CROSSTALK

Rebuttal from Jeremy R. Beitler, Rolf D. Hubmayr and Atul Malhotra

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More than a decade after low tidal volume ventilation for acute respiratory distress syndrome (ARDS) first gained widespread acceptance, it is still unknown how best to manage its effects on minute ventilation. High respiratory rate, or permissive hypercapnia? Limiting respiratory rate has been shown in preclinical models to reduce lung injury even at a constant arterial CO_2 tension (P_{aCO_2}; Vaporidi *et al.* 2008). Curley and colleagues (2013) go one step further, making the case for additional benefit from hypercapnia during low tidal volume ventilation.

As we find no great fault with the balanced case put forward by our Canadian colleagues, our rebuttal focuses on challenges in designing more definitive trials. First, how might the independent effects of respiratory rate, P_{aCO_2} and pH each be considered? Tris-hydroxymethyl amino-methane (THAM) buffer might be used to identify the effects of hypercapnia independent of acidaemia. To isolate the effects of respiratory rate from P_{aCO_2}, inspired CO_2 could be administered during high respiratory rate to induce hypercapnia to a degree comparable to a low-rate strategy. Optimizing respiratory rate must also consider airflow dynamics since high rates may lead to auto-positive end-expiratory pressure (auto-PEEP).

Second, what is the minimum acceptable pH, and how should severe acidaemia be managed? A minimum pH approaching 7.15 was well tolerated haemodynamically in a heterogeneous ARDS population (Carvalho *et al.* 1997), while other studies specified a pH nadir between 7.05 (Brochard *et al.* 1998) and 7.30 (Brower *et al.* 2000) before encouraging intervention. THAM has shown promise as an effective buffer during fixed minute ventilation (Kallet *et al.* 2000), although further study is warranted before its widespread adoption as a rescue therapy.

Finally, how do we ensure the protection of patients at highest risk of harm from hypercapnia? Patients with intracranial hypertension may fare poorly from hypercapnia-induced cerebral vasodilatation, as may patients with pre-existent right ventricular compromise facing hypercapnic pulmonary vasoconstriction (Curley *et al.* 2010). Similarly, anti-inflammatory effects of hypercapnia may be deleterious in pulmonary or extra-pulmonary sepsis compared to other ARDS precipitants. Moreover, increased sedation or paralysis, with associated risk of iatrogenic injury, may be required during hypercapnia to maintain patient–ventilator synchrony and minimize large swings in transpulmonary pressures from spontaneous breathing efforts (Malhotra & Drazen, 2013).

Only with carefully designed studies will the role be defined for optimizing respiratory rate, P_{aCO_2} and pH in individual patients with varying comorbidities and ARDS severity. The range of preclinical findings and heterogeneity of current clinical practice indicate a great need for further research in this area.

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References

Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondéjar E, Clémenti E, Mancebo J, Factor P, Matamis D, Ranieri M, Blanch L, Rodi G, Mentec H, Dreyfuss D, Ferrer M, Brun-Buisson C, Tobin M & Lemaire F (1998). Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. *Am J Respir Crit Care Med* **158**, 1831–1838.

Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT & Wheeler A. (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* **342**, 1301–1308.

Carvalho CR, Barbas CS, Medeiros DM, Magaldi RB, Filho GL, Kairalla RA, Deheinzelin D, Munhoz C, Kaufmann M, Ferreira M, Takagaki TY & Amato MB (1997). Temporal hemodynamic effects of permissive hypercapnia associated with ideal PEEP in ARDS. *Am J Respir Crit Care Med* **156**, 1458–1466.

Curley G, Laffey JG & Kavanagh BP (2010). Bench-to-bedside review: carbon dioxide. *Crit Care* **14**, 220.

Curley GF, Laffey JG & Kavanagh BP (2013). There is added benefit to providing permissive hypercapnia in the treatment of ARDS. *J Physiol*. **591**, 2763–2765.

Kallet RH, Jasmer RM, Luce JM, Lin LH & Marks JD (2000). The treatment of acidosis in acute lung injury with tris-hydroxymethyl aminomethane (THAM). *Am J Respir Crit Care Med* **161**, 1149–1153.

Malhotra A & Drazen JM (2013). High-frequency oscillatory ventilation on shaky ground. *N Engl J Med* **368**, 863–865.

Vaporidi K, Voloudakis G, Priniannakis G, Kondili E, Koutsopoulos A, Tsatsanis C & Georgopoulos D (2008). Effects of respiratory rate on ventilator-induced lung injury at a constant PaCO2 in a mouse model of normal lung. *Crit Care Med* **36**, 1277–1283.

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.

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