Oxygen therapy in critical illness: friend or foe? A review of oxygen therapy in selected acute illnesses 1A01, 1A03

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In recent years there has been a gradual shift away from using uncontrolled high concentrations of inspired oxygen in some acute illnesses. Oxygen is perhaps the most frequently used drug in medicine, and understanding the balance of benefits and harms is essential knowledge for all anaesthetists and intensivists. While current teaching and practice emphasise avoiding hypoxaemia over concerns about hyperoxaemia, it may transpire that oxygen excess is more harmful than previously thought. As with many interventions in intensive care medicine, striving to achieve physiological normality may sometimes do more harm than good, and tolerance of abnormal values may on occasion be in patients' best interests.
Incorporating Single Best Answers (see page 197: answers on page 237).

Keywords: *oxygen therapy; hypoxaemia; intensive care; ARDS; permissive hypoxaemia; precise control of arterial oxygenation*

"Oxygen is addicting; in its grip are the mitochondrial-rich eukaryotes that learned to depend on it during the past 1.4 billion years."
JW Servinghaus, PB Astrup[1]

Introduction

Oxygen undeniably holds a 'grip' over eukaryotic life on Earth. Since its discovery in the late 18th century and subsequent introduction into anaesthetic practice in the 1930s, oxygen has become a cornerstone of the treatment of critically ill patients. Oxygen is one of the most widely given drugs in hospital; in 2011, approximately 13.7% of hospital inpatients were estimated to be receiving supplemental oxygen at any one time.[2,3]

The risks of hypoxaemia and cellular hypoxia and the benefits of oxygen therapy are commonly rehearsed, but the harms that may be associated with excess oxygen therapy are perhaps not so widely recognised. This review aims to summarise what is currently known about the effects of excess oxygen in various acute illnesses. Key mechanisms in the development of hyperoxic damage will be discussed in the context of evidence highlighting the complex relationship between dose, benefit and harm for this important therapeutic gas. We will also explore the novel concepts of 'precise control of arterial oxygenation' (PCAO) and 'permissive hypoxaemia' (PH).

Overview of the role and physiology of oxygen

Acting as a terminal electron acceptor during oxidative phosphorylation, oxygen is integral to the aerobic generation of adenosine triphosphate (ATP). At rest, global oxygen consumption ($\dot{V}O_2$) is approximately 250 mL/min.[4] The crucial role oxygen plays in normal cell function is demonstrated by the sequelae of sustained inadequate tissue oxygenation: apoptotic cell destruction, organ dysfunction, and ultimately death.

$CaO_2 = (1.34 \times [Hb] \times SaO_2) + (0.023 \times PaO_2)$

where:
CaO_2 = oxygen content of arterial blood (mL/dL blood)
1.34 = volume of oxygen bound to 1 gram of saturated haemoglobin (mL/g)
[Hb] = concentration of haemoglobin (g/L)
SaO_2 = percentage of haemoglobin fully saturated with oxygen (%)
0.023 = solubility coefficient of oxygen in plasma (mL/dL/kPa)
PaO_2 = partial pressure of oxygen dissolved in arterial blood (kPa)

Figure 1 Total arterial oxygen content (CaO_2) is therefore the sum of oxygen dissolved in plasma and oxygen bound to haemoglobin.[4,5]

Oxygen in the blood is predominantly transported bound to the intra-erythrocyte protein haemoglobin. Much smaller amounts are dissolved directly into plasma. Measurements of blood oxygen are usually given as the percentage of haemoglobin that is fully saturated with oxygen (SpO_2 or SaO_2), or as the partial pressure of oxygen dissolved in the blood (PaO_2, expressed in kPa), which at sea level is normally 12.0-14.8 kPa (**Figure 1**).

Cellular oxygenation is dependent on the balance between oxygen delivery ($\dot{D}O_2$) and oxygen extraction (O_2ER), occurring as a result of diffusion of oxygen down a concentration gradient generated by oxygen consumption in tissue (**Figure 2**).

Hypoxaemia and hypoxia

Hypoxaemia refers to low oxygen tension in the blood, and cellular hypoxia to low oxygen tension in tissues. Widely

$\dot{D}O_2 = CaO_2 \times \dot{Q}$

Where:
$\dot{D}O_2$ = oxygen delivery to tissue (mL/min)
CaO_2 = oxygen content of arterial blood (mL/dL)
$\dot{Q}$ = cardiac output (L/min)

$O_2ER = \dot{V}O_2/\dot{D}O_2$

where:
O_2ER = oxygen extraction ratio
$\dot{V}O_2$ = oxygen uptake by tissue (mL/min)
$\dot{D}O_2$ = oxygen delivery to tissue (mL/min)

Figure 2 Global oxygen delivery to tissue ($\dot{D}O_2$) is a product of arterial oxygen content and cardiac output, and is approximately 1,000mL/min.[4] The proportion of delivered oxygen taken up by cells (O_2ER) changes according to cell metabolic activity, and differs between tissues.[5]

Critical illnesses requiring supplemental oxygen (British Thoracic Society (BTS)):

- Cardiac arrest or resuscitation
- Shock
- Sepsis
- Major trauma
- Near-drowning
- Anaphylaxis
- Major pulmonary haemorrhage
- Major head injury
- Carbon monoxide poisoning

Figure 3 BTS guidelines on critical illness requiring high flow oxygen, irrespective of whether or not hypoxaemia is present.[3] For the reasons discussed below, a new approach may be necessary.

accepted definitions of hypoxaemia are a PaO_2 <8 kPa or SpO_2 <90%.[3] Regardless of their reason for admission, hypoxaemia is common among critically unwell patients.[4]

Cellular hypoxia results from a mismatch between $\dot{D}O_2$ and $\dot{V}O_2$. Problems with $\dot{D}O_2$ can arise due to low oxygen content (hypoxaemia), or due to reduced cardiac output (heart failure).[4] Alternatively, impaired cellular utilisation of oxygen may cause hypoxia when $\dot{D}O_2$ is adequate.[4] The 'critical $\dot{D}O_2$' below which cellular respiration cannot be maintained by changes in O_2ER is approximately 4 mL/kg/min.[5] At this point oxygen consumption becomes supply-dependent.

The precise level at which tissue hypoxia causes cell death is uncertain, and is likely to differ between individuals.[3] Evidence suggests mitochondrial oxidative phosphorylation declines at an intracellular PO_2 between 0.01-0.13 kPa.[4] Although anaerobic respiration can temporarily maintain a reduced level of ATP production during hypoxia, this comes at the expense of progressive lactic acidosis.

Hyperoxaemia and hyperoxia

In practice the terms 'hyperoxia' and 'hyperoxaemia' are used interchangeably. However, this review uses 'hyperoxia' to describe higher than normal oxygen tension in the lung tissue (eg elevated FiO_2) and 'hyperoxaemia' for supranormal PaO_2. The distinction is an important one: a patient may be simultaneously hyperoxic (eg, have lung tissue at a high FiO_2) and hypoxaemic (eg, have diffusion limitation in acute respiratory distress syndrome (ARDS)).

Possibly owing to the variation in definitions of what constitute 'normal' oxygenation, several authors have chosen to define hyperoxaemia as >16 kPa.[1,6,7]

Current practice in oxygen therapy

Traditional teaching emphasises avoidance of hypoxaemia in critically ill patients, with little attention focussed on the consequences of unrestricted supplemental oxygen (**Figure 3**).[3] While this approach may be important when lethal cellular hypoxia is a risk, adopting a 'one size fits all' strategy to oxygen therapy may render many patients hyperoxaemic.

The British Thoracic Society (BTS) emergency oxygen guideline recommendation for titration of oxygen therapy to oxygen saturations is predicated on concerns about ventilatory failure and hypercapnia in patients who are critically dependent on hypoxic drive. In this context, re-evaluation of the balance between beneficial and harmful effects of oxygen therapy in all critically ill patients may be worthwhile, and future guidelines may have to be adapted in the light of improved understanding and ongoing research in this area.

Hyperoxia and hyperoxaemia: at what level do they become damaging?

It is hard to define precisely what level and duration of elevated FiO_2 is harmful. Unsurprisingly, as the interface with inspired gas that is exposed to the highest concentrations of oxygen, the lungs show signs of damage before any other organ. Evidence of pulmonary damage rarely occurs below an FiO_2 of 0.5, although atelectasis may occur at much lower concentrations.[8-10] The first overt signs of acute hyperoxic lung injury often manifest as tracheobronchitis, which in healthy individuals breathing an FiO_2 ≥0.95 may occur after as little as four hours.[9] Prolonged exposure to high inspired oxygen concentrations (>48 hours of FiO_2 ≥0.5) may produce radiological and cellular changes in the lung similar to those of ARDS.[9,11]

Susceptibility to hyperoxic damage varies between individuals: cases exist of healthy subjects tolerating an FiO_2 of 1.0 for 48 hours with few apparent ill-effects.[12] One potential contributor to these differences in vulnerability may be mutations of the gene coding for nuclear factor erythroid-2 related factor (NRF_2), a transcription factor found on the long arm of chromosome 2. Among major trauma patients polymorphisms in NRF_2 have been associated with a significantly increased risk of developing acute lung injury.[13]

Hyperoxia and lung injury

Inflammation and reactive oxygen species

Hyperoxia is thought to harm tissues through the production and accumulation of reactive oxygen species (ROS). ROS may be 'free radicals' (molecules with unpaired electrons in their outer shell), or oxygen species able to react in a way

resembling free radicals.[14] ROS readily form covalent bonds with other molecules, leading to cell injury via lipid peroxidation. DNA damage and alteration of protein structure.[14] ROS are also a by-product of constitutive metabolic processes and have many roles in normal cell function.

While the body is normally able to neutralise ROS using the enzymes superoxide dismutase and catalase (**Figure 4**), in hyperoxia, production may overwhelm these physiological antioxidants.[14] Paradoxically, ROS production may also increase during cellular hypoxia. Ischaemic ROS accumulation is believed to be crucial in the development of reperfusion injury when blood flow is restored.[4]

Damage from ROS may lead to cell apoptosis and necrosis. A review of studies in the field of hyperoxic lung damage suggested that ROS may trigger apoptotic pathways within pulmonary cells but may also inhibit completion of apoptosis in some instances. In these cells, necrotic death occurs, causing an acute inflammatory response. In addition to being a possible trigger for apoptosis and necrotic cell death, hyperoxia may directly instigate the release of proinflammatory agents from pulmonary epithelial cells.[14]

Upregulation of resident inflammatory cell activity may provoke increased macrophage and neutrophil migration to the lung.[9,14] Leucocytes gather in the alveoli, interstitium and pulmonary circulation to release more ROS into the region.[9] A cyclic pattern of cell necrosis and inflammatory cell recruitment occurs, each serving to exacerbate the other. Once the 'acute' phase of hyperoxic lung damage has been resolved, a subacute 'proliferative' phase may ensue. This is characterised by type II pneumocyte proliferation and interstitial pulmonary fibrosis.[13]

Changes in lung defences and flora

Despite evidence of increased leucocyte recruitment during hyperoxia, animal models have also shown direct inhibition of alveolar macrophage function. Mice exposed to 'sublethal' high inspired oxygen for four days and inoculated with *Klebsiella pneumoniae* show impaired destruction of bacteria by alveolar macrophages, as well as a significantly greater rate of septic bacterial dissemination from the lungs.[15] This, combined with the fact that hyperoxia alters tracheal flora in favour of potentially virulent bacterial species such as *Pseudomonas*, may increase the risk of nosocomial pneumonia.[16]

ARDS and atelectasis

The net result of prolonged hyperoxic inflammation may be changes in the lung reminiscent of ARDS.[11] Common findings in both severe oxygen toxicity and ARDS include pulmonary oedema, hyaline membrane formation, thickening of pulmonary arterioles and worsening of PaO_2/FiO_2 ratio.[9,11] There is some overlap in pathophysiology between the two conditions; hyperoxia increases levels of the proinflammatory transcription factor NF-κB, leading to the release of a host of inflammatory mediators such as TNF-α, IL-8 and HMG1, which have been implicated in the development of ARDS.[14,17]

Through a variety of mechanisms, hyperoxia may also leave the lungs vulnerable to atelec-trauma, a risk factor for ARDS.[4] Some degree of atelectasis is common in sedated patients

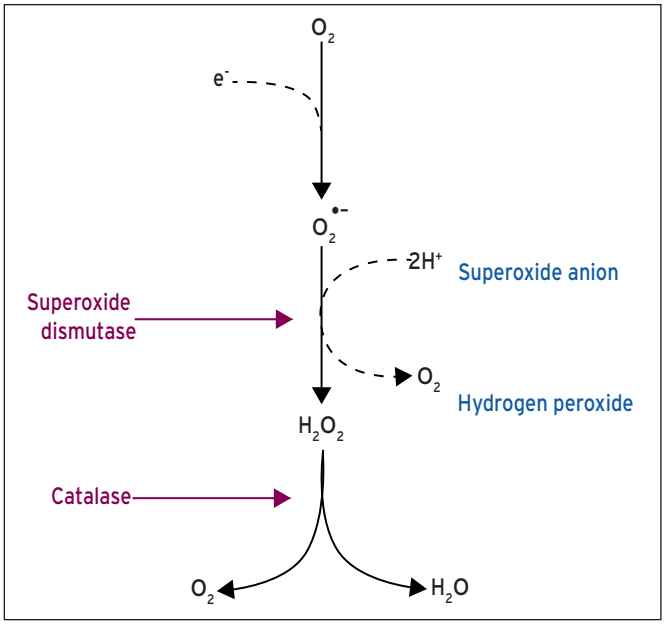

Figure 4 The reduction of oxygen to water in biologic systems, catalysed by two ubiquitous antioxidant enzymes. Adapted with permission from Lumb A, Walton AJ. Perioperative Oxygen Toxicity. *Anesthesiology Clin* 2012;30:591-605. Copyright Elsevier.

receiving oxygen, but both its rate of onset and extent are enhanced by increasing FiO_2.[18] While recruitment manoeuvres and PEEP may be used to reverse/prevent atelectasis, these techniques may in themselves cause harm.[4]

The mechanisms surrounding hyperoxic atelectasis are threefold:

- First, high inspired oxygen may inhibit pulmonary surfactant production, increase alveolar surface tension and so cause collapse upon expiration.[19]
- Second, hyperoxia can increase the viscosity of tracheal mucus and reduce its speed of clearance, leading to mucus plugging.[20]
- Finally, oxygen may increase the rate of absorption atelectasis. When compared to room air, mathematical modelling predicts absorption atelectasis to occur over five times faster in lungs pre-oxygenated at 50% oxygen before anaesthetic induction.[18]

Short-term, atelectasis may be a major causative factor in the high incidence of hypoxaemia seen in the early postoperative period. The common practice of hyperoxic ventilation prior to extubation has been shown to increase the extent of lung collapse after surgery.[21] In patients with poor respiratory effort (eg in pain, obese patients), collapsed regions of lung may persist for up to four days, reducing the ability to mobilise and predisposing to pneumonia.[21] After discharge from the recovery room back to the ward environment, staffing pressure and equipment constraints (eg lack of humidified oxygen delivery systems) may contribute to prolonged atelectasis.

The role of oxygen in the development of lung injury may be exacerbated when it is administered in conjunction with harmful ventilatory strategies. Even at relatively moderate amounts of supplemental oxygen (FiO_2=0.5), studies in mice imply a synergistic harmful relationship effect between

hyperoxia and high tidal volume ventilation.[22] Moreover, although low tidal volume ventilatory strategies are known to improve outcome in acute lung injury,[23] compliance with this intervention may be poor.[24]

Clinical similarities between ARDS and hyperoxic pulmonary damage make it hard to distinguish between progression of the underlying pathology and the adverse effects of oxygen therapy.[9] Oxygen-induced atelectasis may leave the lungs vulnerable to ARDS, and may increase the risk of postoperative complications.

Hyperoxaemia and critical illness

Cardiovascular pathophysiology

Hyperoxaemia leads to a reduction in resting heart rate and cardiac output, potentially due to increases in vagal tone.[25] Increased systemic vascular resistance also occurs, thought to be due to reductions in prostaglandin synthesis, impaired endothelial nitric oxide (NO) production and increased oxidative NO destruction.[25,26] A systematic review of studies in this area reported that hyperoxaemia may also reduce coronary blood flow, increase coronary vascular resistance (reducing myocardial oxygen delivery) and depress myocardial oxygen consumption.[27] Thus, in critically ill patients with hyperoxaemia and concurrent anaemia a theoretical, but counterintuitive, risk of myocardial hypoxia may exist.

Myocardial infarction

While supplemental oxygen has traditionally been given in the treatment of acute myocardial infarction (AMI), recent evidence raises important questions about this practice. A 2010 systematic review concluded that oxygen may increase the risk of death, although the authors could not rule out this being a chance finding.[28] Another systematic review found some evidence that giving supplemental oxygen can increase infarct size.[29] Suggested mechanisms for this include reperfusion injury and hyperoxaemic vasoconstriction.

Both reviews highlighted the limited availability of data in this area, and the pressing need for further research.[28,29] In this context, the Australian 'AVOID' randomised controlled trial comparing the effects of administration of either air or oxygen in the management of AMI was due to be completed in late 2013.[30] Currently however, there is no evidence for the benefits of oxygen therapy in AMI, and suggestive evidence that it may cause harm.

Post cardiac arrest

As with AMI, information concerning the dangers of liberal oxygen use after resuscitation from cardiac arrest is limited and inconsistent. A retrospective, cohort study conducted on patients who suffered a nontraumatic cardiac arrest within the 24 hours preceding ICU admission found hyperoxaemia was associated with significantly higher in-hospital mortality, compared to hypoxia and normoxaemia.[31] Secondary analysis did not find a threshold above which hyperoxaemia caused harm, but incremental 25 mm Hg (3.3 kPa) rises in postresuscitation PaO_2 increased the relative risk of in-hospital death by 6%.[32]

A similar study using the same inclusion criteria but a much larger sample produced a more mixed picture. It was found that when defined as a PaO_2 of >200 mm Hg (26.6 kPa), hyperoxaemia was a significant predictor of worse outcome.[33] Conversely, when PaO_2 readings were ranked into deciles and covariates such as length of stay and severity of disease controlled for, arterial oxygen was no longer predictive of in-hospital mortality.[33]

Current guidelines recommend high flow oxygen until the patient is stabilised, then titrating PaO_2 and SpO_2 to within physiological levels.[3] In the absence of any proven benefits for hyperoxaemia post cardiac arrest this would seem a logical conclusion.

Sepsis

The vascular effects of hyperoxaemia may not be limited to the coronary circulation. In patients with septic shock, 20 minutes of 100% oxygen may cause a reduction in brachial artery blood flow.[34] Similar results have been seen in the lower limbs of healthy patients after breathing 100% oxygen.[35]

Conversely, the haemodynamic consequences of hyperoxaemia may have benefits during the early stages of severe sepsis. In one study where pigs were randomised to either hyperoxic or room air ventilation immediately after induced faecal peritonitis, hyperoxia prompted a redistribution of blood flow in favour of the hepatosplanchnic organs, improvements in renal function and an attenuation of the rate of metabolic acidosis.[36] Furthermore, hyperoxic animals had significantly better pulmonary compliance and PaO_2:FiO_2 ratios than controls after 12 hours of 100% oxygen.[36]

However, in a similar study where porcine models were randomised to hyperoxic or room air ventilation 12 hours post faecal inoculation, the benefits of hyperoxia were less pronounced. After 24 hours of peritonitis, no difference in arterial pH was seen between the groups, however the hyperoxic group showed a small improvement in creatinine clearance. There was no significant difference in lung function between hyperoxic and control groups.[37]

Taken together, these studies suggest there may be advantages to administering 100% oxygen from the time of a massive bacterial insult, or up to 12 hours later when early hyperdynamic sepsis had ensued. While it may appear in these models that there is little difference between oxygen-induced damage and lung injury arising as part of a severe inflammatory response, the relatively short timeframes may mean that any hyperoxic damage was not yet clinically evident.[36,37] Furthermore, as the models were not followed up beyond 24 hours, the effect of hyperoxaemia on survival is unknown.

Wound healing and surgical site infection

Acutely, low oxygen tension in tissues may provide a stimulus for tissue repair and angiogenesis. However, chronic tissue hypoxia may have the opposite effect, slowing rates of fibroblast proliferation and decreasing collagen secretion.[38] In addition, extrapulmonary bacterial destruction by neutrophils is greatly enhanced by increasing PO_2 within a tissue, providing a 'respiratory burst' that increases ROS production.[38] However, oxygenation of skin tissue relies not only upon CaO_2, but also on the effectiveness of regional

microcirculation.[38] Therefore hyperoxaemia alone may not raise oxygen tension in a wound.

Several large studies have investigated the potential of supplemental oxygen in reducing the instance of abdominal surgical site infection (SSI). One trial compared an FiO_2 of 0.3 with 0.8 during abdominal surgery and found that the relative risk of SSI was significantly reduced in the high FiO_2 group.[39] That said, this study excluded patients with important co-morbidities (eg, diabetes mellitus) which increase the likelihood of postoperative infection. Conversely, another randomised trial concluded that, in a sample of general surgical patients, using an FiO_2 of over 0.8 significantly increased the incidence of SSI.[40]

Meta-analyses have also been inconsistent in their support for perioperative hyperoxaemia. One 2009 meta-analysis found that perioperative hyperoxia exerted a significant benefit in preventing SSI, particularly after colorectal surgery.[41] However, in one of its key studies there was no primary intention to induce hyperoxaemia – the effect was secondary to avoidance of nitrous oxide. The most recent meta-analysis excluded this study, and incorporated the results of the large 'PROXI' randomised control trial. It concluded there was no overall effect of high inspired oxygen in preventing SSI.[42] Interestingly, subgroup analysis again suggested potential benefit in colorectal surgery. Both meta-analyses recognised that, major inconsistencies between studies in key areas such as antibiotic prophylaxis and a standardised definition of SSI, may have influenced the conclusions.[41,42]

In summary, there is no convincing evidence that using high inspired oxygen concentrations accelerates wound healing. Outside of potential benefits in colorectal surgery, meta-analysis suggests that perioperative hyperoxia has no protective effect against SSI in general surgical patients.[41,42] However, inconsistencies in studies in the field mean that more robust data are required.

Traumatic brain injury

Traumatic brain injury (TBI) may disrupt cerebral blood flow, causing reductions in brain tissue oxygen tension ($PbtO_2$) and altering neuronal mitochondrial function.[43] The theoretical benefit of hyperoxaemia is that it may attenuate secondary injury by raising the oxygen tension in the hypoxic brain.

One challenge to this notion is that if a patient's haemoglobin is fully saturated, even an FiO_2 of 1.0 under normobaric conditions will produce a negligible rise in CaO_2.[5] That said, even a relatively small increase in PaO_2 may improve mitochondrial oxygen uptake. In TBI microvascular destruction, perivascular oedema and endothelial swelling may increase the distance across which oxygen will have to diffuse to reach mitochondria.[43,44] According to Fick's first law of diffusion, the rate of oxygen diffusion will be directly proportional to the difference in oxygen tension between vasculature and mitochondrion.[4] Boosting PaO_2 will increase this arterial-mitochondrial gradient, theoretically improving oxygen flux in the injured brain.[43-45]

Despite debate over which measurable criterion best describes clinically beneficial improvements in cerebral oxygenation, studies have shown that hyperoxaemia does lead to an increase in $PbtO_2$.[43] The effect on mitochondrial function has been less convincing; positron emission topography in patients with TBI found no significant change in cerebral metabolic activity during hyperoxaemia.[46] Notwithstanding this, the net effect of increased $PbtO_2$ may be improved outcomes. A retrospective study of over 3,000 patients concluded that both hypoxaemia and extreme hyperoxaemia result in significantly poorer rates of survival in TBI.[47] In the study logistic regression defined an 'optimum range' for PaO_2 in TBI between 14.7-65 kPa, a range that has been demonstrated elsewhere.[47,48]

As such, the effects of supranormal oxygen in TBI are uncertain. While studies have associated hyperoxaemia with improved outcome in TBI, the mechanisms by which it may be beneficial are yet to be clarified. One suggestion put forward in a 2009 review could be a large randomised control trial resembling the MRC-CRASH study, which hopefully would provide a definitive answer.[45]

Ischaemic stroke

Many have called for research into normobaric hyperoxaemia on the basis of oxygen's 'ideal' neuroprotective properties.[49] As with TBI, theoretically hyperoxaemia may improve mitochondrial function, helping to recover tissue in the ischaemic penumbra and limit infarct size.[45]

A small, randomised trial published in 2007 appeared to confirm this hypothesis. Compared to controls, hyperoxaemic acute ischaemic stroke patients were found to have significantly lower levels of cerebral lactate, and higher levels of N-acetyl-aspartate (a marker of neuronal mitochondrial function).[50] This was interpreted as evidence of improved cerebral aerobic metabolism and mitochondrial activity in the hyperoxaemia group. Delaying hypoxic cell death in the ischaemic penumbra may also prolong the window period available for thrombolysis. In one study the time span for effective thrombolysis was extended in hyperoxaemic rats (PaO_2 range 44-49 kPa) by up to two hours compared to normoxaemic rats.[51] However, to date little evidence exists regarding the net impact of hyperoxaemia on long-term morbidity and mortality in acute ischaemic stroke. In one study, patients given supplemental oxygen after admission to hospital had a higher one-year mortality (31.2% *vs* 27.1% given room air).[52]

Currently, supplemental oxygen does not feature in guidelines for non-hypoxaemic patients with acute ischaemic stroke.[3] As with TBI, while the results of small trials and animal models have been intriguing, insufficient evidence is available to support its routine use.

Hyperoxaemia: the net effect

The net result of the cardiovascular and other physiological effects of hyperoxaemia may be poorer outcomes for critically ill patients. While it is a generalisation to group 'critically ill' patients together under the same banner irrespective of underlying pathology, studies using this broad definition have produced conflicting data.

A large retrospective observational study conducted in the Netherlands demonstrated a U-shaped relationship between PaO_2 and mortality. After correcting for disease severity, the

1. PH should only be applied to patients who have had time to adapt to a state of hypoxaemia, and not in acute resuscitation.

2. PH should only be used when normoxaemia is unachievable, or places the patient at risk of hyperoxic injury or ventilator-induced lung injury.

3. To avoid the dangers of insufficient oxygen, PH should be used in conjunction with specific SpO_2 and PaO_2 targets decided on an individual basis ('precise control of arterial oxygenation').

4. Markers of cellular hypoxia should continue to be measured to assess toleration of hypoxaemia.

5. Various groups exist where PH may not be suitable (eg TBI).

Figure 5 Potential rules for implementing permissive hypoxaemia.[59]

odds of in-hospital death in the first 24 hours post ICU admission for hyperoxaemic patients were 1.23 that of normoxaemic individuals.[53] However, a similar study of over 150,000 ICU patients did not confirm this relationship. After adjusting for disease severity, only hypoxaemia was associated with increased in-hospital mortality.[6]

Is hyperoxia a problem in practice?

International studies have shown considerable variation in the amount of oxygen clinicians are willing to prescribe to normalise PaO_2. Surveys of Canadian and Australian intensivists show a great degree of variability in what is deemed the lowest acceptable FiO_2 for a patient with an SpO_2 of 85%, and how long clinicians would be willing to tolerate an SpO_2 <85% in an ARDS patient.[54,55] In a cohort of 5,498 Dutch ICU patients, 22% were found to be hyperoxaemic (PaO_2 >16 kPa).[7] Researchers found when the FiO_2 was ≤0.4 in a hyperoxaemic patient, it was unlikely that ventilator settings would be adjusted to lower PaO_2.[7] The conclusion drawn from this was that hyperoxaemia was not seen as potentially hazardous if FiO_2 was below a certain threshold.[7] While this may be true in terms of preventing overt hyperoxic lung damage (known to be rare at FiO_2 <0.5), as discussed earlier hyperoxaemia may be detrimental in its own right, and the cumulative effect of many small harms at a population level can still contribute significant morbidity and mortality.

Against this must be balanced the reduced oxygen reserve available in the event of an acute respiratory or cardiovascular disturbance. Balancing the possible harm of short-term high FiO_2 in the large population of patients undergoing anaesthesia, with the benefit of increased oxygen reserves to mitigate rare but catastrophic harm in the small group of patients who have short-term airway obstruction, for example, is extremely difficult.

Oxygen sparing strategies

Accepted strategies for reducing supplementary oxygen requirements in critically ill patients include lowering cellular oxygen demand (eg, cooling, paralysis), improving the PaO_2/FiO_2 ratio (eg, using inhaled nitric oxide, prone positioning) and normalising the oxygen-carrying capacity of blood (eg, transfusion).[56] However, in cases of 'refractory' hypoxaemia, these techniques may prove ineffective, leaving patients vulnerable to hyperoxic injury. A 'hallmark of ARDS',[57] refractory hypoxaemia has been defined as a PaO_2/FiO_2 ratio of <13.3 kPa despite intensive oxygen therapy.[56]

On the basis that few ARDS patients die purely from hypoxaemia,[58] some have proposed the acceptance of lower targets for PaO_2 in specific cases – an idea termed 'permissive hypoxaemia' (PH).[57,59] Its advocates propose a combination of goal-directed manipulation of cardiac output and haemoglobin concentration in selected individuals who have adapted to tolerate hypoxaemia.[59,60] The aim is to minimise the possible harmful effects of interventions aimed at increasing arterial oxygenation, specifically high inspired oxygen levels and high levels of mechanical ventilation. Precise control of arterial oxygenation (PCAO) involves targeting PaO_2/SpO_2 to specific values within a tightly controlled range in order to avoid uncontrolled hyperoxaemia.[59,61]

Innate adaptive mechanisms to hypoxaemia include increased oxygen extraction by tissues, a shift to the right of the oxyhaemoglobin dissociation curve and changes in regional microvasculature to improve tissue blood delivery.[59,60] Furthermore, cellular down-regulation of non-essential processes in the face of chronic, sublethal hypoxia may help mitigate the effects of low oxygen levels.[59,60] A study at altitude has demonstrated the apparent efficacy of these adaptations. Healthy human subjects were able to tolerate severe hypoxaemia (PaO_2 <4 kPa) without signs of clinically significant tissue hypoxia.[62]

Problems with PH include the absence of biomarkers currently available to define when these adaptive mechanisms are occuring.[59] Harmful cellular hypoxia is a potential consequence of implementing PH inappropriately in a patient who has not yet adapted to conditions of hypoxaemia. **Figure 5** demonstrates factors which should be taken into account when considering a patient's suitability for PH.

Regardless, PH is a novel strategy for protecting patients from the harms of hyperoxia and mechanical ventilation with high average or high end-expiratory pressures. The identification of biomarkers that signify hypoxic adaptation would represent a significant leap in our understanding of hypoxaemia, and would open the door to widespread investigation of PH as a strategy in the intensive care setting.

Conclusion

> *"Oxygen is toxic. It rusts a person in a century or less... If introduced today, this gas might have difficulty getting approved by the Food and Drug Administration."*
>
> *JW Servinghaus, PB Astrup*[1]

Oxygen is simultaneously a 'blessing' and a possible 'curse.' Improved awareness of both its hazards and benefits mean that existing guidelines may need to be re-evaluated; a 'one size fits all' approach to therapy may no longer be sustainable. Hyperoxia may confer benefit in sepsis, colorectal surgery and TBI. In other circumstances, avoidance of excess oxygen therapy through strategies such as 'precise control of arterial oxygenation' may be prudent.

Recent insights into the adaptive capability of humans to conditions of low oxygen have sparked debate over whether the traditional paradigm of targeting normoxaemia is always best for all patients. It is increasingly recognised that aggressively pursuing normoxaemia may harm patients, and that in select patient groups innate adaptation may allow individuals to tolerate subphysiological levels of oxygen. However, further evaluation of safety, efficacy and effectiveness is required before 'permissive hypoxaemia' could be recommended in clinical practice. Development of biomarkers of susceptibility to and tolerance of hypoxaemia may be useful in guiding such an approach.

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Based on an essay by Nick Ridler which won the ICS Medical Student essay prize

Oxygen therapy in critical illness

Single Best Answer (SBA) questions

1. The BTS guidelines make recommendations about the fraction of inspired oxygen that should be administered to critically unwell patients. A 49-year-old gentleman comes into the emergency department with respiratory distress. His respiratory rate is 33 and his initial oxygen saturation is 91% in room air. Which of the following statements is most correct?

A. Oxygen therapy will relieve dyspnoea so should be administered in this scenario regardless of oxygen saturations.
B. His saturations are above 88% therefore he does not currently require oxygen therapy.
C. A non-rebreathe trauma mask at a flow rate of 15 L/min will administer 85-95% oxygen.
D. He is in respiratory distress and his saturations are low so he should be given 100% oxygen immediately until a blood gas is performed.
E. This gentleman's closing capacity (CC) is likely to encroach upon his functional residual capacity (FRC) regardless of positioning.

2. Permissive hypoxaemia (PH) is potentially a therapeutic strategy for acute respiratory failure leading to hypoxaemia and tissue hypoxia. Select the best statement regarding PH:

A. PH has not been rigorously tested in randomised controlled trials; despite this it may still be wise to adopt this in patients with severe ARDS.
B. For a patient with severe ARDS, PH may better balance the harms and benefits of oxygen therapy than attempts to achieve normoxia.
C. If PH was initiated in a patient with severe ARDS the current recommendations are to keep the PaO_2 >5.5 KPa.
D. The Pasteur point represents the lowest oxygen tension that a mitochondrion can tolerate; if it falls below this value of around 1 mm Hg (0.13 kPa) then aerobic metabolism takes over.
E. Hypoxia is among the leading causes of death in ARDS and PH could be one way to decrease mortality.

3. Which of the following patients would benefit most from oxygen therapy?

A. A patient on the intensive unit with acute severe pancreatitis has started to deteriorate over the last three hours with gradually falling oxygen saturation. SpO_2 is now 92% in room air; he complains of abdominal pain and has a respiratory rate of 32.

B. A 66-year-old man with a 50-pack-year smoking history arrives in the ED breathless and struggling to speak in full sentences; his oxygen saturation is 89% in room air.
C. A 34-year-old female patient is brought to the ED who has been in a house fire; she has singed eyebrows and appears drowsy. SpO_2 is 96% in air and her respiratory rate is 17.
D. A 19-year-old man has a spontaneously developed 4 cm pneumothorax. He is asymptomatic and his SpO_2 is 96% in room air.
E. A 45-year-old gentleman with sickle cell trait has been involved in an RTC and has an open femoral fracture. SpO_2 is 92% in air.

4. Choose the best statement with regard to hyperoxia:

A. Reactive oxygen species (ROS) may be 'free radicals' (molecules with paired electrons in their outer shell), or oxygen species able to react in a way resembling radicals. ROS form ionic bonds with other molecules, leading to cell injury via lipid deposition, DNA damage and alteration of protein structure.
B. ROS accumulation is believed to be crucial in the development of reperfusion injury when blood flow is restored.
C. Hyperoxia has little effect on lung macrophages but does seem to affect other leucocytes causing increased recruitment.

Turn to page 237 for the answers.

D. High inspired oxygen concentrations may promote pulmonary surfactant production, decreasing alveolar surface tension and so causing collapse upon inspiration.
E. Preoperative atelectasis has only been shown to be an issue for surgery where anaesthesia lasts for greater than five hours.

5. Oxygen transport is crucial to prevent hypoxia. Regarding oxygen delivery ($\dot{D}O_2$), oxygen uptake ($\dot{V}O_2$) and oxygen extraction (O_2ER), which of the following statements is incorrect?

A. Oxygen flux is the amount of oxygen delivered to the tissues each minute and is approximately 1,000 mL per minute in health. This is composed of chemical oxygen delivery and dissolved oxygen delivery.
B. The proportion of dissolved oxygen carried in the blood is relatively small, therefore oxygen in this format is of limited importance to mitochondria.
C. Huffner's number is a constant that describes how much oxygen can combine with each gram of haemoglobin when fully saturated.
D. In health oxygen consumption is around 250 mL/min.
E. $O_2ER=\dot{V}O_2/\dot{D}O_2$ and differs between tissues in the body. $\dot{V}O_2$ max in a 'normal' individual will usually be around 12 times this value, but in a trained individual could be up to 32 times this value.