# Is it time for permissive hypoxaemia in the intensive care unit?

Gilles Capellier and Rakshit Panwar

## Oxygen and historical practice

Much research has made clinicians aware of the risks of volutrauma, barotrauma and biotrauma. Yet the risks of high $FiO_2$ and hyperoxaemia seem to have been forgotten,[1] and the dominant view is that some excess oxygen is better than almost *any* oxygen deficiency.[2,3] This view is held despite the failure of research to demonstrate a beneficial impact on outcome of increasing $DO_2$,[4-6] and despite wide variability between intensivists in terms of target $SaO_2$, $PaO_2$ or $FiO_2$.[7,8] Most Australian intensivists (85%) are more concerned about barotrauma than high $FiO_2$-induced lung injury.[9] Thus, in the intensive care unit, $SaO_2$ is often maintained around 95%–96%.[10,11] In some studies of patients with acute respiratory distress (ARDS) or acute lung injury (ALI), however, clinicians have targeted $SaO_2$ levels at around 88% and even 80%.[12-14] Whether this practice of permissive hypoxaemia in ARDS is beneficial or injurious has never been explored. In a recent randomised controlled study of patients with chronic obstructive respiratory disorder, oxygen treatment titration to $SaO_2$ around 80% decreased the risk of death by 78%, compared with maintaining a mean $SaO_2$ of 98% in the control higher-flow oxygen group.[15] Below this hypoxaemic boundary, many high-risk techniques (recruitment, jet ventilation, nitric oxide, extracorporeal membrane oxygenation) have been proposed to improve arterial oxygen saturation.[14,16,17] It remains unknown whether these approaches are beneficial or injurious. Given such large variability in clinicians' choice of target $SaO_2$, $PaO_2$ or $FiO_2$ targets, however, it is important to review the available evidence.

## Oxygen is toxic

It is unclear whether life emerged on Earth because oxygen enabled its development, or because organisms finally became able to resist its toxic oxidising effects. Nonetheless, we know with a high degree of certainty that a high $FiO_2$ is toxic to the lungs. Animal models confirm the findings in humans.[18-20] Prolonged exposure to a high $FiO_2$ causes histopathological changes similar to those seen in ARDS, including high-permeability pulmonary oedema, hyaline membrane formation, pulmonary vascular lesions and eventual pulmonary fibrosis.[21] High $FiO_2$ can exacerbate ventilator-induced lung injury.[22,23] Rabbits ventilated with a large tidal volume and an $FiO_2$ of 0.5 develop significantly more severe lung injury than animals treated with room air.[24] The addition of oxygen during ventilation, irrespective of $FiO_2$ (1.0 or 0.21%), causes marked changes in lung tissue.[25] Absorption atelectasis occurs at $FiO_2$ as low as 0.3–0.5, and will increase V/Q mismatch.[26] The relative contribution of oxygen, and of ventilation specifically, to ventilator-induced lung injury and changes in lung structure is largely unknown, although several studies show that both have separate contributing roles.[21,24,25,27]

High $FiO_2$ alters the immune response and promotes pulmonary infection, and increased morbidity and mortality have been demonstrated during or after exposure to sublethal hyperoxia.[28,29] This injury is oxygen dose-dependent.[30] Oxygen alters the tracheal flora, leading to colonisation by *Pseudomonas* and *Proteus* species.[31] This could explain the high risk of secondary infections,[32] such as pneumonia, among ARDS patients.[33] Oxygen may further exacerbate acute lung injury by interrupting a lung-protective hypoxia-driven adenosine-$A_{2A}$-receptor-mediated anti-inflammatory pathway.[30]

Progression of the initial lung insult is frequent in ICU.[34] In the ALIVE study, 35% of ARDS and ALI occurred a median of 3 days after ICU admission.[35] In humans, a pre-existing mild injury may change the susceptibility to oxygen-induced lung damage and accelerate the development of ALI.[21,30,36,37] However, survival after longer exposure to high $FiO_2$ has been reported,[38,39] and one recent trial found no decrease in mortality when a lower fraction of oxygen (decreased by 37%) was used in patients with high positive end-expiratory pressure (PEEP).[40] However, these studies remain underpowered to detect realistic effects. It also remains unclear whether the acceptance of permissive hypoxaemia should be gradual.

## Hypoxaemia or hyperoxaemia — which is worse?

A high arterial $PaO_2$ may also be dangerous[41] independent of $FiO_2$, despite clinicians showing little concern about it.[2] ARDS patients die more often of multiple organ failure than hypoxaemia or hypoxia, and ventilator-induced lung injury increases local and systemic inflammation.[42-44] The roles of high $PaO_2$ levels and/or high $FiO_2$ therapy in such injurious phenomena have never been adequately investigated.[45,46] Recent human trials have demonstrated increased oxidative stress with hyperoxic therapy.[47,48] It is plausible that high oxidative stress due to hyperoxaemia may impair cell repair processes and delay recovery of organ function in critically ill patients. There is no prospective study of different $PaO_2$ targets in ARDS patients. Thus, we have to rely on studies

conducted in other groups of patients to consider the dangers of hyperoxaemia. For example, after cardiac surgery, exposure to an $FiO_2$ of 1.0 was followed by increased shunting compared with an $FiO_2$ of 0.35.[49] In a recent multicentre randomised controlled trial of 1400 adults undergoing laparotomy, an $FiO_2$ of 0.8, compared with 0.3, during and for 2 hours after surgery, did not decrease surgical site infection (19% v 20%; $P = 0.5$), but caused a 1.5% increase in 30-day mortality ($P = 0.13$).[50] After cardiac arrest, hyperoxia (defined as $PaO_2 > 300$ mmHg) in the first 24 hours may be associated with an increased mortality rate.[51] In newborn term and premature babies, $SaO_2$ targets as low as 85% have been recommended.[52,53] In a retrospective observational study of 36 307 ICU admissions, inhospital mortality was linearly related to $FiO_2$ in the first 24 hours, and had a U-shaped relationship with $PaO_2$.[10]

## Adaptive mechanisms to avoid tissue hypoxia during hypoxaemia

Several adaptive mechanisms may prevent tissue hypoxia in the presence of hypoxaemia, including a change in 2,3-DPG (2,3-disphosphoglyceric acid) erythrocytic activity to shift the oxygen-binding curve in favour of easier haemoglobin unloading. Permissive hypercapnia and respiratory acidosis also enhance the unloading of oxygen at the tissue level. After 2–3 days, the Krebs cycle and the respiratory chain will express hypoxia-resistant iso-enzymes.[54,55] Organs may reduce their oxygen uptake and reduce oxygen utilisation, presumably through hibernation, stunning, preconditioning phenomena, or enhanced efficiency of oxygen utilisation.[56] The critical low-range value for arterial oxygen content is estimated to be about a third of the normal value.[55] Severe hypoxaemia ($PaO_2 < 40$ mmHg) is generally thought to reduce renal blood flow. However, there are conflicting reports on the renal effects of moderate hypoxaemia, and mild hypoxaemia without concomitant hypercapnia, on renal haemodynamics.[57] Climbers who reach the summit of Mount Everest without supplemental oxygen have a $PaO_2$ less than 25 mmHg without clinically important hyperlactataemia (mean lactate concentration, 2.2 mmol/L).[58] The lower safe limit of hypoxaemia (especially if gradually introduced) in ventilated ARDS patients remains unexplored.

## Management of acute respiratory distress: what is the target $PaO_2$?

There is no clinical study evaluating therapeutic hyperoxia/hyperoxaemia or a conservative approach to oxygen supplementation for patients with ARDS.

In the ARDSNet study comparing two strategies of PEEP adjustment, the $FiO_2$was non-deliberately lower in the high-PEEP group (lower by 21% from 0.53 in low-PEEP patients), with no significant difference in mortality or ventilator-free days.[40] However, this study was seriously underpowered. Oxygen remains an untested/unstudied drug in the context where it might matter most: ARDS. As Branson and Robinson wrote: "If introduced today, oxygen might have difficulty getting approved by the Food and Drug Administration".[2]

Given the above concerns, it is time to re-evaluate our therapeutic targets, particularly for patients with ARDS. Oxygen therapy has not been systematically evaluated in critical illness in general and in ARDS in particular. Targeting $SaO_2$ or $PaO_2$ levels in the normal range in ARDS patients may be unnecessary and perhaps even deleterious. It is time to explore the potential advantages of permissive hypoxaemia in ARDS, with and without permissive hypercapnia.

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