CROSSTALK

CrossTalk opposing view: There is not added benefit to providing permissive hypercapnia in the treatment of ARDS

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Current ventilator strategies for acute respiratory distress syndrome (ARDS) aim to impact lung function and clinical outcomes in several ways: low tidal volumes to minimize overdistension, titrated positive end-expiratory pressure (PEEP) to prevent alveolar derecruitment, and recruitment manoeuvres to promote parenchymal homogeneity. Among these interventions, only low tidal volume has been shown definitively to improve mortality from ARDS (Malhotra, 2007). During low tidal volume ventilation, practice varies substantially on whether to allow some degree of alveolar hypoventilation with incidental hypercapnic acidosis (Amato *et al.* 1998), or to increase respiratory rate to maintain alveolar ventilation, often requiring respiratory rates >30 breaths min^{-1} (Brower *et al.* 2000). As the independent effect of hypercapnia has never been tested in humans, it remains unclear whether such permissive hypercapnia has protective or deleterious effects in ARDS.

Two major questions surrounding permissive hypercapnia include (1) whether the mechanical effects of limiting respiratory rate *per se* yield clinical benefit, and (2) what the effects are of hypercapnia, independent of minute ventilation, on end-organ injury.

Low tidal volumes, which may contribute to hypercapnia, minimize mechanical lung injury. Ventilation at high tidal volumes causes alveolar overdistension, leading to alveolar epithelial and capillary endothelial cell junction breaks, cell detachment from the basement membrane, intracapillary blebs, and alveolar and interstitial oedema (Fu *et al.* 1992). Further contributing to regional wall stress are shear forces created by inflation of normal alveoli adjacent to atelectatic or flooded alveoli (Perlman *et al.* 2011). Additionally, atelectrauma occurs from cyclic recruitment and collapse of atelectatic lung units during respirations. Resultant formation and destruction of foam bubbles contributes interfacial stress that disrupts intracellular plasma membrane–cytoskeletal adhesions, leading to bleb formation and plasma membrane disruption (Oeckler *et al.* 2010). Low tidal volumes may reduce atelectrauma if lung units with high opening pressures remain closed throughout the respiratory cycle.

In response to deformation-induced cell strain, alveolar epithelial cells rapidly translocate lipid molecules to the plasma membrane to increase cell surface area and reduce strain, thereby minimizing risk of membrane rupture and facilitating repair when injury does occur (Vlahakis *et al.* 2002). Alveolar overdistension and cyclic atelectasis also induce extensive cytokine release that contributes further to end-organ injury (Imai *et al.* 2003). Low tidal volume ventilation directly reduces cyclic overdistension and thus risk of lung injury.

Additionally, limiting end-inspiratory plateau pressure is used commonly to minimize barotrauma. However, airway pressures do not delineate the often substantial contribution of the chest wall to respiratory system mechanics (Talmor *et al.* 2006). Plateau pressures may underestimate alveolar distension in patients with negative pleural pressures, such as during spontaneous respirations. In a recent study demonstrating reduced mortality in severe ARDS with neuromuscular blockade (Papazian *et al.* 2010), the incidence of barotrauma halved with paralysis compared to placebo despite similar initial airway plateau pressures. This may suggest that high transpulmonary pressures (defined as the pressure difference between the airway opening and pleural space) during spontaneous respirations worsened lung injury. Similarly, in a preclinical model of ARDS, lung injury worsened despite unchanged plateau pressures when spontaneous breathing generated high transpulmonary pressures (Yoshida *et al.* 2012). To account for patient differences in pleural pressures and chest wall mechanics, some advocate tailoring mechanical ventilation in ARDS to

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transpulmonary pressure by estimating pleural pressure with oesophageal manometry (Talmor *et al.* 2008).

In addition to reducing tidal stretch, limiting respiratory rate may prevent biomechanical injury by reducing the frequency of cyclic recruitment and collapse of damaged alveoli and of repetitive shear stress in the heterogeneously diseased lung. The cumulative effects of such repetitive stress may lead to frequency-dependent membrane failure known as fatigue behaviour (Marini *et al.* 2003), analogous to bending a paperclip back and forth repeatedly to cause its eventual breakage. Indeed, lower respiratory rate reduces lung injury in preclinical models of ARDS (Hotchkiss *et al.* 2000). Moreover, dynamic hyperinflation may occur with high respiratory rate, increasing risk of regional overdistension (Marini, 2011).

However, it is entirely unclear whether resultant hypercapnia offsets or augments the advantageous biomechanical effects of low tidal volume and respiratory rate. Among the proposed additional benefits, hypercapnia attenuates oxygen free radical formation, NF-κB activation, and TNFα, IL-1, IL-6 and IL-8 cytokine production (Taylor & Cummins, 2011) increases sympathetic tone with associated haemodynamic improvements (Wang *et al.* 2008), and theoretically reduces the oxygen delivery required to meet cellular energetic demand (Hillered *et al.* 1984).

Many of these theoretical benefits of hypercapnia may be deleterious when translated into the clinical realm. The immunomodulatory effects of hypercapnia delay bacterial clearance and worsen lung injury in pulmonary sepsis models (O'Croinin *et al.* 2008), of particular concern because pneumonia is a leading risk factor for ARDS (Gajic *et al.* 2011). Permissive hypercapnia's adrenergic effects should be viewed with caution in light of recent data demonstrating increased morbidity and mortality in ARDS with β-agonist therapy from unclear mechanisms (Matthay *et al.* 2011; Gao Smith *et al.* 2012). Ongoing β3 adrenergic receptor stimulation may also lead to progressive deterioration in cardiac function (Gauthier *et al.* 1996). Moreover, hypercapnic pulmonary vasoconstriction augments hypoxic pulmonary vasoconstriction and may worsen right heart strain (Mekontso Dessap *et al.* 2009). The reduced oxygen consumption from hypercapnia is at least partly due to mitochondrial dysfunction, shown to impair alveolar epithelial cell proliferation (Vohwinkel *et al.* 2011).

Hypercapnia additionally may have deleterious effects directly on the injured lung. While most alveolar cells survive deformation-induced injury by translocating lipids to the injured plasma membrane (Vlahakis *et al.* 2002), hypercapnic acidosis impairs plasma membrane wound healing in ventilator-injured lungs in a pH-dependent fashion (Caples *et al.* 2009). Hypercapnia, independent of pH, also impairs alveolar fluid reabsorption by inhibiting epithelial Na^+-K^+-ATPase (Briva *et al.* 2007).

Finally, the cardiopulmonary response to hypercapnia may lead further to harm. Heightened ventilatory drive during hypercapnic acidosis may require deeper sedation or paralysis to prevent patient–ventilator dyssynchrony, excess tidal excursions and double-triggering of the ventilator. If not blunted, this heightened ventilatory drive may generate more negative pleural pressures (Yan *et al.* 1993), thereby increasing transpulmonary pressure and alveolar stress. Enhanced pulmonary blood flow via hypercapnia-induced catecholamine release may worsen alveolar damage, capillary leak and oedema formation (Broccard *et al.* 1998). Even during moderate alveolar overdistension insufficient to cause lung injury alone, increasing pulmonary blood flow leads to lung injury that otherwise would not occur (Guery *et al.* 1998). The combined effects of occult increased transpulmonary pressure and increased pulmonary blood flow from permissive hypercapnia may create precisely this environment wherein occult lung injury is likely to occur.

As investigation of permissive hypercapnia transitions to humans, focus must be placed on distinguishing the effect attributable to minimizing biomechanical injury from that attributable to hypercapnia itself. Whether the independent effect of hypercapnia *per se* is harmful or protective is unknown. At the very least, there is sufficient concern to give pause. Most data suggesting improved outcomes associated with permissive hypercapnia are probably attributable primarily to the mechanical benefits of limiting tidal volume and respiratory rate.

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Conflict of interest

J. R. Beitler and R. D. Hubmayr have no conflicts of interest to declare. A. Malhotra previously received consulting and/or research income from Philips, SGS, SHC, Apnex, Apnicure and Pfizer, but has relinquished all outside personal income since May 2012.