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Should We Be Permissive with Hypercapnia?

Boulos Nassar, M.D., M.P.H.

Division of Pulmonary Diseases, Critical Care, and Occupational Medicine, University of Iowa Hospitals and Clinics, Iowa City, Iowa

ORCID ID: 0000-0002-1722-0347 (B.N.).

Protective lung ventilation, focusing on low tidal volumes and low alveolar pressures, reduces mortality in patients with acute respiratory distress syndrome (ARDS) (1). Such ventilator strategies implemented to reduce lung stretch and lung injury led to an improvement in patient outcomes, albeit with a higher incidence of hypercapnia (2). This was deemed to be an acceptable tradeoff, given the clinical improvement observed. Hypercapnia, now routinely seen and tolerated, triggered an interest in understanding the impact of CO_2 itself in critically ill patients.

Animal and preclinical studies revealed that hypercapnia influences multiple organ systems and causes various physiologic effects (3). Although hypercapnia can increase local alveolar ventilation, improving ventilation–perfusion ($\dot{V}/\dot{Q}$) matching, it can worsen pulmonary vasoconstriction, aggravating cor pulmonale and precipitating right ventricular failure (4, 5). Hypercapnia reduces myocardial contractility, but through vasodilation and reflex sympathoadrenal activation, cardiac output is maintained (6). The impact on the immune system is wide, ranging from reducing cytokines (such as interleukin [IL]-5, IL-6, and tumor necrosis factor-α) to inhibiting neutrophils and phagocytosis (3). This was used to justify observations that early in the course of sepsis, hypercapnia can be beneficial by attenuating the inflammatory response (7). However, late exposure to hypercapnia could accelerate bacterial growth (8).

These observations made from preclinical studies were difficult to replicate at the bedside. The few clinical studies examining the impact of hypercapnia and hypercapnic acidosis are observational and offered different, sometimes conflicting results. Some have shown hypercapnia to be independently associated with increased mortality, but others have not (9–11).

In this issue of *AnnalsATS*, Tiruvoipati and colleagues (pp. 245–254) investigate the association between hypercapnia and mortality in a large cohort of 3,153 patients with 84,819 arterial carbon dioxide tension/pressure (Pa_{CO_2}) measurements (12). In this multicenter observational study, the investigators attempted to answer the following: *1*) What is the impact of hypercapnia on patient outcomes, and is the impact of hypercapnic acidosis different?; *2*) Is there a CO_2 "dose" effect, estimated from the length of stay in the intensive care unit (ICU)?; and *3*) Could CO_2 effect differ between ventilated and nonventilated patients and for pulmonary versus nonpulmonary sources of sepsis?

The investigators found that, in their large population of critically ill patients with sepsis, hypercapnia ($Pa_{CO_2} \geq 45$ mm Hg) and severe hypercapnia ($Pa_{CO_2} > 55$ mm Hg) were common, well tolerated, and not associated with increased mortality. This was in contrast to prolonged exposure to hypercapnic acidosis, which was associated with increased mortality in patients with nonpulmonary sepsis and in mechanically ventilated patients. Perhaps to the surprise of the investigators, there was also a strong signal for increased mortality due to prolonged exposure to hypocapnia.

These results are in line with another recently published multicenter observational study that similarly showed no evidence for benefit or harm from hypercapnia (11). That study also highlighted that sustained hypocapnia in patients with ARDS was associated with increased ICU mortality. These results are in sharp contrast to earlier studies showing hypercapnia to increase mortality (8, 9).

To better interpret this conflicting data, one should understand the pathophysiology

DOI: 10.1513/AnnalsATS.202108-997ED

of hypercapnia in the critically ill patient and some of the limitations of these studies. Hypercapnia usually develops in patients with ARDS because of the inability to eliminate CO_2, as would happen with $\dot{V}/\dot{Q}$ mismatch, dead space, or ventilation strategies implemented to mitigate poorly compliant lungs. CO_2 production could be increased because of fevers and sepsis but not to the level to cause hypercapnia. Interpreting the impact of CO_2 solely, without taking into consideration the degree of lung injury or ventilator strategies, is fraught with problems. Moreover, studying the impact of hypercapnia or hypercapnic acidosis is problematic without taking into consideration the bigger picture of various acid–base disturbances critically ill patients often have.

Although the investigators attempted to accurately reflect the duration of exposure to hypercapnia, they are at the mercy of what is collected at the bedside, which might not align with what is needed to reflect a complete picture of CO_2 exposure.

Although the focus has been on hypercapnia, there is a strong signal that hypocapnia is associated with higher mortality (11, 12). Without accounting for ventilator management, one wonders if worse outcomes associated with hypocapnia are because of liberal ventilator practices or overzealous attempts to correct hypercapnia. Excessive ventilation is associated with ventilator induced lung injury and worse outcomes. In the noninvasively ventilated patient, hypocapnia can be due to excessive patient effort and drive, which can precipitate self-induced lung injury (11).

How should the readers interpret these findings? Tiruvoipati and colleagues show that hypercapnia in patients with sepsis is not associated with increased mortality. In mechanically ventilated patients, the clinician should maintain focus on lung protective strategies, which are known to improve outcomes. There is currently no evidence to alter this approach, if hypercapnia does develop. In noninvasively ventilated patients, in light of the signal that hypocapnia might be harmful, future studies should investigate the safest strategy moving forward when such patients develop hypocapnia.

The authors acknowledge that conclusions made from observational studies need to be replicated in well-designed prospective trials. Their study lays the groundwork for randomized controlled trials with the goal to clarify if targeting specific CO_2 levels, or a more liberal approach, would change patient outcomes. Such studies should analyze the impact of CO_2 levels while accounting for (and hence independently of) ventilator settings. Pilot studies should also integrate the impact of mixed acid–base disorders. Although we think of hypercapnia and hypercapnic acidosis along a continuum, their clinical impact probably differs. Should we target the CO_2 or the pH? It would also be imperative in future pilot studies to accurately quantify the CO_2 exposure and analyze the impact of CO_2 swings, when present.

There are currently no concrete guidelines on how to address hypercapnia in critically ill patients. Although most have adopted the permissive hypercapnia approach, which remains valid, hypocapnia has emerged as either harmful by itself or a signal of harmful clinical practices. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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