Pathophysiological determinants of arterial carbon dioxide tension (PaCO$_2$) in spontaneously breathing and mechanically ventilated patients

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Received: 19 January 2021; Accepted: 21 March 2021.

doi: 10.21037/jeccm-21-7

View this article at: http://dx.doi.org/10.21037/jeccm-21-7

Changes in PaCO$_2$ in hospitalised patients are common and associated with an increased risk of morbidity and mortality. Although many clinicians are aware of the physiological mechanisms for PaCO$_2$ homeostasis, they often have difficulty understanding how different compensatory mechanisms interact, and why such interactions are not always successful in achieving normocapnia. Incorrect interpretation of PaCO$_2$ level—even when it is within the normal range—can have dangerous consequences in a spontaneously breathing patient (1). In this correspondence, we briefly describe how we can visually interpret the interactions of different pathophysiological mechanisms in determining PaCO$_2$ in a spontaneously breathing or mechanically ventilated patient.

In a spontaneously breathing patient, there are two determinants of PaCO$_2$. The respiratory drive from the brain is an active system (which can increase minute ventilation up to 10 L/min for every 3 mmHg PaCO$_2$ increment unless PaCO$_2$ is exceedingly high) (1); whilst the mathematical relationship between alveolar CO$_2$ tension (or PaCO$_2$ for simplicity), carbon dioxide production (VCO$_2$ ~200 mL/min for an average adult that can increase up to 10 folds with vigorous exercise) and minute alveolar ventilation represents a passive system (Figure 1A) (2). Minute alveolar ventilation is equal to the minute ventilation minus the wasted ventilation due to the physiological dead space which is the sum of anatomical and alveolar dead space. The interaction between the active and passive systems defines the PaCO$_2$.

An increase in respiratory drive due to hypoxia or metabolic acidosis will increase the ‘slope’ of the active respiratory drive system, resulting in an increase in minute ventilation which will reduce PaCO$_2$. As such, a PaCO$_2$ within the normal range is actually abnormal in the presence of significant metabolic acidosis, and would signify concomitant respiratory drive depression (1). Respiratory depression due to opioids and sedatives will shift the active respiratory drive system to the right (Figure 1B), resulting in a lower minute ventilation and a higher PaCO$_2$. An increase in VCO$_2$ will shift the passive system upward, resulting in a higher PaCO$_2$; until the active respiratory drive system shifts the slope upward to normalise the PaCO$_2$ (Figure 1C).

An increase in alveolar dead space—which can occur due to emphysema, reduced pulmonary blood flow without a corresponding reduction in ventilation or over-ventilating poorly perfused alveoli [i.e., ↑ overall ventilation to perfusion (V/Q) ratio], ↑ V/Q heterogeneity in acute respiratory distress syndrome (ARDS) and pneumonia (3), or attenuation of the normal hypoxic pulmonary vasoconstriction due to oxygen supplementation)—will shift the passive system to the right, resulting in a higher PaCO$_2$ (Figure 1D). Acute pulmonary embolism would theoretically increase alveolar dead space; an elevation of PaCO$_2$ is, however, often not observed. This is because any increase in PaCO$_2$ and reduction in arterial oxygen tension (PaO$_2$) will be sensed by the medullary and carotid

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body chemoreceptors, respectively, which will increase the respiratory drive to increase minute ventilation, thereby lowering PaCO₂. In fact, ‘overcompensation’ resulting in respiratory alkalosis in acute pulmonary embolism due to reflex stimulation of irritant and juxta capillary sensors in the lung is common (4). As for a patient with emphysema, administering excessive oxygen can increase the patient’s alveolar dead space and aggravate any existing hypercapnia by abolishing the hypoxic pulmonary vasoconstriction. Due to an overinflated chest cavity and a flattened diaphragm, patients with emphysema will have a limited capacity to increase their minute ventilation to normalise their PaCO₂. Furthermore, oxyhaemoglobin has a relatively linear and also lower CO₂ binding capacity than deoxyhaemoglobin. Increasing PaO₂ with excessive supplemental oxygen can further aggravate hypercapnia through the Haldane effect (2).

Understanding the pathophysiological determinants of PaCO₂ also has utility for patients who are mechanically ventilated. Under such circumstances, the active respiratory drive system is replaced by the setting on the ventilator and the passive system affects the PaCO₂ level through its interactions with the ventilator. Increasing ventilating rate or tidal volume excessively in a patient with emphysema can induce dynamic hyperinflation which can increase hypercapnia by increasing alveolar dead space, in addition to creating a disadvantage in the respiratory mechanics disallowing any spontaneous breaths (2). In patients with ARDS, excessive positive-end-expiratory-pressure (PEEP) can over-distend alveoli that are already

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**Figure 1** Pathophysiologial determinants of arterial carbon dioxide tension (PaCO₂). (A) Shows that PaCO₂ is determined by interaction between the active respiratory drive system and one passive system that is affected by alveolar dead space, CO₂ production and minute ventilation. (B) Shows how changes in the active respiratory drives would affect PaCO₂. (C) Shows why an increase in CO₂ production may not affect the PaCO₂ due to the compensatory changes in respiratory drive. (D) Shows the importance of alveolar dead space in determining PaCO₂. VＤ, alveolar dead space. Vₜ, tidal volume. Numerical data in the graphs are constructed by the authors for illustrative purposes and may not be necessarily translatable to real clinical conditions.
well-ventilated, increasing alveolar dead space and hypercapnia (3). In judging whether a patient is ready for weaning off from a ventilator, a high PaCO\(_2\) (>45 mmHg) despite a high minute ventilation (>10 l/min) suggests that there is a substantial elevation in alveolar dead space. In this situation, weaning is unlikely to be successful until an improvement in the underlying lung condition (e.g., ARDS and its associated increased V/Q heterogeneity) has occurred—which means more time on the ventilator is needed (1).

In summary, understanding how the pathophysiological determinants of PaCO\(_2\) is useful in the appropriate interpretation of PaCO\(_2\) and hence also the treatment of patients with type II respiratory failure.

**Acknowledgments**

**Funding:** None.

**Footnote**

**Provenance and Peer Review:** This article was a standard submission to the journal. The article has undergone external peer review.

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jeccm-21-7). Dr. KMH serves as an unpaid editorial board member of Journal of the Emergency and Critical Care Medicine rom May 2017 to April 2021. The other authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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