Permissive hypercapnia in acute respiratory distress syndrome — is now the time to get strict?

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Although mechanical ventilation is frequently a life-saving intervention for patients with acute respiratory distress syndrome (ARDS), there is an increasing awareness that mechanical ventilation itself can initiate or exacerbate lung injury. Over the past two decades, there has been a major shift in how we ventilate these patients. Despite the increase in our understanding, the ideal ventilation strategy and the appropriate management of ventilation (control of $Paco_2$) and oxygenation (control of Pao_2) for patients with ARDS is still controversial. Many clinicians still aim for physiologically "normal" arterial blood gas parameters and, in this pursuit, may induce additional pulmonary injury, thus increasing morbidity and mortality.

Permissive hypercapnia — what's the story?

The term "permissive hypercapnia" was coined after two case series by Hickling and colleagues in the early 1990s that suggested that limitation of airway pressure (P_{AW}) and tidal volume (V_T), with a tolerant approach to elevations in alveolar and arterial CO_2 (permissive hypercapnia, mean maximum $Paco_2$ 66.5 mmHg)[1] was associated with lower hospital mortality than predicted by Acute Physiological and Chronic Health Evaluation (APACHE) II scores.[1,2] Subsequently, Amato and colleagues randomly allocated 53 patients with ARDS to receive either "protective" low V_T (< 6mL/kg), high positive-end expiratory pressure (PEEP) and a permissive approach to CO_2 control (initial $Paco_2$ up to 80 mmHg), or conventional V_T (12 mL/kg) with respiratory rate adjusted to maintain $Paco_2$ in the normal range.[3] The protective ventilation strategy was associated with an increase in survival at 28 days. These results demonstrated that a protective ventilation strategy, which limited P_{AW} and V_T by tolerating increases in $Paco_2$, could be associated with a survival benefit among patients with ARDS.

However, the subsequent multicentre ARDSNet trial, which also demonstrated a survival advantage for a low V_T and P_{AW} strategy compared with the control group, used an active approach to prevent hypercapnia or acidosis (by increasing respiratory rate and V_T and administering sodium bicarbonate).[4] This suggested to some that it was irrelevant whether a permissive or active approach to the management of CO_2 was adopted, as long as P_{AW} and V_T were limited.

However, there is a growing body of evidence suggesting that such an active approach may be deleterious, and that a permissive approach minimises lung injury and facilitates the goals of the ideal protective ventilation strategies for patients with ARDS.

Active control of carbon dioxide may be deleterious in acute respiratory distress syndrome

There appears to be no safe V_T or P_{AW} cut-off in ARDS, and there are additive advantages to further decreasing both, thus minimising volutrauma and barotrauma.[5] Furthermore, the cyclic opening and closing of acteletatic alveolar units with each breath is deleterious.[6] The simple act of increasing the respiratory rate from 12 to 30 breaths per minute (to control CO_2) adds over 25 000 additional opening and closing cycles per day to an already injured lung. These mechanical interactions also act as an engine for a systemic inflammatory response, multiorgan failure and death in patients with ARDS.[7,8] Therefore, increasing the V_T or respiratory rate to combat rises in CO_2 may further augment lung injury and worsen outcomes. In addition, the exogenous administration of sodium bicarbonate to control pH may be ineffective and actually increase acidosis in ARDS patients, as well as being associated with other detrimental effects (ie, hypocalcaemia or hypokalaemia).[9,10] These findings suggest that the ARDSNet practice of increasing V_T, increasing respiratory rate, and infusing exogenous bicarbonate to control CO_2 or acidosis may actually increase injury.

Permissive hypercapnia may do more than allow low distension ventilation

Laboratory studies suggest that hypercapnic acidosis may have anti-inflammatory effects that can attenuate acute lung injury.[11] Fortunately, these immunomodulatory effects appear not to be deleterious in infective models of lung injury when appropriate antibiotic therapy is administered.[12,13] These findings suggest that hypercapnia is not just an associated side effect of ventilation strategies that aim to minimise lung stretch, but that it could have specific beneficial effects. Interestingly, a recent multivariate logistic regression analysis of the ARDSNet trial, after controlling for comorbidities and severity of lung injury, found that the patients who had hypercapnic acidosis on study Day 1 had a reduced 28-day mortality in the higher V_T group, a result consistent with a protective effect of hypercapnic acidosis

against ventilator-induced lung injury.[14] Taken together, these findings suggest that there are potential additional beneficial effects of a permissive approach to hypercapnia that may have been lost in the ARDSNet strategy.

Permissive hypercapnia — time to be strict about its application in ARDS

Several low V_T prospective multicentre randomised controlled trials have been conducted in patients with acute lung injury or ARDS to compare high and low PEEP (±recruitment ventilation strategies).[15,16] While these trials demonstrated a clear improvement in oxygenation and a suggestion that high PEEP may reduce ventilator days, no survival benefit was noted in the high-PEEP groups. Despite these results, the interest in high-PEEP strategies has not diminished.[17] This is partly because of perceived design flaws of these trials; in particular, allowing similar ventilator driving pressures in the high-PEEP and the low-PEEP arms, resulting in higher plateau pressures in the high-PEEP arm of the trials, a clear confounding factor. This has prompted the development of newer strategies that not only aim to open the closed acteletatic segments with recruitment manoeuvres and higher PEEP, but also recognise that the use of ultralow tidal volumes are necessary in the face of higher PEEP to minimise airway pressure and realise the true potential benefits of protective open lung ventilator strategies.[18] To safely achieve these ventilator goals a permissive approach to hypercapnia is essential. Pilot work suggests that such an approach may be beneficial in ARDS.[17]

There is growing evidence in the management of critical illness that the short-term aim of "normal" physiological variables, although attractive, can actually result in worse long-term outcomes.[19] The time has come where we need to provide the most protective mechanical ventilation strategy if we are not adopting a deliberate policy of permissive hypercapnia for patients with ARDS.

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