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REVIEW

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Permissive hypercapnia — role in protective lung ventilatory strategies

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Abstract 'Permissive hypercapnia' is an inherent element of accepted protective lung ventilation. However, there are no clinical data evaluating the efficacy of hypercapnia per se, independent of ventilator strategy. In the absence of such data, it is necessary to determine whether the potential exists for an active role for hypercapnia, distinct from the demonstrated benefits of reduced lung stretch. In this review, we consider four key issues. *First*, we consider the evidence that protective lung ventilatory strategies improve survival and we explore current paradigms regarding the mechanisms underlying these effects. *Second*, we examine whether hypercapnic acidosis may have effects that are additive to the effects of protective ventilation. *Third,* we consider whether direct elevation of CO_2, in the absence of protective ventilation, is beneficial or deleterious. *Fourth*, we address the current evidence regarding the buffering of hypercapnic acidosis in ARDS. These perspectives reveal that the potential exists for hypercapnia to exert beneficial effects in the clinical context. Direct administration of CO_2 is protective in multiple models of acute lung and systemic injury. Nevertheless, several specific concerns remain regarding the safety of hypercapnia. At present, protective ventilatory strategies that involve hypercapnia are clinically acceptable, provided the clinician is primarily targeting reduced tidal stretch. There are insufficient clinical data to suggest that hypercapnia per se should be independently induced, nor do outcome data exist to support the practice of buffering hypercapnic acidosis. Rapidly advancing basic scientific investigations should better delineate the advantages, disadvantages, and optimal use of hypercapnia in ARDS.

Keywords Hypercapnic acidosis · Mechanical ventilation · Acute lung injury · ARDS · Ventilation-induced lung injury · Buffering

Introduction

'Permissive hypercapnia' is an inherent element of accepted protective lung ventilatory strategies. However, the precise role of hypercapnia remains unclear, with no clinical data comparing the efficacy of protective lung ventilatory strategies in the presence and absence of hypercapnia. Furthermore, it is unlikely that such a trial will be carried out, at least in the medium term. In the absence of such data, it is appropriate to investigate whether the potential exists for an active role for hypercapnia per se, distinct from the demonstrated benefits of reduced lung stretch. This review first considers the evidence that protective lung ventilatory strategies reduce lung injury and improve survival. We examine current paradigms regarding the mechanisms underlying this protective effect, and the passive role presently attributed to hypercapnia. We focus on whether

hypercapnia and/or acidosis may have effects that are distinct from the effects of protective ventilator parameters. In addition, the current status of buffering hypercapnic acidosis is reviewed.

Protective lung ventilatory strategies — current paradigms

It is increasingly clear that mechanical ventilation can potentiate or even cause lung injury and worsen outcome in ARDS patients [1, 2]. The likely mechanisms underlying this 'ventilator associated lung injury' (VALI) are increasingly well characterized [3], and several plausible theories have been proposed. Mechanotrauma, which results from repetitive over-stretching and damage of lung tissue and cyclic recruitment-derecruitment of collapsed areas of lung [4–9], plays a pivotal role (Fig. 1). These effects may be particularly important, because increased mechanical stress may directly activate the cellular and humoral immune response in the lung [8–11], although this is controversial, with conflicting results reported [12]. The potential for intrapulmonary mediators and pathogens to access the systemic circulation is clear from experiments demonstrating translocation of prostaglandins [13], cytokines [14] endotoxin [15], and bacteria [16], across an impaired alveolar-capillary barrier, following high stretch mechanical ventilation. The potential for mechanical ventilation to induce a systemic cytokine response in the clinical context, and for a protective lung ventilation strategy to attenuate this response, has been demonstrated [17]. However, the contribution of cytokine release to the pathogenesis of ventilator induced ALI in the clinical context remains unclear [10, 18].

VALI may be limited by permitting hypoventilation in order to reduce mechanotrauma and the resulting inflammatory effects. This invariably involves a reduction in the tidal volume, and generally leads to an elevation in $PaCO_2$, an approach that has been termed "permissive hypercapnia". These protective lung ventilation strategies

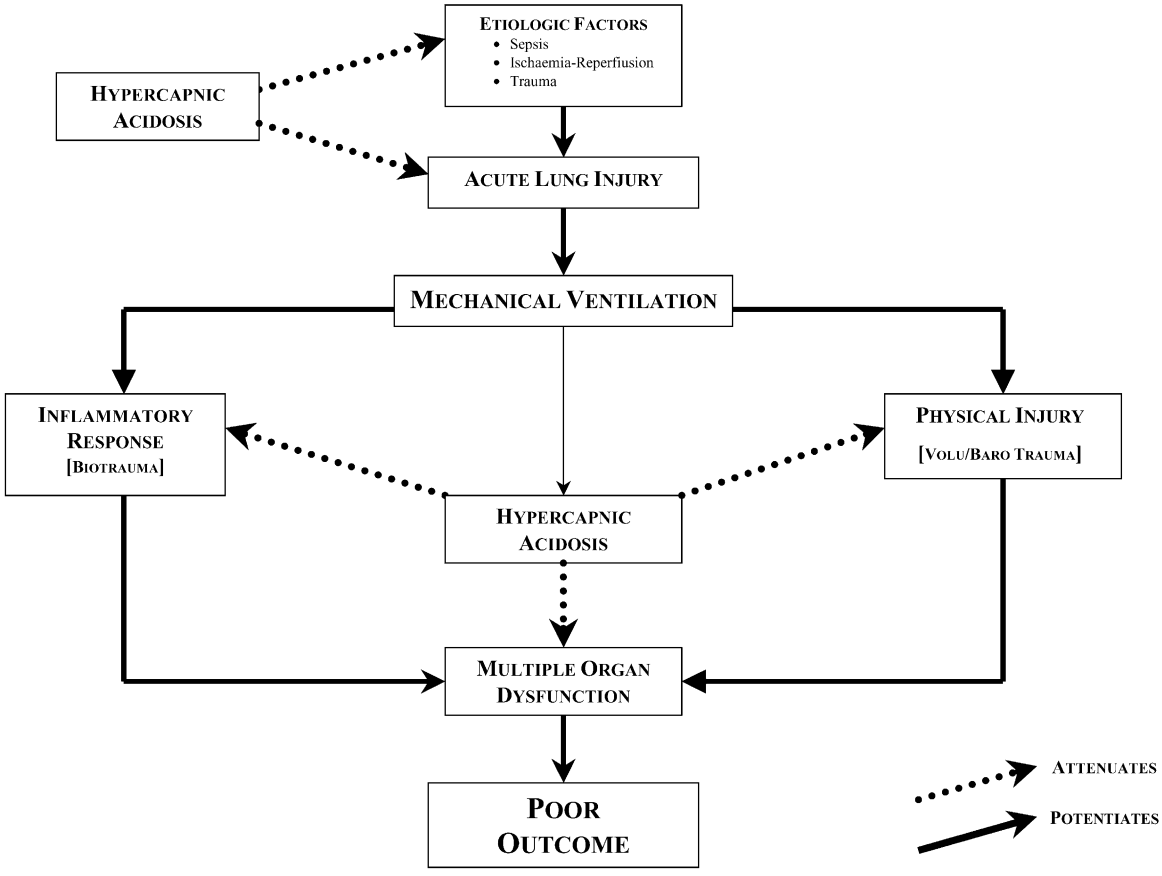

Fig. 1 Mechanical ventilation may contribute to ALI by causing direct physical injury (baro- and/or volutrauma) to the lung and by activating the inflammatory response, which in turn may lead to multiple organ dysfunction and adverse outcome. Hypercapnic acidosis may protect the lung and systemic organs via several mechanisms. These include attenuation of key etiologic factors that lead to ALI, reduction of physical lung damage, inhibition of key aspects of the inflammatory response, and direct protection of systemic organs. *Solid arrows* indicate potentiation of effect; *broken arrows* indicate inhibitory effect

improve survival in acute respiratory distress syndrome (ARDS) patients [1, 19, 20]. The reported levels of $PaCO_2$ and pH (mean maximum $PaCO_2$ 67 torr, mean pH 7.2) in the study of Hickling et al. [19] reflect typical levels observed with institution of this technique. Accordingly, there has been a shift towards greater clinical acceptability of hypercapnia in acute lung injury (ALI) and ARDS. However, 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. Accordingly, the potential for hypercapnia to exert clinically important effects in this context has received little attention to date.

Permissive hypercapnia — potential for beneficial effects

Protective ventilatory strategies that involve hypoventilation result in both limitation of tidal volume and elevation of systemic PCO_2. Of course, lung stretch is distinct from elevated PCO_2, and by manipulation of respiratory parameters (frequency, tidal volume, dead-space, inspired CO_2) can to some extent be separately controlled in humans. The ARDSnet study [2] demonstrated that mechanical ventilation of patients with ARDS with a tidal volume of 6 ml kg^{-1} (actually, a complex protocol involving limitation of tidal volume and plateau pressure [21]) resulted in a 25% reduction in mortality when compared with a more traditional tidal volume of 12 ml kg^{-1} and a lower frequency. This study minimized the potential for hypercapnia and instead permitted increased respiratory rates (respiratory frequency of 29 min^{-1}); as a result $PaCO_2$ levels were only modestly elevated, and pH modestly decreased, in the low stretch group. In fact, the need to substantially reduce tidal volumes in order to improve outcome in ARDS patients has recently been questioned [22, 23], and it is increasingly clear that most clinicians (*including expert investigators* [24]) seldom use very low tidal volumes in practice. An acceptance of more moderate tidal volumes, whether by analysis [22], or by observation of actual current practice [25, 26] may reduce the need for — and acceptability of — permissive hypercapnia. Therefore, the context in which elevated CO_2 will be encountered in the future is less likely to be as a passive/permissive accompaniment of 'protective' ventilation.

These issues underscore the necessity for (and difficulty in) consideration of the effects of hypercapnia in isolation. If hypercapnia was proven to have independent benefit, then deliberately elevating $PaCO_2$ could provide 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 generally accepted benefits of lessened lung stretch. Because outcome in ICU might be related to systemic injury — as opposed to simply lung injury — it is necessary to examine the effects of hypercapnia on pathophysiologic 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.

Clearly, the presence of an acidosis — whether hypercapnic or metabolic — indicates loss of physiologic homeostasis and the presence of disease and/or organ dysfunction. In fact, the extent and severity of acidosis is predictive of adverse outcome in diverse clinical contexts, including cardiac arrest [27, 28] sepsis [29–31] and in the immediate postpartum neonate [32]. However these data indicate an *association* rather than a cause and effect relationship, and do not indicate that acidosis is directly harmful. The systemic haemodynamic effects of hypercapnic acidosis are relatively benign, even as the pH falls to 7.15, with the typical patient experiencing no change or small increases in cardiac output and blood pressure [33, 34]. There is a body of evidence in the critical care literature attesting to the safety of hypercapnic acidosis. In many studies of patients undergoing permissive hypercapnia, a pH of well below 7.2 appeared to have been well tolerated [19, 20, 33, 35–39]. The safety of hypercapnic acidosis is further supported by reports that individuals, both adults [40] and children [41], have survived exposure to extreme levels. Therefore, although acidosis is common in the setting of critical illness, and may herald an adverse prognosis, it is likely that the aetiology of the underlying condition resulting in the acidosis, rather than the acidosis per se, is the key factor [34, 42]. Indeed acidosis may constitute a protective adaptation in the context of cellular stress, and may in fact constitute beneficial effects in the setting of acute organ injury (Table 1) [42].

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 communication [43], where Kregenow and co-workers examined mortality as a function of permissive hypercapnia in patients enrolled in the ARDSnet study [2]. Using multivariate logistic regression analysis, and controlling for other co-morbidities and severity of lung injury, they demonstrated that permissive hypercapnia reduced mortality in patients randomized to the higher tidal volume (12 ml kg^{-1}) [43]. However, there was no additional protective effect of permissive hypercapnia in patients randomized to receive the lower tidal volume (6 ml kg^{-1}) [43]. Nevertheless, the potential for hypercapnia to protect against the deleterious effects of mechanical ventilation, is clear (Fig. 1).

Table 1 Published studies of induced hypercapnic acidosis in models of acute organ dysfunction. *ALI* acute lung injury, *IR* ischaemia-reperfusion, K_{fc} capillary filtration coefficient, P_{aw} peak airway pressure, P_{cap} pulmonary capillary pressure, P_{iso} pulmonary capillary isographic pressure, *A-a O_2 gradient* alveolar-arterial oxygen gradient, *BALF* bronchoalveolar lavage fluid, *TNFα* tumour necrosis factor alpha, *NO* nitric oxide, *NMDA* N-methyl-D-aspartate

	Animal model	Injury process	Key findings
Acute lung injury			
Shibata et al. 1998 [44]	Ex vivo isolated perfused (rabbit) lung	1. Lung free radical induced ALI	1. HCA attenuated indices of ALI (K_{fc}, P_{aw}, P_{cap}, P_{iso})
		2. Lung ischemia — reperfusion-induced ALI	2. HCA attenuated indices of ALI (K_{fc}, P_{aw}, P_{cap}, P_{iso})
Laffey et al. 2000 [45]	Ex vivo isolated perfused (rabbit) lung	Lung ischemia — reperfusion	Acidosis attenuated indices of ALI (K_{fc}, P_{aw}, P_{cap}, P_{iso}). Hypercapnic acidosis more protective than metabolic acidosis. Buffering of hypercapnic acidosis abolished protective effect.
Laffey et al. 2000 [46]	In vivo whole animal (rabbit) model	Lung ischemia — reperfusion	HCA attenuated indices of ALI (lung permeability, A-a O_2 gradient, compliance, P_{aw}) and inflammation (BALF TNFα, free radical injury) following unilateral lung IR. Potential mechanisms included attenuation of nitrotyrosine formation, and attenuation of lung apoptosis.
Broccard et al. 2001 [49]	Ex vivo isolated perfused (rabbit) lung	Ventilator-induced high lung stretch	HCA attenuated indices of ALI (lung permeability, BALF protein, K_{fc}). Potential mechanism attenuation of lung NO formation.
Sinclair et al. 2002 [50]	In vivo whole animal (rabbit) model	Ventilator-induced high lung stretch	HCA attenuated indices of ALI (lung permeability, A-a O_2 gradient, compliance, histologic injury) and inflammation (BALF neutrophils).
Laffey et al, 2003 [47]	In vivo whole animal (rat) model	Mesenteric Ischemia-Reperfusion	HCA attenuated indices of ALI (lung permeability, A-a O_2 gradient, compliance, P_{AW}) following Mesenteric IR. HCA was protective if applied following initiation of mesenteric reperfucion, indicating therapeutic potential.
Laffey et al, 2003 [51]	In vivo whole animal (rabbit) model	Ventilator-induced high lung stretch	HCA attenuated (A-a O_2 gradient) while hypocapnic alkalsois worsened (P_{AW}) indices of ALI.
Myocardial Injury			
Nomura et al. 1994 [52]	Ex vivo isolated perfused (neonatal lamb) heart	Myocardial ischemia — reperfusion	HCA improved postischemic myocardial function Metabolic acidosis to an equivalent pH did not improve postischemic function
Kitakaze et al. 1997 [53]	In vivo whole animal (rabbit) model	Myocardial ischemia — reperfusion	Acidosis (hypercapnic and metabolic) during reperfusion decreased myocardial infarct size
Neurologic Injury			
Vannucci et al. 1995 [54]	In vivo whole animal (rat) model	Unilateral common carotid artery occlusion, followed by hypoxia	HCA decreased histologic brain damage Dose response seen with 6% CO_2 more neuroprotective than 9% CO_2
Vannucci et al. 1997 [55]	In vivo whole animal (rat) model	Unilateral common carotid artery occlusion, followed by hypoxia	HCA decreased histologic brain damage Mechanisms may include improved cerebral blood flow and attenuation of NMDA receptor activation.
Vannucci et al. 2001 [73]	In vivo whole animal (rat) model	Unilateral common carotid artery occlusion, followed by hypoxia	Severe HCA (15%CO_2) *worsened* histologic brain damage

Hypercapnia and acidosis — insights from laboratory models

It is not currently feasible to examine the direct effects of hypercapnic acidosis, independent of ventilator strategy, in humans. However, important insights may be gained from evaluation of the direct effects of hypercapnia and acidosis in experimental models of organ injury (Table 1).

Protective effects of hypercapnic acidosis

There is an evolving body of evidence suggesting that hypercapnic acidosis exerts biologically important beneficial effects in experimental models (Table 1). Hypercapnic acidosis directly attenuates both primary [44–46] and secondary [47] ischaemia-reperfusion-induced ALI, without reductions in lung stretch. Hypercapnic acidosis also directly protects against free-radical-induced ALI [44] and endotoxin-induced lung injury independent of ventilation strategy [48]. In addition, hypercapnic acidosis attenuates lung injury induced by excessive lung stretch in both ex vivo [49] and in vivo [50, 51] models, by a surfactant independent mechanism [51].

Hypercapnic acidosis may also protect other vital organs from injury (Table 1). In the heart, reperfusion with a hypercapnic acidotic perfusate potentiates recovery of myocardial function following prolonged ischaemia ex vivo [52] and limits myocardial infarct size for in vivo [53] models. In the brain, hypercapnic acidosis attenuates hypoxic-ischaemic brain injury in the immature rat [54, 55]. Hypercapnic acidosis protects the porcine brain from hypoxia/reoxygenation-induced injury [56]. Hypercapnic acidosis is more effective than comparable degrees of metabolic acidosis in prevention of lipid peroxidation in cortical homogenates [57].

Beneficial effects — acidosis or hypercapnia?

While it is widely accepted that reduction in pH has profound effects on normal tissue function, it is also clear that hypercapnia per se, in the absence of alterations in pH, may exert biologically important physiologic effects distinct from those produced by acidosis. Of potential importance in the context of acute lung injury, hypercapnia per se exerts effects on systemic [58] and pulmonary vascular tone [58, 59] and pulmonary vascular remodeling [60] that are increasingly well characterized. Thus, the protective effects of hypercapnic acidosis may be a function of the acidosis or the hypercapnia 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 acidemia*) were found to be protective, then further research efforts should be directed to finding better buffering strategies in order to maximise the benefits of hypercapnia.

There is increasing evidence that the protective effects of hypercapnic acidosis in ALI appear to be a function of the acidosis, rather than elevated CO_2 per se [45, 61]. Hypercapnia at normal pH caused injury to alveolar epithelial cell monolayers [61] and decreased surfactant protein A function in vitro [62]. In the isolated lung, the protective effect of hypercapnic acidosis in ischaemia reperfusion induced ALI was greatly attenuated if the pH was buffered towards normal [45]. In fact there appeared to be no significant protective effect detectable with buffered hypercapnia (Table 1). Conversely, normocapnic (i.e. metabolic) acidosis attenuates primary ischaemia-reperfusion induced ALI in an ex vivo model, although it is less effective than hypercapnic acidosis in this model [45].

The protective effects of hypercapnic acidosis in models of systemic organ injury also appear to be a function of the acidosis. The myocardial protective effects of hypercapnic acidosis are also seen with metabolic acidosis both in ex vivo [63] and in vivo [53, 64] models. In cortical brain homogenates, the protective effects of hypercapnic acidosis are also seen with metabolic acidosis, albeit to a lesser extent [57]. Metabolic acidosis appears to exert protective effects in other models of organ injury. In the liver, metabolic acidosis delays the onset of cell death in isolated hepatocytes exposed to anoxia[65] and to chemical hypoxia [66, 67]. Correcting the pH to 7.4 abolished the protective effect and in fact accelerated hepatocyte cell death [67]. Finally, isolated renal cortical tubules exposed to anoxia have improved ATP levels on reoxygenation at acidotic — compared with alkalotic — environmental pH levels [65].

Hypercapnic acidosis — underlying mechanisms

The models of ALI and ARDS are not precise representations of the clinical context; indeed most clinical scenarios differ from each other. Therefore, it is important to understand the cellular and biochemical mechanisms underlying the protective effects of hypercapnic acidosis if we are to be able to apply the findings to the bedside, and particularly, to extrapolate the principles to a variety of disease states. Hypercapnic acidosis attenuates key components of the host inflammatory response, including: lung neutrophil recruitment [48], pulmonary and systemic cytokine concentrations [46], cell apoptosis [46, 68], and both free-radical production [44, 45] and free-radical tissue injury [46, 57]. In the brain, hypercapnic acidosis attenuates glutathione depletion and lipid peroxidation [56]. One promising potential mechanism underlying

these protective actions of hypercapnic acidosis is attenuation of the activation of the transcription regulator nuclear factor kappa beta (NF-κB) [69]. NF-kB regulates the expression of several genes involved in inflammatory response and its activation represents a pivotal early step in the activation of the inflammatory response.

Concerns regarding hypercapnia

There are concerns regarding the potential for hypercapnia and/or acidosis to exert deleterious effects that suggest the need for caution when considering its use in the clinical context. The potential for hypercapnic acidosis to exert adverse haemodynamic effects in patients with ARDS is clear [70]. However, the potential for detrimental effects on cardiac output [71] and on the peripheral circulation [72] may be overstated. In addition, beneficial effects of moderate hypercapnia may be counterbalanced by a potential for adverse effects at higher levels. This is supported by the experimental evidence demonstrating that protection from the adverse effects of brain ischaemia was better when the inspired CO_2 was set at 6% rather than at 9% [54]. Of concern, severe hypercapnia produced by 15% CO_2 has been more recently demonstrated to worsen neurologic injury in this context (Table 1) [73]. In isolated hepatocytes, the degree of protection from anoxic injury conferred by a metabolic acidosis was greater at pH 6.9 than at pH 6.6 [65]. Furthermore, acidosis attenuates the neutrophil respiratory burst and superoxide production, which are necessary for neutrophil bactericidal activity [74]. This may impair bacterial killing, resulting in unopposed bacterial proliferation, with deleterious consequences, in patients with sepsis induced ARDS.

There are reports of lung [75] and intestinal [76] injury following induction of metabolic acidosis by hydrochloric acid infusion in whole animal models. However, it is important to recognise that infusion of hyperosmolar solutions of strong acids into whole animal preparations may produce toxic effects close to the infusion site and adverse systemic effects, at least some of which are unrelated to any change in pH [77]. Thus, the effects of infusion of strong acid in any given experiment in vivo is likely to represent the sum of potentially beneficial and adverse actions. This contrasts with the situation with hypercapnic acidosis, which is easy to produce, is well tolerated, and does not produce toxic local effects. In ex vivo experiments, where a changes in pH and/or PCO_2 can be produced independently, and without the need for acid infusion close to the tissue, metabolic acidosis is directly protective against ischaemia-reperfusion induced ALI [45].

Of perhaps more concern is the potential for hypercapnia to increase tissue nitration. Peroxynitrite is a potent free radical produced in vivo largely by the reaction of nitric oxide with superoxide radicals, which are greatly increased in acute inflammatory states [78–80]. Peroxynitrite oxidizes a variety of biomolecules including sulfides, thiols, lipids, nucleic acids, transition metals and selenoproteins [78–80]. These oxidation reactions result in altered cellular function and tissue damage. Peroxynitrite also causes nitration of phenolic amino acid residues in proteins, including tyrosine residues, which leads to alteration of protein function [78, 79, 81, 82]. Two recent in vitro studies demonstrate that increased CO_2 and a reduction in pH below the normal physiological value inhibit oxidation by peroxynitrite while promoting nitration reactions [83, 84]. The potential for hypercapnia to promote the formation of nitration products from peroxynitrite has been clearly demonstrated in recent in vitro experiments [61, 62]. Peroxynitrite-mediated tissue nitration has been suggested to be a key mechanism of tissue damage in inflammatory conditions, including ALI [78, 79, 81, 82].

Finally, an important limitation when extrapolating to the clinical context is the relatively short duration of the ALI models in which hypercapnic acidosis has been studied to date. The common clinical scenario in ARDS patients is that of a more prolonged hypercapnia, during which time the acidosis may be partially, or even completely, compensated. As we have seen, there is reason to believe that the acidosis generated by acute hypercapnia may be the protective factor in acute models of ALI. The need to study the effects of hypercapnia in ALI models of considerably longer duration is therefore clear.

In summary, these findings demonstrate that hypercapnic acidosis, induced by direct administration of CO_2, is protective in multiple models of acute lung and systemic organ injury. These protective effects appear to be a function of the acidosis rather than the hypercapnia per se. While significant concerns remain regarding hypercapnia, in particular, its potential to increase tissue nitration, the potential for hypercapnia to attenuate acute lung and systemic organ injury is clear (Fig. 1).

Hypercapnia — with or without buffering?

Buffering of the acidosis induced by hypercapnia in ARDS patients remains a common, albeit controversial, clinical practice [85, 86]. Buffering with sodium bicarbonate was permitted in the ARDSnet study [2]. The need to examine the effects of buffering a hypercapnic acidosis is emphasised by the fact that both hypercapnia and acidosis per se may exert distinct biologic effects. However, as already discussed, there is evidence that the protective effects of hypercapnic acidosis in ALI are a function of the acidosis, rather than elevated CO_2 per se [45, 61]. In addition, there are specific concerns regarding the use of bicarbonate to correct an acidosis. These

concerns have resulted in the removal of bicarbonate therapy from routine use in cardiac arrest algorithms [87, 88]. The effectiveness of bicarbonate infusion as a buffer is dependent on the ability to excrete CO_2, rendering it less effective in buffering a hypercapnic acidosis. In fact, bicarbonate may further raise systemic CO_2 levels under conditions of reduced alveolar ventilation, such as ARDS [89]. While bicarbonate may correct arterial pH, it may worsen an intracellular acidosis because the CO_2 produced when bicarbonate reacts with metabolic acids diffuses readily across cell membranes, whereas bicarbonate cannot [90]. Bicarbonate may exert detrimental effects when used to buffer a lactic acidosis. The potential for bicarbonate infusion to augment the production of lactic acid has been demonstrated in the experimental and clinical setting [91–97]. Bicarbonate infusion exerted deleterious cardiovascular effects in a model of hypoxia-induced lactic acidosis [93, 94]. The safety of bicarbonate in diabetic patients has also been questioned. Bicarbonate administration slowed the rate of decrease of ketoacids in patients with diabetic ketoacidosis [98]. Of even more concern, bicarbonate administration is associated with a four-fold increase in risk of cerebral oedema in children with diabetic ketoacidosis [99].

The administration of sodium bicarbonate constitutes a significant osmolar load, which may exert independent beneficial effects independent of any associated changes in pH. Osmolar loads, such as hypertonic saline, may improve the haemodynamic profile in hemorrhagic shock [100], attenuate key aspects of the immune response [100–102] and prevent organ injury in experimental models [101–103]. In fact, when compared with an equimolar dose of sodium chloride, bicarbonate administration does not improve the hemodynamic status of critically ill patients who have lactic acidosis [104]. A follow-up study in an in vivo model of lactic acidemia found that bicarbonate exerted haemodynamic effects (mean arterial pressure, cardiac output, left ventricular contractility), which were indistinguishable from those seen in response to an equimolar dose of sodium chloride [105]. These data give cause for concern about the practice of buffering metabolic acidosis, and comparable questions may exist in the setting of hypercapnic acidosis.

There may be a role for the use of buffers, such as the amino alcohol tromethamine (tris-hydroxymethyl aminomethane, THAM), in specific situations where the physiologic effects of hypercapnic acidosis are of concern. THAM penetrates cells easily and can buffer pH changes and simultaneously reduce PCO_2 [106]. Unlike bicarbonate, which requires an open system for CO_2 elimination in order to exert its buffering effect, THAM is effective in a closed or semi-closed system [106]. THAM rapidly restores pH and acid-base regulation in acidaemia caused by CO_2 retention [106]. A common rationale for buffering is to ameliorate the haemodynamic consequences of acidosis. In a small, but carefully performed clinical study in ARDS patients, rapid induction of a hypercapnic acidosis for a two-hour period resulted in significant hemodynamic alterations, including decreased systemic vascular resistance, increased cardiac output, decreased myocardial contractility, decreased mean arterial pressure and increased mean pulmonary arterial pressure [70]. Buffering of the hypercapnic acidosis with THAM rapidly attenuated the haemodynamic alterations and restored myocardial contractility in these patients [70].

In summary, although it is a widely accepted clinical practice, there are no long-term clinical outcome data (e.g., survival, duration of hospital stay) to support the practice of buffering a hypercapnic acidosis. Taken together, the above literature suggests that, in the absence of correcting the primary problem, buffering a hypercapnic acidosis with bicarbonate is not likely to be of benefit. If the clinician elects to buffer a hypercapnic acidosis, the rationale for this practice should be clear (e.g. to ameliorate potentially deleterious haemodynamic consequences of acidosis). THAM may have a role in these clinical situations.

Conclusions

The optimal ventilatory strategy, and the role of 'permissive hypercapnia' in that strategy, is not yet clear. The protective effect of reducing lung stretch in improving outcome in ARDS patients are beyond doubt. There is growing evidence to support the contention that hypercapnic acidosis may contribute to the benefits seen with protective lung ventilation. While direct induction of a hypercapnic acidosis is protective in multiple models of acute lung and systemic organ injury, the potential for hypercapnia to increase peroxynitrite-mediated tissue nitration is of concern and requires further investigation.

At present, ventilatory strategies that involve hypercapnia are clinically acceptable only provided the clinician is primarily targeting reduced tidal stretch. There are insufficient clinical data to suggest that hypercapnia per se should be independently induced, outside the context of a protective ventilatory strategy. Furthermore, 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. If that becomes the case, then the clinical study of hypercapnia will become less feasible in the setting of permissive hypercapnia, and will require the deliberate induction of hypercapnia (i.e., 'therapeutic' hypercapnia). Pre-clinical studies are urgently needed to clarify the advantages, disadvantages, and optimal use of hypercapnia in ARDS.

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