

The undiscovered country: therapeutic targeting of carbon dioxide levels in critically ill patients

Alistair D Nichol

In the current issue of *Critical Care and Resuscitation*, there are two complementary articles: one reviewing the biological effects of hypercapnia in sepsis¹ and another reporting the tidal volume delivery (including the effects on carbon dioxide [CO₂] levels) in patients without acute respiratory distress syndrome (ARDS) in Victoria, Australia.² These manuscripts highlight the profound and commonly unrecognised effects that altered CO₂ levels may have on our patients, and show how routine care in the intensive care unit (ICU) may significantly alter CO₂ homeostasis. It is important for bedside clinicians to appreciate both the physiological and the immunological effects of hyper- and hypocapnia but also for researchers seeking an easily inducible therapeutic agent with the potential to change patient outcomes. Given the ease by which CO₂ levels can be altered in critically ill ventilated patients, it is somewhat surprising to note the limited clinical data examining the long term effects of targeted CO₂ management in the ICU population to date.

First, Tiruvoipati and colleagues¹ review the extensive basic science and limited clinical studies describing the effects of hypercapnic acidosis and buffered hypercapnia (hypercapnia with a normal pH) in clinical practice.³ This review highlights the current limits of our understanding, but also shows that hypercapnic acidosis has the potential to be a potent immunomodulator with immune suppressant effects in critically ill patients, including those with sepsis. Some animal models have suggested that this immunomodulator effect may be beneficial in sterile models of tissue injury but may be detrimental in live bacterial models (ie, with lack of adequate source control).⁴ However, our current understanding is that hypercapnia is not detrimental in the presence of appropriate antibiotic therapy, suggesting it may be a safe therapeutic intervention.^{4,5} This review summarises the growing body of evidence that hypercapnia, in addition to its profound physiological effects (ie, increasing heart rate, pulmonary vascular resistance etc), has potent immunomodulatory effects. More clinical studies of therapeutic hypercapnia are clearly needed.

Secondly, Eyeington and colleagues² describe the Victorian practice of mechanical ventilation management in patients without ARDS. This statewide observational study indicates a worrying “one size fits all” approach to mechanical ventilation in this cohort. While this article

describes the delivery of tidal volumes in many patients far greater than what is currently recommended, it is interesting to examine the effects this “hyperventilation” has on CO₂ levels and acid base balance. Despite a prevailing trend towards tolerance of elevated levels of CO₂ in patients with ARDS to permit safe, low tidal volume ventilation (so-called permissive hypercapnia), this study would suggest that the opposite (ie, hypocapnia) is common in ICU patients without ARDS. It is likely that the potential immunological effects of this inadvertent alteration in CO₂ level are not appreciated in this cohort of patients.

It is difficult to think of another example of our practice where we would use an agent with the potential for chronotropic, inotropic, systemic vasodilator and pulmonary vasoconstrictor effects combined with the potential for immunomodulation without thoughtful consideration. Furthermore, while there are situations (ie, traumatic brain injury, right-sided heart failure, pulmonary hypertension etc) where we assess and tightly control CO₂ levels due to unwanted physiological effects, or situations where we tolerate hypercapnia to minimise lung stretch (ie, severe ARDS), in the majority of patients, we continue not to value or study the therapeutic potential of hypercapnia. Hopefully, the two studies reported in this issue of the Journal will help trigger more research in this field.

We are starting to see the targeting of CO₂ levels to alter long term outcomes, so-called therapeutic hypercapnia, for the first time. The TAME (Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest) study (ClinicalTrials.gov identifier NCT03114033) a large ($n = 1700$) randomised controlled trial of comatose patients after out-of-hospital cardiac arrest aims to randomly assign patients to normocapnic or hypercapnic management for 24 hours after promising phase 2 work.⁶

It is clear from the two studies in this issue of *Critical Care and Resuscitation* that we need to consider how we manage CO₂ levels in many different patient populations in the ICU, and that we need to consider a broader role for therapeutic hypercapnia. Further studies and clinical trials in this field are an important additional research agenda in critical care medicine.

Competing interests

I am an investigator in the TAME study.

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