrated [72–74]. More recently, Montalto *et al.* [75] CO_2 demonstrated that pneumoperitoneum may reduce distant organ injury induced by CLP sepsis. The beneficial effects of hypercapnia in systemic sepsis may relate to improved splanchnic microcirculatory oxygenation, counteracting the adverse hemodynamic effects of sepsis [76▪▪].

Pulmonary hypertension

Pulmonary hypertension is a common complication of many clinical syndromes including ARDS, COPD and sepsis [77]. Although hypercapnia and acidosis should be clearly avoided in the context of severe established pulmonary hypertension, experimental data suggest that hypercapnia may attenuate pulmonary hypertension-induced vascular remodeling and impaired right ventricular function [78–82]. Peng *et al.* [80] recently demonstrated that hypercapnia reverses both structural and functional changes of hypoxia-induced pulmonary hypertension in juvenile rats by inhibition of RhoA/Rho-kinase pathways and augmentation of lung tissue endothelial nitric oxide synthase and nitric

Table 2. Summary of publications on the effect of hypercapnia and/or acidosis in live bacterial pneumonia and systemic sepsis models

Study	Animal model	Injury	Applied CO_2 level	Effect
Pulmonary sepsis				
Ni Chonghaile *et al.*, 2008 [64]	*In vivo* (rat)	*Escherichia coli* pneumonia (early)	Inspired 5% CO_2	HCA reduced lung injury induced by evolving *E. coli* pneumonia.
Chonghaile *et al.*, 2008 [65]	*In vivo* (rat)	*E. coli* pneumonia (established)	Inspired 5% CO_2	HCA reduced lung injury induced by established *E. coli* pneumonia.
O'Croinin *et al.*, 2008 [66]	*In vivo* (rat)	Prolonged *E. coli* pneumonia (48 h)	Inspired 8% CO_2	HCA worsened lung injury induced by prolonged untreated *E. coli* pneumonia.
Nichol *et al.*, 2009 [67]	*In vivo* (rat)	*E. coli* pneumonia	Inspired 5% CO_2, physiologic buffering	Buffered hypercapnia worsened *E. coli* pneumonia.
Gates *et al.*, 2013 [68▪▪]	*In vivo* (mouse)	Pseudomonas pneumonia (96 h)	Inspired 10%, physiologic buffering	Buffered hypercapnia worsened pseudomonas pneumonia.
Systemic sepsis				
Wang *et al.*, 2008 [69]	*In vivo* (sheep)	Fecal peritonitis	Targeted $paCO_2$ 55–65 mmHg	CO_2 improved tissue oxygenation in septic shock.
Costello *et al.*, 2009 [70]	*In vivo* (rat)	CLP sepsis, septic shock (3, 6 h)	Inspired 5% CO_2	CO_2 decreased CLP sepsis-induced lung injury.
Higgins *et al.*, 2009 [71]	*In vivo* (rat)	CLP sepsis (96 h)	Inspired 5% CO_2	Buffering ablates benefit of CO_2on lung injury in septic shock.
Hanly *et al.*, 2005 [72]	*In vivo* (rat)	CLP sepsis (0.5 h)	CO_2 pneumoperitoneum	CO_2 pneumoperitoneum decreased CLP-induced mortality
Fuentes *et al.*, 2006 [73]	*In vivo* (rat)	Endotoxemia and laparotomy (7 h)	CO_2 pneumoperitoneum	CO_2 pneumoperitoneum increased survival
Metzelder *et al.*, 2008 [74]	*In vivo* (mouse)	CLP sepsis, septic shock (6 h to 7 days)	CO_2 pneumoperitoneum	CO_2 pneumoperitoneum increased survival
Montalto *et al.*, 2011 [75]	*In vivo* (rat)	CLP sepsis and laparotomy (7 h)	CO_2 pneumoperitoneum	CO_2 pneumoperitoneum decreased hepatic and pulmonary inflammation

CLP, cecal ligation and puncture.

oxide levels. Hypercapnia significantly decreased pulmonary vascular resistance and improved right ventricular performance following bleomycin-induced lung injury, and reduced lung macrophage recruitment and TNF-α expression [81]. The effect of HCA on hypoxemic pulmonary vasoconstriction (HPV) remains unclear. A recent study has shown that CO_2 – independently from acidosis – increased hypoxemic pulmonary vasoconstriction during sustained hypoxemia and increased indices of lung edema possibly through increased inducible nitric oxide synthase activity [82].

Alveolar fluid dynamics

The accumulation of pulmonary edema is the hallmark of ARDS, whereas subsequent clearance of alveolar fluid is central to ARDS resolution [83]. HCA reduces alveolar edema formation by inhibiting the increase in pulmonary capillary permeability included by free radicals [54], ischemia–reperfusion [61] and high stretch ventilation [45]. In contrast, hypercapnia decreases alveolar fluid clearance, a process dependent on intact Na^+ transport across the apical surface of alveolar epithelial cells. Hypercapnia – independent of pH – reduces alveolar fluid removal through intracellular activation of the protein kinase C ζ isotype, followed by phosphorylation and endocytosis of the Na^+/K^+-ATPase pump [84]. Hypercapnia also activates ERK1/2, a key regulatory molecule in Na^+/K^+-ATPase endocytosis [85]. Lecuona *et al.* [86▪▪] showed that hypercapnia increases cAMP levels, activates PKA-Iα that leads

Table 3. Summary of recent publications on the potential molecular mechanisms of hypercapnia and/or acidosis involving the NF-κB pathway

Study	Model	Injury	Applied CO_2	Effect on NF-κB pathway
Takeshita *et al.*, 2003 [88]	In-vitro pulmonary endothelial cells	Endotoxin	10%	Hypercapnia reduced cell injury and prevented IκB degradation. NF-κB dependent cytokine (IL-8. ICAM-1) production was reduced.
O'Toole *et al.*, 2009 [53]	In-vitro SAEC, HBE, A549 cells	Scratch injury (repair)	10, 15%	HC reduced the rate of wound closure by reducing cell migration. HC also inhibited p65 translocation and IκB degradation.
Helenius *et al.*, 2009 [89]	*Dorsophila* and in-vitro S2 cells	Sepsis	13, 20%	HC suppressed NF-κB-dependent antimicrobial protein gene expression and increased the susceptibility to multiple bacterial strains and increased mortality. NF-κB pathway was inhibited by CO_2 rather than pH independent of IκB degradation.
Cummins *et al.*, 2010 [90]	In-vitro six different cell lines	Endotoxin stimulated	5, 10%	CO_2 directly facilitated IKK-α nuclear transport, reduced IκB degradation and nuclear p65 translocation. Expression of NF-κB-dependent proinflammatory genes was blunted (CCL2, ICAM-1, TNF-α) whereas anti-inflammatory gene (IL-10) expression was increased.
Wang *et al.*, 2010 [91]	In-vitro human and mouse macrophages	Endotoxin stimulation	5, 9, 12.5, 20%	HC independent of pH inhibited macrophage phagocytosis, cytokine release (IL-6, TNF-α). CO_2 inhibited Il-6 promoter driven luciferase activity independent of NF-κB activation.
Contreras *et al.*, 2012 [49]	In-vivo (rat) and in-vitro pulmonary epithelial cells	VILI	5, 10%	HCA reduced VILI, and BAL cytokines (IL-6, TNF-α, CINC-1). Moderate VILI prevented cytoplasmic IκB degradation and nuclear p65 translocation. This was confirmed in in-vitro stretch injury.
Wu *et al.*, 2012 [62]	*Ex vivo* (rat) lung	Pulmonary IR	10%	HCA reduced inflammation by inhibiting IκB degradation, p65 translocation and DNA binding activity, and IKK phosphorylation in lung tissue.
Wu *et al.*, 2013 [57▪▪]	Ex-vivo (rat) and in-vitro alveolar epithelial cells	Pulmonary IR	5%	HCA reduced lung permeability and inflammation. HCA also increased HO-1 activity by inhibition of the IKK-NF-κB pathway.

A549, lung epithelial cell; CCL2, chemokine ligand 2; CINC-1, cytokine-induced neutrophil chemoattractant-1; HBE, human bronchial cells; IκB, inhibitory kappa B; ICAM-1, intercellular adhesion molecule 1; IKK-α, inhibitory kappa B kinase complex-α; IL-10, interleukin-10; IL-8, interleukin-8; NF-κB, nuclear factor kappa B; S2, Schneider 2 cells (*Drosophila melanogaster* cell line); SAEC, small airway epithelial cell.

to the activation of α-adductin – a cytoskeletal protein – mediated endocytosis of the Na^+/K^+-ATPase complex (Fig. 1). Others have shown that increasing levels of CO_2 – not acidosis – rapidly activate c-jun N terminal kinase (JNK) resulting in decreased Na^+/K^+-ATPase pump activity [84,87].

Hypercapnia and NF-κB pathway

Several beneficial and the deleterious effects of HCA are mediated by the inhibition of the NF-κB pathway, a pivotal transcriptional activator in inflammation, injury and repair (Table 3) [49,53,57▪▪,62,88–91]. Takeshita *et al.* [88] first reported that HCA prevented IκB-α degradation in endotoxin-stimulated pulmonary endothelial cells. Recently, Contreras *et al.* [49] demonstrated that HCA protected against VILI by inhibiting NF-κB activation. Importantly, HCA also reduces pulmonary epithelial wound repair by NF-κB pathway inhibition [53]. Cummins *et al.* [90] proposed the existence of an intracellular CO_2 molecular sensor linked to NF-κB pathway as a connection to innate immunity and inflammation. Others have shown that elevated CO_2 suppressed

host defence by inhibiting NF-κB-dependent antimicrobial peptide gene expression in *Drosophila* resulting in increased mortality to bacterial infection [89]. High levels of CO_2 have also been shown to inhibit IL-6, TNF-α induction and phagocytosis in endotoxin-stimulated macrophages [91]. In the two latter studies, hypercapnia inhibited the NF-κB pathway without affecting IκB-α degradation, suggesting that other pathways or regulatory steps may have been involved in mediating the immunosuppressive effect of hypercapnia.

HYPERCAPNIA IN THE CLINICAL CONTEXT

Hypercapnia is frequently encountered in the setting of acute respiratory failure, both as a consequence of the disease process and as a result of strategies to minimize the potential of mechanical ventilation to stretch and further injure the lung.

Acute respiratory distress syndrome

To date, there have been no clinical trials examining the direct effect of hypercapnia on patients with ARDS. The potential of PHC to improve ARDS patients' survival as part of a protective ventilation strategy was suggested first by Hickling *et al.* [92,93]. Subsequently, two RCTs comparing 'traditional' versus low V_t showed improved survival in patients with ARDS [1,2]. The secondary analysis of the ARMA trial suggested that patients with moderate HCA on study day 1 had significantly less odds ratio of death at 28 days in the setting of higher – but not lower – V_t [94]. Because the primary aim of these trials was to investigate the effect of low stretch ventilation on ARDS, the direct relationship between PHC and lung protection remains to be determined. In a recent pilot study, a combination of stepwise recruitment–derecruitment with PHC was compared with lung protective ventilation [95]. This 'open lung' strategy resulted in significantly better lung compliance, systemic oxygenation in a 7-day period. However, arterial CO_2 and pH were not different between the two groups, suggesting that the achieved benefits were more likely related to better recruitment maneuver in the open-lung strategy group than to PHC *per se*.

Asthma

The utility of PHC in status asthmaticus was reported first by Darioli in 1984 [96]. Subsequent studies also confirmed that lowering minute ventilation, in conjunction with longer expiratory time, significantly reduces dynamic hyperinflation [97,98]. In these studies, arterial CO_2 was kept intentionally at moderately elevated levels (63, 68 mmHg), whereas extremely high arterial CO_2 levels (150–200 mmHg) were also well tolerated in case series involving more severe presentations of asthma [99]. In spite of lack of RCTs to guide mechanical ventilation in status asthmaticus, PHC has been frequently used in patients with severe asthma admitted to ICUs both in Europe [100] and in North America [101].

Chronic obstructive pulmonary disease

Respiratory failure during COPD exacerbations is a direct result of an acute increase in airway narrowing, with increased respiratory workload, similarly to acute severe asthma. Although noninvasive ventilation is the first-line ventilation strategy in patients with COPD exacerbations [102], extreme respiratory muscle fatigue, CO_2 retention-induced 'coma' may necessitate invasive ventilation. The primary aim of mechanical ventilation in this setting is to reduce over-inflation and prevent VILI by reducing minute ventilation, decreasing inspiratory–expiratory ratio and increasing inspiratory flow rate. PHC is a useful approach to achieving these goals [103].

Neonatal respiratory failure

Advances in perinatal medical care and ventilatory support have reduced mortality in high-risk newborns [104]. Prolonged mechanical ventilation, however, remains an important cause of pulmonary complications, such as bronchopulmonary dysplasia. Early observational studies suggested that PHC may lower the risk for bronchopulmonary dysplasia in premature infants. Mariani *et al.* [105] first reported that ventilation strategies allowing higher $PaCO_2$ levels (45–55 versus 35–45 mmHg) in preterm infants, in the first 96 h of life, result in faster weaning from mechanical ventilation. Subsequently, a larger multicenter RCT compared PHC with conventional ventilation with dexamethasone or placebo using a 2×2 factorial design [106]. Although the trial was stopped due to adverse events in the dexamethasone groups, PHC decreased need for assisted ventilation at 36-week gestational age from 16% to just 1%. The potential of PHC to cause intracranial hemorrhage and adverse neurological outcomes in premature infants is a significant concern. Although an early meta-analysis of PHC in newborn infants demonstrated some trends toward decreased incidence of intracranial hemorrhage in the PHC group [107], in a recent study higher ranges of hypercapnia ($PaCO_2$: 55–65 mmHg) were associated with a significant

increase in combined mental impairment and death in extremely preterm infants [108]. These data indicate that more research is needed to determine the optimal range of hypercapnia to balance the benefits and potential harms of PHC in preterm infants.

EXTRA-CORPOREAL CO_2 REMOVAL: THE FUTURE?

In recent years, new-generation extracorporeal CO_2 removal ($ECCO_2$-R) devices have been developed that offer lower resistance to blood flow, have small priming volumes and have much more effective gas exchange [109]. These devices may further facilitate lung protective ventilation by allowing greater reductions in V_t and plateau pressures in patients with severe ARDS, while avoiding the potential for severe hypercapnia – beyond levels that are generally well tolerated by patients under current PHC approaches. The rationale for $ECCO_2$-R derives from studies demonstrating that lung hyperinflation still occurs in approximately 30% of ARDS patients despite lung protective ventilation strategies and the potential to further decrease mortality by reducing plateau pressures [110]. In a recent proof-of-concept study, Terragni *et al.* [111] demonstrated that $ECCO_2$-R could improve pulmonary protection and decrease pulmonary cytokine concentrations by allowing very low V_t ventilation (3.5–5 ml/kg of PBW) in patients with ARDS. Most recently, Bein *et al.* [112▪▪] demonstrated the feasibility of combining ECCO2-R with a tidal volume strategy of 3 ml/kg in 79 patients with established ARDS.

CONCLUSION

Protective ventilatory strategies involving PHC are widely used in patients with severe respiratory failure, particularly in ARDS, status asthmaticus, COPD and neonatal respiratory failure. The physiologic effects of hypercapnia are increasingly well understood, whereas important recent insights have emerged regarding the cellular and molecular mechanisms of action of hypercapnia and acidosis. Acute HCA is protective in multiple models of nonseptic lung injury. These effects are mediated by potent effects on the host immune system, with key effects mediated by inhibition of the NF-κB pathway. Hypercapnia-mediated NF-κB inhibition may also explain several deleterious effects, including delayed epithelial wound healing and decreased bacterial killing, which has been demonstrated to cause worse lung injury in prolonged untreated pneumonia models. The potential for extracorporeal CO_2 removal technologies to facilitate even greater reductions in tidal and minute ventilation is clear, but awaits definitive studies.

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Conflicts of interest

None.

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- ▪ of special interest
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Lung parenchymal strips from rats were exposed to normoxic hypocapnia (pCO_2: 20 mmHg, pH: 7.68) or hypercapnia (pCO_2: 53mmHg, pH: 7.26) and length–tension curves were determined. Increasing CO_2 from hypocapnic to hypercapnic condition induced parenchymal relaxation, and this effect was reversed with actin-myosin blocking agent. This is the first study to demonstrate that hypercapnia increases lung parenchymal compliance, providing a mechanism by which alveolar pCO_2 may modulate ventilation–perfusion matching.

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This study investigates the separate effect of alveolar and systemic CO_2 on lung tissue and airways in dogs using cardiopulmonary bypass. Alveolar hypercapnia had no effect on pulmonary mechanics, whereas severe hypocapnia (15.2 mmHg) resulted in peripheral bronchoconstriction and worsened ventilation–perfusion matching. Systemic hypercapnic acidosis caused vagal nerve-mediated central airway constriction. This study highlights that the biologic effect of CO_2 and/or pH may convey distinct physiologic responses in the lung depending on the site of action, which is alveolar versus systemic.

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The authors randomized mechanically ventilated piglets to receive normocapnia or hypercapnia ($paCO_2$: 55–70 mmHg) for 72 h. To assess in-vivo diaphragmatic contractile force, transdiaphragmatic pressure (Pdi) was determined every 12 h. PDI decreased gradually by 25% in the normocapnia group, whereas HCA was associated with preserved diaphragmatic contractility. Although the mechanism of HCA was not explored in this study, the results provide potentially important piece of evidence on the beneficial effect of HCA in mechanically ventilated patients.

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This study provides novel mechanistic insights into the biologic effect of HCA on diaphragmatic function with particular relevance to prolonged mechanical ventilation. Male rats were ventilated for 18 h under normocapnic or hypercapnic condition. Control group included nonventilated animals. Hypercapnia prevented myosin loss and muscle atrophy evidenced by reduced concentration of myosin heavy chain concentration in isolated muscle fibers and less reduction in cross-sectional area of muscle fibers in ventilated rats. HCA was also associated with more preserved contractile function. Diaphragmatic inflammation and proteolysis were inhibited by HCA.

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SSI is inversely related to tissue oxygenation. Furthermore, mild hypercapnia has been shown to improve tissue oxygenation in a number of experimental and human studies. The investigators hypothesized that moderate hypercapnia would reduce SSI compared with normocapnia in patients undergoing elective colon surgery. Patients were randomly assigned to intraoperative normocapnia (ETCO2: 35 mmHg, $n = 623$) or hypercapnia (ETCO2: 50 mmHg, $n = 592$). The primary outcome was SSI rate within 30 postoperative days. The SSI rate was 13.3% in the normocapnia and 11.2% in the hypercapnia group ($P = 0.29$). The study was stopped after recruiting 1206 patients due to small treatment effect.

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Wu *et al.* [57▪▪] implicated the protein hemeoxygenase-1 (HO-1) in HC-induced protection by NF-κB suppression. HO-1 is an antioxidant enzyme shown to protect against ischemia–reperfusion injury in the lung (Constantin, 2012). After the induction of ischemia–reperfusion injury in isolated rat lung preparations, HCA was induced by ventilation with a 10% CO_2 gas mixture. *In vitro*, cells were subjected to 24 h of hypoxia followed by 4 h of NC (5% CO_2) or HC (10% CO_2) incubation. HC without injury was shown to induce HO-1 expression and protein levels in isolated lungs compared with NC. The indices of ischemia–reperfusion injury were shown to be reduced by HC at a physiologic level (decreased PAP and edema, improved pathology) and a molecular level in which NF-κB pathway activation was decreased. siRNA targeting HO-1 in A549 cells abolished HCA inhibition of the NF-κB pathway.

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In this study, prolonged exposure (96 h) to 10% environmental CO_2 resulted in a significantly higher mortality rate in mice with *Pseudomonas aeruginosa* pneumonia than in animals exposed to room air. Physiologic buffering – that is, placing the animals into a CO_2 chamber before bacterial inoculation – was associated with similar degree of mortality as CO_2 exposure after bacterial inoculation. Hypercapnia did not affect neutrophil recruitment; however, it impaired neutrophil phagocytosis and bacterial killing capacity. Hypercapnia increased bacterial load in the lung. Systemic dissemination of bacterial sepsis was reflected in increased spleen and liver bacterial load. This study further confirms the potential harmful effect of hypercapnia on bacterial pneumonia.

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In a feasibility study, 79 ARDS patients were randomized to low V_t ventilation ($\approx$3 ml/kg) combined with extracorporeal CO_2 elimination or to a ARDSNet strategy ($\approx$6 ml/kg) without the extracorporeal device. The primary outcome was 28-day and 60-day ventilator-free days. Ventilator-free days within 60 days were not different between the two groups. However, a subgroup analysis in more hypoxemic patients (PaO2/FIO2 $\leq$150) demonstrated significantly higher ventilation-free days with very low V_t ventilation group (40.9 $\pm$ 12.8) compared with control (28.2 $\pm$ 16.4, $P = 0.033$).