Hypercapnia *vs* normocapnia in patients with acute respiratory distress syndrome

Lung protective ventilation was adopted for management of acute respiratory distress syndrome after the landmark ARMA trial showed significant mortality benefit using volume and pressure limited ventilation (6 ml/kg *vs* 12 ml/kg ideal body weight, plateau pressure <30 cmH_2O) (Brower et al, 2000). However, some patients cannot tolerate this strategy without significant elevation in partial pressure of arterial carbon dioxide ($PaCO_2$). This article examines the benefits and drawbacks of using permissive hypercapnia *vs* normocapnia in patients with acute respiratory distress syndrome.

The case for permissive hypercapnia

Permissive hypercapnia was historically thought of as a benign and tolerable consequence of lung protective ventilation for acute respiratory distress syndrome but evidence for its routine clinical use has not been adequately tested in prospective randomized clinical trials. A retrospective secondary analysis of the ARMA trial by Kregenow et al (2006) reported that hypercapnic acidosis was associated with lower 28-day mortality in the group randomized to tidal volume of 12 ml/kg but no mortality difference for patients randomized to 6 ml/kg; the latter representing current standard of care.

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Permissive hypercapnia does, however, avoid some of the risks associated with strategies to maintain normocapnia. For example, attempts to aggressively reduce alveolar dead space with lung recruitment and optimal positive end-expiratory pressure titration can lead to alveolar overdistention and can negatively affect pulmonary haemodynamics and right ventricular function (Barnes et al, 2017). In addition, the use of higher respiratory rates to increase minute ventilation is poorly tolerated in some patients because of the development of dynamic hyperinflation and right ventricular dysfunction (Barnes et al, 2017).

The case for normocapnia

Hypercapnia in patients with acute respiratory distress syndrome can result from lung protective ventilation but can also occur with increasing dead space associated with disease severity. Nonetheless, severe hypercapnia has harmful physiological effects in patients with acute respiratory distress syndrome. In particular, acute right heart failure is associated with severity of hypercapnia. Several studies have found that elevated $PaCO_2$ was predictive of developing acute cor pulmonale, even while using lung protective ventilation (Barnes et al, 2017).

A secondary analysis of 1899 patients with acute respiratory distress syndrome from three prospective non-interventional cohort studies (Nin et al, 2017) demonstrated that patients with moderate to severe acute respiratory distress syndrome and severe hypercapnia ($PaCO_2$ ≥50 mmHg) had higher ventilator-associated complication rates, higher rates of organ dysfunction and increased mortality. Furthermore, a large multivariate analysis of 252 812 mechanically-ventilated critically ill patients showed significantly increased in-hospital mortality across all admission types in patients with acute hypercapnic acidosis and compensated hypercapnia compared to normocapnic patients (Tiruvoipati et al, 2017).

Conclusions

Severe hypercapnia has deleterious effects in patients with acute respiratory distress syndrome, and lung protective ventilation with permissive hypercapnia in conjunction with moderate to severe acute respiratory distress syndrome may exacerbate acute cor pulmonale. Current trials (SUPERNOVA and REST) are looking at ultra low tidal volume ventilation (3–4 ml/kg) with maintenance of normocapnia using extracorporeal CO_2 removal to determine if there is additional benefit compared to current standards of lung protective ventilation. It remains to be determined whether early institution of therapies such as extracorporeal CO_2 removal to normalize $PaCO_2$ in conjunction with current standards of lung protective ventilation will benefit patients with moderate or severe acute respiratory distress syndrome. **BJHM**

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