

Commentary

Recently published papers: a little less ventilation, a little more oxygen please?

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Abstract

Recent papers discussed include two large, multicentre, high-positive end-expiratory pressure trials in acute lung injury and reflects upon the usefulness of such trial designs. Further papers considered include the emerging story of β_2 -agonists for pulmonary oedema, highlights the newly described, iatrogenic demon, of ventilator-induced diaphragm injury, promotes the addition of B-type natriuretic peptide testing to the prediction of extubation success, and muses again over the oxygen debate.

Emerging clarity in setting positive end-expiratory pressure?

Minimising ventilator-induced lung injury while providing optimal respiratory support remains challenging. Limiting tidal volumes to 6 ml/kg (predicted body weight) has been widely adopted, in theory at least, but numerous other debates remain – perhaps most contentiously – regarding positive end-expiratory pressure (PEEP). Two large trials investigating the optimal ventilatory approach to patients with acute lung injury have recently been published.

In the first, a combined Canadian, Australian and Saudi Arabian multicentre study, 983 patients were randomised to a 6 ml/kg (predicted body weight) tidal volume with either established ARDSnet PEEP settings or a 'high PEEP strategy with recruitment manoeuvres' [1]. Of note, plateau pressures in the lower PEEP group were limited to 30 cmH₂O whilst those in the high-PEEP group were limited to 40 cmH₂O. The protocol produced a significantly higher average PEEP in the experimental group, with consequently higher plateau pressures. There was no difference between the two groups with regard to the 28-day mortality, ventilator days, intensive care unit days or days of hospitalisation. There was a significant reduction in the high-PEEP group in the incidence of refractory hypoxaemia and the use of rescue therapies. In short, the high-PEEP strategy did no harm – and may have done some good, in terms of improvements in short-term

physiology – but these results did not translate into statistically significant outcome improvements, although there was a trend suggesting that a significantly larger trial might produce such an outcome.

The second study, a French multicentre randomised control trial, investigated 767 patients with acute lung injury [2]. The patients were randomised to either a minimal distension strategy (intrinsic plus extrinsic PEEP 5 to 9 cmH₂O) or a recruitment strategy, in which the PEEP was maximised and plateau pressures were maintained between 28 and 30 cmH₂O. A detailed ventilatory protocol including weaning was employed. Patients were recruited, on average, 24 hours after initiation of mechanical ventilation. The recruitment group received significantly higher PEEP and plateau pressures. There was no difference in 28-day or 60-day mortality. There was a significant reduction in ventilator-free days, organ-failure-free days and the need for adjunctive therapies in the recruitment group.

In short, two large studies asking similar questions with significantly different, detailed, protocols reach the same conclusion – that setting a higher PEEP is noninjurious and is possibly beneficial, but only in secondary endpoints. Of note, due to the real-world practicalities of trial recruitment, the majority of patients had received many hours of 'routine' mechanical ventilation prior to study entry, thus potentially missing the vital early effect of any strategy.

Alongside these impressive studies are two editorials that discuss not only these two papers but also the wider problem of how to investigate complex care in the critically ill patient. A series of similar papers and editorials have also appeared over the past few months.

There appears to be a growing consensus that trials, such as the two discussed above, represent a huge amount of work

BNP = B-type natriuretic peptide; PEEP = positive end-expiratory pressure.

but are rarely, if ever, likely to result in clear evidence upon which to base the treatment of an individual patient. For example, if one takes lung-protective ventilation to its logical extreme, then alternative modes of ventilation such as airway pressure release ventilation or high-frequency oscillatory ventilation should provide even greater benefit than a low-tidal-volume high-PEEP strategy, yet they remain principally the province of enthusiasts or are reserved for rescue modalities. Similarly, the use of permissive hypoxaemia and hypercapnia in such patients results in less injurious ventilation strategies, but awaits large-scale investigation. To conclude, despite the very great efforts employed by the investigators of these two studies, there remain more questions than answers.

Accumulating evidence for β_2 -agonists in the treatment of all-cause pulmonary oedema

β_2 -agonists have been shown to enhance the clearance of alveolar and interstitial pulmonary oedema in a number of experimental settings. Two recent studies add further evidence to this intervention.

In the first study, 24 patients undergoing elective lung resection, who were preoperatively assessed to be at high risk of postoperative pulmonary oedema, were given nebulised salbutamol and ipratropium at 6-hourly intervals in a randomised order and in a blinded fashion [3]. The oxygenation index, cardiac index, extravascular lung water index and pulmonary vascular permeability index were assessed preoperatively and postoperatively as well as pre and 50 minutes post each nebulised therapy. The extravascular lung water index and pulmonary vascular permeability index both increased postoperatively. Salbutamol, but not ipratropium, induced on average a 20% reduction in both parameters, together with a sustained improvement in the oxygenation index and cardiac index.

In the second study, a rat model of acute lung injury was used to test the effects of terbutaline instillation versus systemic administration [4]. Radiolabelled proteins were quantified in various body compartments over time to assess the flux across the alveolar epithelium and pulmonary capillary endothelium. In a complex series of experiments involving a variety of injurious ventilation strategies, pulmonary instillation of terbutaline reduced protein flux across both barriers whereas systemic terbutaline only reduced the flux from the circulation into the alveoli – in essence, suggesting that β_2 -agonists may be more efficacious when nebulised rather than when administered systemically.

Ventilator-induced diaphragm injury

In stark contrast to the large acute lung injury trials described above, a small trial has been published investigating the effects of complete diaphragmatic inactivity coupled, of course, with mechanical ventilatory support [5]. The investigators took diaphragm biopsies from 14 brain-dead organ

donors and compared them with eight patients having elective thoracic surgery. The former had been ventilated for 18 to 69 hours, and the control group for 2 to 3 hours. Histological assessment of the biopsies revealed dramatic atrophy with evidence of apoptosis.

The study adds significantly to a number of previous small studies suggesting that maintaining at least some spontaneous breathing effort in mechanically patients should be attempted. The diaphragmatic injury caused by mandatory ventilatory modes coupled with the sedation and sometimes neuromuscular blockade required to achieve them may well have been underestimated, to say nothing of the deleterious effects on ventilation and perfusion in the dependent lung. Ventilator-induced diaphragm injury appears to be yet another potentially avoidable, organ-supportive, iatrogenic injury to add to the seemingly ever-growing list.

Weaning and B-type natriuretic peptide

To round off the respiratory theme, a simple but elegant study has been published that examines the added value of measuring B-type natriuretic peptide (BNP) before and after a spontaneous breathing trial in predicting extubation failure [6]. There has been a plethora of studies assessing the diagnostic value of BNP testing in the patient presenting with dyspnoea, with elevated levels being associated with cardiac dysfunction and, most usefully, with a negative predictive value rather than a positive one. In the critically ill patient, however, BNP is merely a marker of cardiac strain and is universally elevated in hyperdynamic and shocked patients, regardless of the aetiology.

In this study, 41 patients who met a standard set of criteria for extubation were subjected to a 2-hour T-piece trial to assess their suitability. BNP levels were measured just prior to and at the end of the trial. A greater than 20% increase in BNP levels accurately and reliably predicted extubation failure. This cutoff value was then prospectively tested in a further cohort of 49 patients with almost identical results. With the potential advent of near-patient testing for BNP, this may prove to be a valuable adjunctive assessment to promote both a more successful and possibly a more aggressive approach to liberating patients from mechanical ventilation.

Oxygen, the magic bullet in severe sepsis?

As I have previously commented in this series of editorials, oxygen – perhaps the first therapy we instigate in critically ill patients – remains poorly understood in terms of both benefit and injury [7]. To highlight this subject, another detailed animal experiment has been published suggesting that hyperoxia has significant beneficial effects as a component of early resuscitation in severe sepsis. Barth and colleagues induced faecal peritonitis in 20 anaesthetised pigs, and randomised one-half to receive just enough oxygen to maintain arterial haemoglobin oxygen saturations $\geq 90\%$ and the other half to receive 100% inspired oxygen [8]. The

animals were very intensively monitored and continuously resuscitated with fluids and vasopressors for 24 hours before being euthanised. The hyperoxic pigs showed no evidence of oxygen toxicity but instead demonstrated attenuated end-organ dysfunction in the lungs, liver and kidney.

Whether an anaesthetised pig with continuous and aggressive haemodynamic support represents a good model for the shocked human is debateable, but with the increasing evidence in favour of hyperoxia and very limited data of oxygen toxicity in humans, this simple, cheap and easily available therapy warrants investigation in patients.

Competing interests

The author declares that they have no competing interests.

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