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PERSPECTIVE

The lung and carbon dioxide: implications for permissive and therapeutic hypercapnia

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Although acute respiratory acidosis may be a sign of impending respiratory failure in spontaneously breathing patients, it is commonly encountered in intubated patients with acute lung injury (ALI). This is especially the case now that limiting tidal volumes and airway pressures have been proven to reduce mortality in ALI, presumably by reducing additional lung injury caused by mechanical ventilation itself [1]. A respiratory acidosis arising from lung-protective ventilation strategies has been termed permissive hypercapnia [2–5]. As the name indicates, permissive hypercapnia has been regarded as an inconvenient side-effect that must be tolerated in order to realise the mortality benefits of a low lung-stretch strategy.

There is growing evidence that hypercapnic acidosis may itself minimise or reduce lung injury as a result of suppressing inflammatory events. The mechanism(s) for this effect is (are) not entirely known. Nonetheless, there was sufficient suggestive data from cell culture and isolated organ studies over the past two decades for LAFFEY and KAVANAGH [6] not only to support the use of permissive hypercapnia but also to advocate the use of "therapeutic hypercapnia" through the addition of carbon dioxide (CO_2) to the inspired gas. In addition to the possibility of improved outcomes due to anti-inflammatory effects, hypercapnic acidosis has effects on ventilation-perfusion matching that improve gas exchange. Therapeutic hypercapnia has previously been shown to increase arterial oxygenation by this mechanism in normal animals [7, 8] and in a sheep model of *Klebsiella pneumonia* [9]. The only study of changes in gas exchange with permissive hypercapnia in humans with ALI showed an increase in shunt [10]. This was most likely due to a reduction in tidal volume used to produce a hypercapnic acidosis than to permissive hypercapnia itself. Thus, the effects of hypercapnic acidosis on ventilation, perfusion, and their regional matching in injured lungs remain largely unknown.

While the acute respiratory distress syndrome (ARDS) Network data have stated that physiological end-points such as gas exchange do not necessarily correlate with outcome, there are unanswered questions about the tolerable limits of hypoxaemia and acidosis which may influence clinical outcomes. With the growing acceptance of permissive hypercapnia in support of patients with lung injury on mechanical ventilation, studies such as that by NAOKI *et al.* [11] in this issue of the *European Respiratory Journal*, will be essential for a full understanding of the mechanisms by which hypercapnic acidosis affects gas exchange and inflammation. The authors have revealed an obviously complex system controlling microvascular tone that may differ between the normal and injured lung and may be heterogenous across various forms of lung injury. Their work adds to an already vast literature on CO_2 and hydrogen ion (H^+) effects on biochemical and physiological functions in the lung and other tissues. Importantly, they have begun to illuminate vascular events at the level of the microcirculation.

Using fluorescent confocal microscopy on the surface of isolated perfused rat lungs to measure microvessel diameter, NAOKI *et al.* [11] studied the responses to hypercapnic (respiratory) and isocapnic (metabolic) acidoses in normal lungs and those injured by hyperoxia. Research of this calibre has the potential to uncover new and little known interactions. For instance, they demonstrate complex associations between nitric oxide (NO), a molecule regarded primarily as a potent vasodilator, and cyclo-oxygenase (COX), an enzyme generating both inflammatory and vasoactive eicosanoids such as prostaglandins, prostacyclin, and thromboxane. Specifically, they sought to determine the roles of NO and arachidonate metabolites, along with the responsible NO synthase (NOS) and cyclo-oxygenase isoforms, in controlling microvascular tone in the setting of respiratory and metabolic acidoses. The authors observations are both interesting and somewhat surprising. Hyperoxic lung injury leads to increased NO production by upregulation of endothelial cell NOS (ecNOS or NOS III). The importance of ecNOS induction was confirmed by the effects of nonselective NOS inhibition, lack of effect with selective inducible NOS (iNOS) inhibition, and Western blot analysis of lung homogenates. This is in contrast to other reports of lung injury in which iNOS is the isozyme usually induced by injury [12, 13]. At the whole lung level, they found that CO_2 and isocapnic acidosis caused a mild elevation in pulmonary artery pressure in normal lungs and that this pressure increase was doubled in hyperoxic lung injury. If it is assumed that left atrial pressure was

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unchanged, then this pressure change represents an increase in pulmonary vascular resistance because lung perfusate flow was constant. By clever use of combinations of NOS and COX isozyme inhibitors and NO donors, the authors established that upregulated endogenous NO production paradoxically contributes to hypercapnic (but not isocapnic) acidosis-associated vasodilation by the curious route of inhibiting COX-1 mediated formation of vasoconstricting prostaglandins in hyperoxic-injured lungs. However, when exogenous NO is provided in overwhelming amounts (with nitroprusside) then NO more classically acts as a direct vasodilator.

The measurements of acinar microvessel diameter revealed interesting and divergent responses, at the microvascular level, that would not be readily predicted by the changes in total pulmonary vascular resistance (PVR). As an example, the authors found that hypercapnic acidosis caused small venular dilation even in the face of increased resistance in upstream arterial resistance. To add to the complexity of understanding the effects of hypercapnia, they showed that small arterioles did not change with CO_2, but unexpectedly dilated when ecNOS activity was inhibited. Furthermore, they found that this effect was blocked by COX-1 inhibition. The variety of findings they describe are not easily explained, but clearly the data reveal a complexity of PVR control and show how it may vary depending upon the exact circumstances, particularly in lung injury.

Although isolated perfused unventilated lungs, such as those highlighted by the authors, may be distinctly different from the *in vivo* activity of the lung, studies such as these are a necessary first step. While the acinar microvessels reveal several interesting results, it must be borne in mind that the arterioles and venules that play the dominant role in determining PVR and the distribution of pulmonary blood flow were not examined in this study. Nevertheless, the acinar microcirculation clearly does respond to both injury and agents that block or stimulate the production of vasoactive substances. Understanding the events that occur at the microvessels and capillaries is critical because they represent the largest surface area of the lung and it is here where oedema forms.

Carbon dioxide and hydrogen ion chemistry

When the large body of work on CO_2 and acidosis is surveyed, the data, including that of NAOKI *et al.* [11], are not always consistent. CO_2 and pH may act unpredictably and sometimes oppositely depending upon the experimental or clinical conditions. Generally, acidosis suppresses most cellular functions, and it is for this reason that the body uses a variety of strategies to defend its intra- and extracellular acid-base status within remarkably narrow limits [14–17]. The complexity in CO_2 effects rests in the many ways that it directly and indirectly alters the extra- and intracellular milieu critical to "normal" functioning. The addition of CO_2 leads to a greater H^+ concentration by its spontaneous and carbonic anhydrase-catalysed combination with water to form carbonic acid. The protons thus generated are free to react (or be buffered) with titratable groups in certain amino acids resulting in secondary and tertiary structural changes of many proteins and enzymes in cell membranes and cellular aqueous environments. In addition to its direct acidifying properties, CO_2 can react with some free amine groups in proteins to form carbamate residues [18–20]. This binding of CO_2 also modifies protein structure and function and may explain some of the differences observed in the effects of CO_2 and H^+ when both lead to equal changes in pH. The best example of the dual chemistry of CO_2 and proteins is the well-known Bohr effect or lowering of haemoglobin-oxygen affinity. Given that these reactions can occur in almost any protein or enzyme, it should not be surprising that CO_2 might act oppositely under different circumstances. One such example is the occasional study in which it is found that CO_2 reduces pulmonary vascular resistance. How these CO_2/H^+-mediated perturbations in protein activity then alter cell processes is not fully known. They are likely to involve changes in membrane ion transport and electrochemical membrane potential, reductions in intracellular calcium concentration [21], alterations in microtubule assembly [19], decreases in enzyme activity and mediator synthesis, inhibition of apoptosis [22], and changes in gene transcription [23].

With regard to gene transcription, respiratory acidosis may act in ways different from the action of metabolic acidosis [24]. ROUNDS *et al.* [25] have shown that a variety of unidentified proteins are upregulated in the normal lung with hypercapnia. Analogous to the better known effects of hypoxia in altering gene transcription *via* hypoxia-inducible factor, there is very recent evidence for membrane acid-sensing ion channels and acid-responsive gene promotor regions [24, 26, 27]. How the more chronic use of hypercapnia in critically ill patients affects these acid sensing mechanisms and changes in gene transcription remains completely unexplored.

Effects of hypercapnia on inflammation

As discussed earlier, hypercapnia and other forms of acidosis have suppressive effects on inflammatory events. With reference to support of patients with lung injury and multi-organ failure, it has been shown that restoration of blood flow and/or oxygen delivery to a previously ischaemic and/or hypoxic tissue is less injurious if the reperfusing fluid is acidic. Thus, gradual rather than rapid restoration of intracellular pH while cells become re-oxygenated minimises the cellular injury associated with ischaemia-reperfusion. This effect has been labelled the "pH paradox" and was first described for the heart and liver [28–32], but subsequently has also been shown in lung, kidney and brain [33–38]. This paradigm led LAFFEY *et al.* [39] to take permissive hypercapnia one step further by deliberately adding CO_2 to the ventilating gas of ischaemic lungs *in vivo*. Therapeutic hypercapnia markedly reduced the extent of ischaemia-reperfusion injury. Subsequent studies of this strategy have demonstrated reductions in ventilator-induced lung

Table 1. – Immuno-modulatory and protective effects of acidosis

Inhibition of xanthine oxidase and oxygen radical formation
Reduced neutrophil respiratory burst
Reduced leucocyte and vascular endothelial cell cytokine release
TNF-α
IL-8
IL-6
Inhibition of neutrophil chemotaxis
Changes in cellular adhesion molecule expression
Inhibition of NO synthases
Impairment of phagocytosis
Decreased antibody synthesis
Increased complement activation

TNF: tumour necrosis factor; IL: interleukin; NO: nitric oxide.

injury in both isolated perfused lungs and recently in an *in vivo* animal model [40, 41].

Table 1 lists a number of possible CO_2 and pH-mediated anti-inflammatory mechanisms that may contribute to lung protection with therapeutic hypercapnia [6, 42, 43]. Some exceptions have been reported, in part due to antipodal effects of severe acidosis (pH<6.5) and those under more mild-to-moderate conditions (pH>6.8). One example is NO production that rises in conditions of severe acidosis but is often suppressed with mild acidosis [44–47]. Other critical factors include whether *in vitro* studies were performed in CO_2-free artifical buffers or CO_2/bicarbonate (HCO_3^-) buffered systems, and the specific cause of lung injury. It is obvious that acidosis is a two-edged sword that may prove difficult to wield in critically ill patients because infection or the risk of infection is always present. Indeed, this problem has plagued virtually all attempts to use selective and nonselective anti-inflammatory or immune modulating interventions in critical care [48–49].

Effects of hypercapnia on systemic and pulmonary physiology

If permissive or therapeutic hypercapnia is to be used rationally and safely in intensive care settings, there are a number of physiological effects, due to alterations in pH and the CO_2 tension in arterial blood (P_{a,CO_2}), that need to be considered. While adding CO_2 to the gas mixture of artificially ventilated patients who are often tachypnoeic may seem counter-intuitive, there are likely to be select patient populations in whom the benefits of therapeutic hypercapnia may outweigh its risks and inconveniences. Tables 2 and 3 list many of the pulmonary and systemic effects of hypercapnic acidosis that have relevance in situations where therapeutic hypercapnia might be initiated. As is the case for the anti-inflammatory effects, the physician must be aware of the competing and sometimes compensatory nature of these actions.

In the lung, in contrast to the systemic circulation, there is usually constriction in the pulmonary vasculature in response to hypercapnic acidosis. The strength of hypercapnic vasoconstriction is generally

Table 2. – Systemic effects of hypercapnic acidosis

CNS
Ventilatory stimulation
General anaesthesia at high levels
Cerebral vasodilation
Increased intra-cranial pressure
Increased sympathetic tone
Decreased parasympathetic tone
Increased adrenal medullary and cortical output
Cardiovascular
Direct effects
Impaired contractility of cardiac and vascular smooth muscle
Reduced afterload and systemic vasodilation
Opposing consequence of heightened sympathetic tone
Increased cardiac frequency
Increased myocardial contractility
Increased venous capacitance vessel tone
Increased venous return
Increased cardiac output
Metabolism
Reduced oxygen consumption
Altered cellular fuel utilisation
Increased cellular ketoacid and lactic acid uptake
Renal/electrolyte
Increased H^+ secretion and HCO_3 reabsorption
Renal adrenergic-mediated vasoconstriction at high levels
Increased Na^+ reabsorption
Mild hyperkalemia
Blood
Small increase in haematocrit/haemoglobin concentration
Reduced haemoglobin O_2 affinity (increased p50)
Suppression of erythropoietin release

CNS: central nervous system; H^+: hydrogen ion; HCO_3: bicarbonate; Na^+: sodium; O_2: oxygen.

weaker than that of hypoxic pulmonary vasoconstriction (HPV) and its more important effect may be in augmenting HPV. While the membrane and cellular mechanisms of HPV are a focus of intense investigation, less is understood about how CO_2 acts on pulmonary vascular smooth muscle. Analogous to HPV, the effect may be a complex summation of changes in membrane potential, alterations in membrane potassium (K^+) and calcium (Ca^{2+}) channel activity, and alterations in both vascular endothelial cell vasoconstrictor and vasodilator substances. For example, NAOKI *et al.* [11] demonstrated the interaction between NO and prostaglandins. The balance may not be the same in different portions of the pulmonary circulation, such that some segments of the vasculature may respond in an opposing manner to others. This was reported by NAOKI *et al.* [11] in their normal rats in which PVR rose but there was

Table 3. – Pulmonary effects of hypercapnic acidosis

Vagally mediated large airway constriction
Direct small airway dilation
Increased collateral ventilation
Improved surfactant function and increased secretion
Increased parenchymal compliance
Increased pulmonary vascular resistance
Enhanced hypoxic vasoconstriction
Improved V'/Q' matching

V'/Q': ventilation/perfusion.

venular dilation. In addition, the route by which CO_2 is added to the lung (inhaled *versus* delivered by the vasculature) may evoke differing responses among arteries and veins [50]. Although NAOKI *et al.* [11] found no effect of hypercapnic or isocapnic acidosis on capillary diameters, the capillary bed and its surrounding parenchyma do possess contractile elements whose state of tone may be important in setting intercellular gap tensions, transvascular fluid flux, and alveolar-capillary permeability [51, 52].

The airways and lung parenchyma also respond to changing CO_2 and pH as listed in table 3. Again a degree of heterogeneity of effects exists as exemplified by differences in behaviour between large and small airways [53]. The opposing balanced airway action of CO_2 explains why global dynamic airway pressure measurements barely change with CO_2 inhalation. Parenchymal compliance is sensitive to CO_2 and in general increases in response to hypercapnic acidosis. This may be due to increased surfactant secretion and more effective surface tension-lowering properties under acidic conditions [54]. The combined effect of small-airway dilation with CO_2 and increased compliance underlies the phenomenon of hypocapnic broncho- and pneumo-constriction observed with acute regional pulmonary artery occlusions [55, 56]. The vascular, airway, and compliance effects of CO_2 are best considered as mechanisms that serve ventilation/perfusion (V'/Q') matching. They may either alter regional ventilation to keep pace with a primary change in perfusion, or alter regional perfusion to match a primary change in ventilation [57]. Very recently the current authors have shown that if the addition of inspired CO_2 is limited to the latter portion of the inspirate, improved V'/Q' matching occurs without systemic respiratory acidosis [58]. This suggests that therapeutic hypercapnia might be limited selectively to the lung.

The numerous systemic effects of CO_2 present several clinically significant scenarios. Although hypercapnic acidosis reduces cardiac contractility in isolated hearts and vascular smooth muscle, the hypercapnic-mediated sympathoadrenal effects of increased preload, decreased afterload, and increased cardiac frequency lead to a net increase in cardiac output. It is against this background that one must be judicious with hypercapnia in any patient on β-adrenergic antagonists or those with heart failure or coronary artery disease. The increase in cerebral blood flow with hypercapnic acidosis must be considered carefully in any patient as a potential risk for raised intracranial pressure [59]. The marked sympathetic activation of hypercapnic acidosis, particularly when combined with arterial hypoxaemia, can lead to intense renal vasoconstriction (unlike elsewhere in the circulation) and avid tubular Na^+ reabsorption causing depressed glomerular filtration and increased fluid retention [60].

Conclusion

As permissive hypercapnia becomes more commonly accepted, tolerated, and practiced, the issues and physiology discussed in this perspective need to come into sharper focus and be better understood. It is hoped that permissive hypercapnia and therapeutic hypercapnia may offer real benefits, but only well-planned and executed clinical studies will reveal the answer. Furthermore, as with any medication or intervention, the therapeutic index must be quantified and found to be safe enough for widespread use. Much work lies ahead.

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