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Sepsis and Therapeutic Hypercapnia

Sailing Too Close to the Wind?

ALMOST a decade ago, the landmark study of low tidal volume ventilation (6 *vs.* 12 ml/kg ideal body weight) in the acute respiratory distress syndrome (ARDS) showed that a strategy leading in some cases to carbon dioxide retention (permissive hypercapnia) reduced mortality by a remarkable 25%.[1] Lung protective ventilation is now the standard of care for acute lung injury and ARDS. Lack of obvious harm with permissive hypercapnia, except in those with intracranial hypertension or cardiac instability, impelled some to proceed further and purposefully impose a state of hypercapnic acidosis (therapeutic hypercapnia) in various animal models of lung injury; the working hypothesis being that hypercapnic acidosis modulates the excessive inflammatory milieu of ARDS. One of the leading groups from the start has been that of Laffey and coworkers,[2] who in this issue of ANESTHESIOLOGY comprehensively review the many aspects of protection afforded by hypercapnic acidosis in lung injury. What is important in this review to the intensive care physician is the real concern, heretofore largely ignored, that similar to many antiinflammatory or immune-modulating interventions, therapeutic hypercapnia may impair host defenses against pathogens surely to be encountered by mechanically ventilated patients.

The history of therapeutic hypercapnia reaches back to the early days of arterial blood gas analysis and mechanical ventilation. Until the last decade, it was a standard practice to correct hypercapnic acidosis with mechanical ventilation using high tidal volumes and pressures, if necessary, owing to the perceived dangers of respiratory acidosis itself. The evidence for harm, however, had always been weak. Indeed, the advent of clinical blood gas analysis in the 1950s revealed surprisingly profound hypercapnia ($Pa_{CO_2} > 150$ mmHg, pH < 7.0) without negative consequence in thoracic surgical cases involving one-lung ventilation.[3] A Pa_{CO_2} of 501 mmHg from massive grain aspiration in a healthy farmer with complete recovery has been reported.[4] The concept of permissive hypercapnia, purposefully limiting tidal volume and pressure and accepting subsequent hypercapnic acidosis, was first studied in status asthmaticus and gained credence in the mid-1980s. Darioli and Perret[5] reported a mortality reduction from 20% to almost 0%, largely by prevention of pneumothorax and hemodynamic compromise, even with the initial Pa_{CO_2} exceeding 100 mmHg. Acute hypercapnic acidosis is well tolerated as long as perfusion and arterial oxygenation are assured.[6] In rats maintained at 2 atm (50% O_2–50% CO_2), cerebral oxidative metabolism is unaffected even at P_{CO_2} more than 750 mmHg and pH as low as 6.1.[7] The ability to withstand hypercapnic acidosis depends on a strong neuroendocrine response that maintains and/or increases cardiac output and blood pressure despite direct negative inotropic and vasodilating effects of carbon dioxide[8,9] and active intracellular pH defense mechanisms, particularly in critical organs such as brain and heart that transport H^+ into the extracellular space.[6,10,11]

Following on a parallel tack to these studies of hypercapnic tolerance, the concept of a "pH paradox" emerged in the 1970s and 1980s. In tissue culture and isolated organ studies, including the lung (reviewed in Ref. 11), recovery after anoxia and/or ischemia is always greater if resuscitation occurs in an acidic milieu (pH < 7.0), and conversely, damage is far worse with alkalotic resuscitation. These investigations established that metabolic and respiratory acidoses blunt many oxidative and inflammatory cascades and the lethal intracellular calcium uptake initiated when tissues are reoxygenated. As a general rule, because proteins have pH optima in the near physiologic range, it is not surprising that acidosis reduces radical oxygen and nitrogen species generation, diminishes proinflammatory cytokine and chemokine production, impairs neutrophil chemotaxis, and inhibits many proteases, nucleases, and phospholipases activated in injured cells.[2,11]

With growing acceptance of the permissive hypercapnia and pH paradox paradigms, Shibata *et al.*[12] studied prophylactic hypercapnic acidosis (12 or 25% inspired carbon dioxide) in isolated perfused rabbit lungs undergoing ischemia-reperfusion injury or oxidant-induced injury. Their favorable results on alveolar edema, compliance, gas exchange, and histology were followed by positive results in other models of lung injury and then replicated in live animals even when inspired carbon dioxide as high as 10–12% was given to drive arterial pH into the 7.00 to 7.15

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range and $Paco_2$ as high as 80–90 mmHg. These benefits to inspired carbon dioxide are also evident when it is given after the onset of lung injury.[2,11] Despite the preponderant evidence for salutary antiinflammatory and immune-modulatory effects of hypercapnic acidosis, others have reported some proinflammatory effects in their experiments,[13,14,15,16] making the case less than solid in favor of therapeutic hypercapnia.

Furthermore, as the metaphoric subtitles of this editorial and the review by Curley *et al.*[2] intimate that there may be other downsides, one of which this group has begun to explore and define in a series of well-designed experiments. A critical question is what might be the impact of these desirable immune-modulating effects of hypercapnic acidosis on patients with infection-related ARDS or on infections developing in the course of their need for intensive care and mechanical ventilation? The authors discuss a number of their investigations and those of others performed in animals with various forms of bacterial sepsis, including pneumonia, peritonitis, and septicemia, in which hypercapnic acidosis was imposed from several hours to 2 days. These studies taken as a whole considerably allay the fear of unchecked bacterial multiplication occurring in hypercapnic animals, because they had no greater bacterial counts when compared with the nonhypercapnic controls. In addition, various indices of inflammatory damage and lung injury were lessened with hypercapnia as has been shown convincingly in noninfectious forms of lung injury. The single worrisome study by this group[17] was one in which rats were given an intratracheal administration of *Escherichia coli* and then followed up for 2 days breathing spontaneously in either a hypercapnic chamber ($Fico_2 = 0.05$) or in the absence of added carbon dioxide. They found that the hypercapnic rats had higher lung bacterial colony counts, more structural damage, and lower static lung compliance than the normocapnic controls, and their isolated neutrophils had impaired phagocytic capacity. However, when appropriate antibiotics were administered at the outset, there were no differences between the groups. It is certainly the case that we use other immunosuppressive therapies, and we easily assume the need to be more vigilant for infection and administer antibiotics accordingly.

In addition to the risk of impairing host defense mechanisms, hypercapnic acidosis impairs *ex vivo* and *in vivo* wound healing of the airway and alveolar epithelia,[18,19] which might *in vivo* lead to increased bacterial translocation. Another concern is that hypercapnia reduces alveolar fluid clearance in healthy isolated perfused lungs by causing endocytotic withdrawal of Na^+/K^+ ATPase from the basolateral membrane of alveolar epithelial cells.[20] Given the emerging data to suggest better outcomes in ARDS with strategies that minimize alveolar fluid accumulation,[21] this is an unwelcome finding. Whether this is the case *in vivo* and in injured lungs remains to be tested.

At this juncture, despite the largely favorable results in animals, it must be appreciated that a number of clinically relevant factors have not been incorporated into the animal models of hypercapnic acidosis (a critique equally apposite to all models of lung injury prophylaxis or treatment) that in all likelihood would make therapeutic hypercapnia a tougher proposition. These include a longer maintenance of the hypercapnic state than presently studied (only up to 2 days): older age, coexisting chronic medical conditions, and concurrent endogenous or exogenous immunosuppression. Apart from the concern of increased infectious risk raised in this review, we still have no certainty that patients with compromised cardiovascular, renal, and cerebral function can mount and tolerate the resulting strong neurosympathetic activation and cardiovascular responses evoked by hypercapnic acidosis, which may cause myocardial oxygen supply demand imbalance, renal vasoconstriction leading to oliguria, and pulmonary hypertension.

Trials of lung-protective low tidal volume ventilation shed little light because permissive hypercapnia has been neither a target goal nor enthusiastically embraced. In the large ARDS Net trial of 6 *vs.* 12 ml/kg tidal volumes, there was only a mean 5 mmHg greater $Paco_2$ in the more successful lower tidal volume arm.[1] Analyzing this large database, we found that after controlling for other variables predictive of mortality, moderate levels of hypercapnic acidosis (pH 7.15–7.35, $Paco_2$: 45–65 mmHg) lowered the odds ratio of death significantly but only in the 12 ml/kg tidal volume group.[22] Although we found no equivalent protection in the low tidal volume arm, our data nonetheless suggest that permissive hypercapnia may limit the feared ventilator-induced lung injury of higher tidal volumes.

Should hypercapnic acidosis be proven therapeutic, do we administer it by hypoventilation or addition of inspired carbon dioxide? Much of the animal work has used inspired carbon dioxide. This may be the wiser choice if the intention is to make lung tissue homogenously acidotic to suppress local inflammatory events. It is clear from computed tomographic imaging that the lung is not homogenously injured in ARDS, leaving the few better and more compliant units to be quite overventilated with respect to their volume and blood flow. These high ventilation-perfusion units will have lower regional alveolar Pco_2 (< 20 mmHg) and higher local tissue pH. Thus, despite deliberate global hypoventilation, these functioning units may sustain ongoing high tidal volume injury, made worse by their own local respiratory alkalosis.[23] Inspired carbon dioxide guarantees that all lung regions, at a minimum, will always see a Pco_2 equivalent to the inspired value. One could argue for purposes of limiting the immune-modulation to the lung and minimizing the neurosympathetic stress of systemic hypercapnic acidosis a technique of achieving selective lung acidosis would make even better sense. We have performed this in the normal lung by adding carbon dioxide into the latter half of the inspired breath of anesthetized dogs and showing that we attain the same improvement in ventilation-perfusion matching from acidification of the lung observed with carbon dioxide added into the entire inspired volume but without the generation of systemic respiratory acidosis.[24] This strategy of adding a gas to a particular phase of inspiration has also been applied to

nitric oxide to target greater amounts of gas to the periphery and conserve on total gas use.[25]

It is not clear whether more animal work will better define the prospects of therapeutic hypercapnia in human lung injury. Perhaps, the time is right to perform a short duration randomized study of therapeutic hypercapnia (by adding 3–5% CO_2 into the inspired gas) in ARDS patients to assess its tolerability and safety in terms of hemodynamics, gas exchange, and sedation usage, and to measure the changes in the inflammatory and microbial milieu of the lung by bronchoalveolar lavage. If the results demonstrate "proof of concept," then a larger and longer study should follow with the power to assess morbidity and mortality outcomes, including the focus of this article, namely infectious risks. Only then will we determine whether (or not) we can sail this close to the wind.

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