Commentary

Recently published papers: the Jekyll and Hyde of oxygen, neuromuscular blockade and good vibrations?

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Abstract

This issue's recently published papers commentary takes a long hard look at the surprisingly topically issue of oxygen. To give a balanced perspective, topical ventilatory studies are also discussed.

Confused by oxygen?

Several recently published papers have demonstrated both the pros and cons of oxygen therapy. They also serve to illustrate that extrapolating from studies with experimental animal models to the clinical arena requires great caution.

In a rat model of haemorrhagic shock, Brod and colleagues investigated the effects of combined resuscitation with hypertonic saline and oxygen [1]. The authors designed a complex protocol with sequential single interventions and compared 5 ml/kg fluid resuscitation using 0.9% and 7.5% saline and a fraction of inspired oxygen (FiO_2) of 0.21 and 1.0. They measured regional perfusion in several vascular beds together with plasma lactate as a measure of the adequacy of resuscitation. Their results showed that 7.5% saline and 100% oxygen was the superior strategy. Of particular note were the marked haemodynamic effects of increasing the FiO_2 to 1.0. The accompanying editorial [2] considers these results in a wider clinical context. It rightly concludes that the effects of 100% oxygen on regional blood flow, and hence its role in resuscitation, have for too long been neglected and warrant further investigation.

Multiple organ failure syndrome (MOFS) is the final common pathway of critical illness. Imperatore and colleagues have previously demonstrated that intermittent hyperbaric oxygen (HBO) therapy is effective in attenuating this process in a zymosan-induced MOFS model in rats. They have now published a further study concentrating on the effects of HBO on the coagulation cascade [3]. The zymosan insult produced a marked coagulopathy, MOFS and a 50% mortality at 72 hours in the control group. The intervention group, which was subjected to two 60-minute periods of hyperbaric (2 atmospheres absolute (ATA) oxygen (FiO_2 1.0) at 4 and 11 hours after MOFS initiation, demonstrated a markedly attenuated coagulopathy with less severe MOFS and a 100% survival at 72 hours.

In a related study, Buras and colleagues investigated the efficacy of four oxygen regimens in a caecal ligation-and-puncture model of MOFS in mice [4]. In addition to survival, they measured bacterial load and performed experiments on macrophage function, specifically investigating whether IL-10 has a key role in the protective effect of HBO therapy. In comparison with the control group, which received an FiO_2 of 0.21, normobaric FiO_2 of 1.0 for 90 minutes at 12-hourly intervals and HBO at 2.5 ATA for 90 minutes at 24-hourly intervals had no effect on survival at 100 hours (mortality 80%). HBO at 2.5 ATA for 90 minutes at 12-hourly intervals improved survival from 20% to 70%. HBO at 3 ATA for 90 minutes at 12-hourly intervals proved be 100% lethal after approximately 30 hours. The successful strategy did not reduce the bacterial load in the peritoneum but did reduce the load disseminated to the spleen, suggesting that the beneficial effects were not mediated by microbial killing. The macrophage and IL-10 data are complex but, importantly, no benefit of HBO was demonstrated when the experiment was repeated in IL-10-deficient mice, suggesting that it is an essential component of the protective effect of HBO. The enhanced lethality of the 3 ATA regime was unexpected but reinforces the serious potential of HBO for harm as well as benefit.

By coincidence, a state-of-the-art review of the multiple oxygen-sensitive intracellular signalling pathways, mediated

ARDS = acute respiratory distress syndrome; ATA = atmospheres absolute; COPD = chronic obstructive pulmonary disease; FiO_2 = fraction of inspired oxygen; HBO = hyperbaric oxygen; IL = interleukin; IPPV = intermittent positive pressure ventilation; IPV = intrapulmonary percussive ventilation; MOFS = multiple organ failure syndrome; NMB = neuromuscular blockade; PaO_2 = arterial partial pressure of oxygen; PEEP = positive end-expiratory pressure.

by a series of hypoxia-inducible transcription factors, has just been published [5]. This concise and well referenced overview, in particular, considers the prospect that these pathways offer attractive therapeutic targets. Oxygen is evidently a major regulatory factor in a wide variety of cellular and tissue processes. The signal transduction pathways for hypoxia are evolutionarily highly conserved across species. Most of the adaptive effects to hypoxia would seem to evoke cellular protection. Given these facts, the potential detrimental effects of hyperoxia need to be considered carefully.

To muddy the waters further, a recent prepublication report of a retrospective study from the San Diego County Trauma Registry [6], presented at the American Heart Association annual meeting, has found an association between both hypoxaemia and hyperoxaemia with a higher than predicted mortality in traumatic brain injury. From the 3,515 patients with traumatic brain injury on the register, 1,012 had documented hypoxaemia (arterial partial pressure of oxygen (PaO_2) $<$110 mmHg) and 358 had hyperoxaemia (PaO_2 $>$487 mmHg). In comparison with their Trauma and Injury Severity Score (TRISS)-predicted mortality, the hypoxaemic patients had a survival rate 41% lower than predicted and the hyperoxaemic patients had a survival rate 48% lower than predicted. The patients with PaO_2 in the range 110 to 487 mmHg were found to have a survival rate 77% greater than predicted.

It is sobering to consider that we still do not fully understand the pharmacodynamics or pharmacokinetics of oxygen. Until we do, like so many other interventions the conclusion seems to be give more than enough but not too much.

From oxygenation to ventilation

Few would contest that minimising the lung injury caused by intermittent positive pressure ventilation (IPPV) in patients with acute respiratory distress syndrome (ARDS) is now an established clinical approach. However, how best to achieve this remains controversial. A novel and attractively simple approach has been investigated by Forel and colleagues [7]. They conducted a multicentre, investigator-blinded, randomised control trial of neuromuscular blockade (NMB) for 48 hours. They hypothesised that NMB would permit less injurious IPPV and hence reduce pro-inflammatory cytokine production by the lungs. ARDS was diagnosed in 51 patients in the study period, 36 of whom were randomised. Therapy was started, on average, within 1 day of diagnosis. The 18 patients in the control and intervention groups were reasonably well matched at baseline, given the small sample size. It is noteworthy that 28 of the 36 patients had pneumonia as their primary diagnosis. After 48 hours, pro-inflammatory cytokine levels in bronchoalveolar lavage fluid and serum had increased in the control group but not in the intervention group. This difference was statistically significant. There was also a statistically significant greater improvement in PaO_2/FiO_2 ratio in the NMB group over the 120 hours after study entry. As the protocolised ventilatory strategy in this study was based on the low-tidal-volume ARDSnet study, in which positive end-expiratory pressure (PEEP) level was determined by FiO_2, this greater improvement in PaO_2/FiO_2 ratio also resulted in a statistically significant greater reduction in PEEP and plateau pressures over the 120 hours of observation. This study was not powered to detect differences in outcome; indeed, none that were statistically significant were observed in the duration of mechanical ventilation, number of ventilator-free days at 28 days or mortality in the intensive care unit. The authors, together with an accompanying editorial [8], advocate further investigation of this intervention and make a coherent argument to support this conclusion.

However, I have several reservations about this intervention. First, no attempt was made to quantify any positive clinical consequences of altering the pro-inflammatory cytokine profile, especially on the incidence of extra-pulmonary organ dysfunction, nor indeed am I aware of any evidence to support the hypothesis that stabilising cytokine levels is associated with better outcomes. Second, to my knowledge no intervention that has targeted improvement in the PaO_2/FiO_2 ratio in ARDS has yet been shown to affect outcome positively, for example nitric oxide. Third, there is a body of literature that demonstrates significant physiological benefits from the maintenance of spontaneous breathing efforts during IPPV [9]. Fourth, if NMB is to be adopted as a clinical intervention, there is surely an argument to be made for starting it at the time of intubation because the maximal benefit should occur during the initial period of IPPV. Additionally, if short-term NMB is beneficial as a short-term adjunct to IPPV then should its use be considered in any ARDS patient with a rising cytokine profile? Fifth, a duration of 48 hours was arbitrarily chosen. Given that at least some of the beneficial effects persisted for at least 72 hours after cessation, then a shorter period of NMB might be equally efficacious and, in addition, further reduce the potential for increasing the incidence of critical illness neuromyopathy. In conclusion, I am not convinced that this study advances the current debate on how to best ventilate patients with ARDS.

Cue the rhythm section?

December saw the publication of three papers investigating the therapeutic potential of intermittent intrapulmonary percussive ventilation (IPV). This technique, and the devices that deliver it, have been around for about 20 years. However, their use has largely been confined to patients with cystic fibrosis and bronchiectasis [10]. This technique delivers a high-frequency (up to 10 Hz) of high-flow gas bursts. The devices can also be used to deliver aerosols; however, particle size generation and airway deposition are less effective than conventional nebulisation [11,12]. These devices provide a diffusive mode of ventilatory support via a non-invasive, patient-controlled, mouthpiece or mask and via a variety of mechanisms mobilise respiratory secretions and facilitate their clearance.

Antonaglia and colleagues have performed a small-scale trial in 40 patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) comparing 40 historical controls, who had received mask ventilation, with helmet ventilation. In addition, the patients who received helmet ventilation were randomised to receive either a once-daily 30-minute standard respiratory physiotherapy session or a twice-daily 30-minute IPV session, from the second day of helmet ventilation until the patients achieved at least 24 hours of support-free ventilation. The IPV group required a median of 61 hours of ventilatory support, in contrast with 89 and 87 hours in the physiotherapy and historical control groups, respectively. This equated to a shorter median length of ICU stay of 7 days, versus 9 and 10 days, respectively. Although underpowered, this well designed, pragmatic study demonstrates that as an adjunctive technique IPV offers potential advantages over current standard therapy. It may be especially well suited to patients with a significant volume of secretions, not least as conventional mask/helmet ventilation is usually performed with dry gas and has the propensity to inhibit secretion clearance. It is noteworthy that IPV has previously been shown to be efficacious as a sole intervention in mild to moderate acute exacerbations of COPD [13].

Clini and colleagues investigated the use of IPV in a small randomised control trial in a diverse group of slow-to-wean patients who required the persistence of a tracheostomy, after liberation from mechanical support, for secretion management [14]. The control group ($n = 21$) received two 1-hour chest physiotherapy sessions for 15 days. The intervention group ($n = 23$) received identical therapy but preceded by an unspecified period of IPV. Gas exchange, expiratory muscle strength and pulmonary complications during the study period and over a 1 month follow-up period were the study endpoints. Expiratory muscle strength and the incidence of pneumonia were statistically significantly increased and decreased, respectively, in the IPV group. Although hardly ground-breaking, this study demonstrates that IPV is efficacious when compared with conventional physiotherapy. This message is perhaps underlined by a recent systematic review, which finds a paucity of evidence to support prophylactic chest physiotherapy after abdominal surgery [15] and other previous negative reviews [16,17].

Tsuruta and colleagues report the safety and efficacy of superimposing IPV on conventional IPPV, via an endotracheal tube, in a cohort of 10 obese patients with respiratory failure secondary to compression atelectasis, who had failed to improve after optimal IPPV [18]. Although this intervention somewhat mimics standard high-frequency oscillatory ventilation in a spontaneously breathing patient, it differs in that in place of a continuous distending pressure, mandatory convectional ventilation with conventional tidal volumes was maintained. Oxygenation improved in all 10 patients. This coincided with marked radiological improvement. No outcome data are given.

Overall, a comparatively simple method of respiratory support seems to have gained a sudden resurgence of interest and shows early promise as a valuable adjunct to current therapies.

Competing interests

The author declares that they have no competing interests.

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