

# Oxygen Therapy in Anaesthesia



## The Yin and Yang of O<sub>2</sub>

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### Introduction

A continuous supply of oxygen, the gaseous waste product of plant photosynthesis, is essential to sustain cellular metabolism in all aerobic organisms, including humans.<sup>[1]</sup> Oxygen is a highly reactive gas that is capable of combining with most other elements because of the avidity with which it attracts electrons. This process may occur slowly and remorselessly, as is seen when iron rusts, or rapidly and catastrophically, as occurs during forest fires. Controlled oxidation of glucose, and other substrates, to carbon dioxide with the consequent reduction of oxygen to water is the basis of aerobic cellular metabolism, one of the hallmarks of vertebrate physiology.<sup>[2]</sup>

Reactive oxygen species (ROS), also known as oxygen free radicals, contain one or more unpaired electrons and, as their name suggests, are considerably more reactive than their corresponding non-radical form. They are generated within mitochondria during normal cellular metabolism. ROS generation may be accelerated under certain conditions including hyperoxia and, paradoxically, hypoxia. Imbalance between the generation and breakdown of ROS resulting in net gain of ROS species leads to oxidative stress and the potential for harm. Defence against hyperoxic damage has been a central theme of animal evolution. The endosymbiotic integration of primitive bacteria into early unicellular organisms led to the evolution of the mitochondrion as an intracellular organelle. This unusual amalgamation of dissimilar species both conferred protection against increasing atmospheric oxygen levels (through ROS metabolism) and facilitated respiration in host cells that had previously relied on glycolysis and fermentation as sources of chemical energy. The relationship facilitated the evolution of multicellular organisms, a development that can be considered as a sophisticated response to the challenge of defending against cellular hyperoxia.<sup>[2]</sup>

Oxygen is arguably the most widely used drug in anaesthesia and in acute hospital care in general. More than 15% of hospital admissions in the UK are being administered oxygen at any point in time.<sup>[3]</sup> Very few patients receive general anaesthesia or enter a critical care unit without receiving oxygen and there are estimated to be more than 1.5 million major (in-patient) surgical procedures requiring anaesthesia each year in the UK<sup>[4]</sup> and more than 235 000 critical care admissions.<sup>[5]</sup> Furthermore, the vast majority of patients with acute pulmonary (>2.5 million hospital bed days per year in UK)<sup>[6]</sup> or cardiac (>450 000 patients episodes per year in the UK)<sup>[7]</sup> conditions will be administered oxygen at some time during a hospital admission. More than one-third of patients brought to hospital by ambulance are administered oxygen.<sup>[8]</sup> Ultimately, the sickest patients, and therefore those at most risk of adverse outcome, are most likely to receive oxygen therapy.

The near universal use of oxygen therapy in acutely ill patients is based on the premise that minimizing cellular hypoxia is among the highest priorities of urgent care, but also rests on the assumption that excess oxygen is not harmful. Clinical data from a variety of contexts suggest that this assumption may not hold, which in turn suggests that greater attention to the precision with which oxygen is administered may be of benefit to patients. Data from clinical studies are highlighting the potential harms of unrestricted administration of oxygen to patients. For example, small clinical trials have shown increased mortality after acute myocardial infarction and ischaemic stroke in patients administering supplemental oxygen, when compared with patients receiving room air.<sup>[9–11]</sup>

Within the speciality of anaesthesia, oxygen is mainly administered under three intersecting sets of conditions: (i) perioperative care, (ii) critical care, and (iii) resuscitation. New data highlighting the complex relationship between oxygen therapy and clinical outcome are available in all three of these clinical situations.

### Perioperative Care

Several studies have recently sought to evaluate the potential benefit of oxygen in the promotion of postoperative wound healing. Early studies suggested that a high fractional concentration of inspired oxygen

$F_{I_{O_2}}$

reduced surgical site infection after major surgery, but a recent meta-analysis of seven randomized controlled trials (RCTs) incorporating 2728 patients concluded that there was no evidence of overall benefit,<sup>[12]</sup> although there was a suggestion of

benefit in two subgroups (general anaesthesia and colorectal surgery). This is consistent with results from the largest RCT in this area (the PROXI trial) which did not identify any effect on surgical site infection rates in patients receiving perioperative oxygen at 80%

$F_{I_{O_2}}$

compared with those receiving 30%

$F_{I_{O_2}}$

.<sup>[13]</sup> Intriguingly, long-term follow-up (median of 2.3 yr) of patients with cancer within this study revealed reduced survival in the high

$F_{I_{O_2}}$

group.<sup>[14]</sup> This result highlights both the potential serious harm of high concentration oxygen therapy in some groups of patients and also the variability in response between different groups of patients.

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## Critical Care

We have recently reviewed the literature related to oxygen therapy in critically ill patients.<sup>[15]</sup> Hypoxaemia is a common clinical problem in critically ill patients and few critically ill patients avoid cellular hypoxia. However, in contrast to patients undergoing major surgery, critically ill patients may have a more sustained exposure to hypoxaemia, which raises the possibility that they may adapt to it in a manner analogous to the acclimatization that occurs in healthy individuals ascending to high altitude.<sup>[16]</sup> Pulmonary oxygen toxicity, ventilator-associated lung injury, and cerebral haemorrhage after extra-corporeal membrane oxygenation are recognized adverse consequences of strategies to reverse hypoxaemia and normalize blood oxygen values. In such cases, striving to normalize arterial oxygenation may incur more harm than benefit as the interventions used have significant associated risks, and the evidence of benefit from restoring normoxaemia is limited.<sup>[17–19]</sup>

As a facet of the uncertainty about the relationship between arterial oxygenation and clinical outcome in critically ill patients, there is a lack of evidence supporting improved outcomes with better oxygenation.<sup>[20]</sup> This may be the result of complex biological interactions in critically ill patients that prevent the separation of 'signal' from 'noise' in such a heterogeneous cohort. Even in studies of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), there is no clear survival benefit from improved oxygenation. This should perhaps not be surprising when one considers that supplemental oxygen is a supportive therapy and has minimal direct effect on the underlying pathophysiology. Furthermore, hypoxaemia and cellular hypoxia are not prominent features of ARDS-related deaths.<sup>[21,22]</sup> However, recent findings suggest that hypoxaemia may be a risk factor for the development of long-term cognitive and psychiatric impairment after ALI/ARDS,<sup>[23]</sup> and this merits further investigation.

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## Resuscitation

Although there are limited available data on adult resuscitation, the data in neonates have been sufficient to alter practice guidelines. Resuscitation of neonates with 100% oxygen has been shown in several studies to result in increased mortality, myocardial and renal injury, and may be associated with adverse effects on cerebral function.<sup>[24]</sup> There are even some data to suggest an association with a higher risk of childhood leukaemia and cancer.<sup>[24]</sup> Consequently, neonatal resuscitation guidelines have now been amended to advise that the initial resuscitation is with room air, and that supplemental oxygen should be titrated according to clinical response in order to avoid hypoxaemia.<sup>[25]</sup>

In 6000 adult patients resuscitated after cardiac arrest, worse outcomes were seen after hyperoxaemia (

$Pa_{O_2}$

>300 mm Hg/40 kPa) than normoxaemia (60–300 mm Hg/8–40 kPa).<sup>[26]</sup> The authors of this retrospective (observational) study speculated that ischaemic–reperfusion damage to the central nervous system might be an important driver of the adverse outcomes seen after hyperoxaemia.

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## The Case for More Precise Oxygen Therapy

While the harms of profound hyperoxia and hypoxia are well recognized, the harms associated with lesser deviations from 'normal' arterial oxygen levels are less clear. Avoidance of arterial hypoxaemia through the administration of inspired oxygen therapy is central to the practice of acute medicine. Failure to correct hypoxaemia with therapeutic oxygen typically leads to escalation of therapy in the form of increasing the

$F_{I_{O_2}}$ 

in combination with non-invasive or invasive mechanical ventilation. Uncontrolled administration of oxygen, or deliberate prescription of a high

 $F_{I_{O_2}}$ 

, frequently results in hyperoxaemia, rather than normoxaemia, and hyperoxaemia may cause direct harm through oxidative stress (ROS generation) and cardiovascular mechanisms (e.g. coronary vasoconstriction, reduced cardiac output, and increased peripheral vascular resistance). Even if the end result of oxygen therapy is normoxaemia, the levels of inspired oxygen required to achieve this may be directly harmful to the lungs to an extent that may outweigh the benefits of fully normalizing blood oxygen levels.

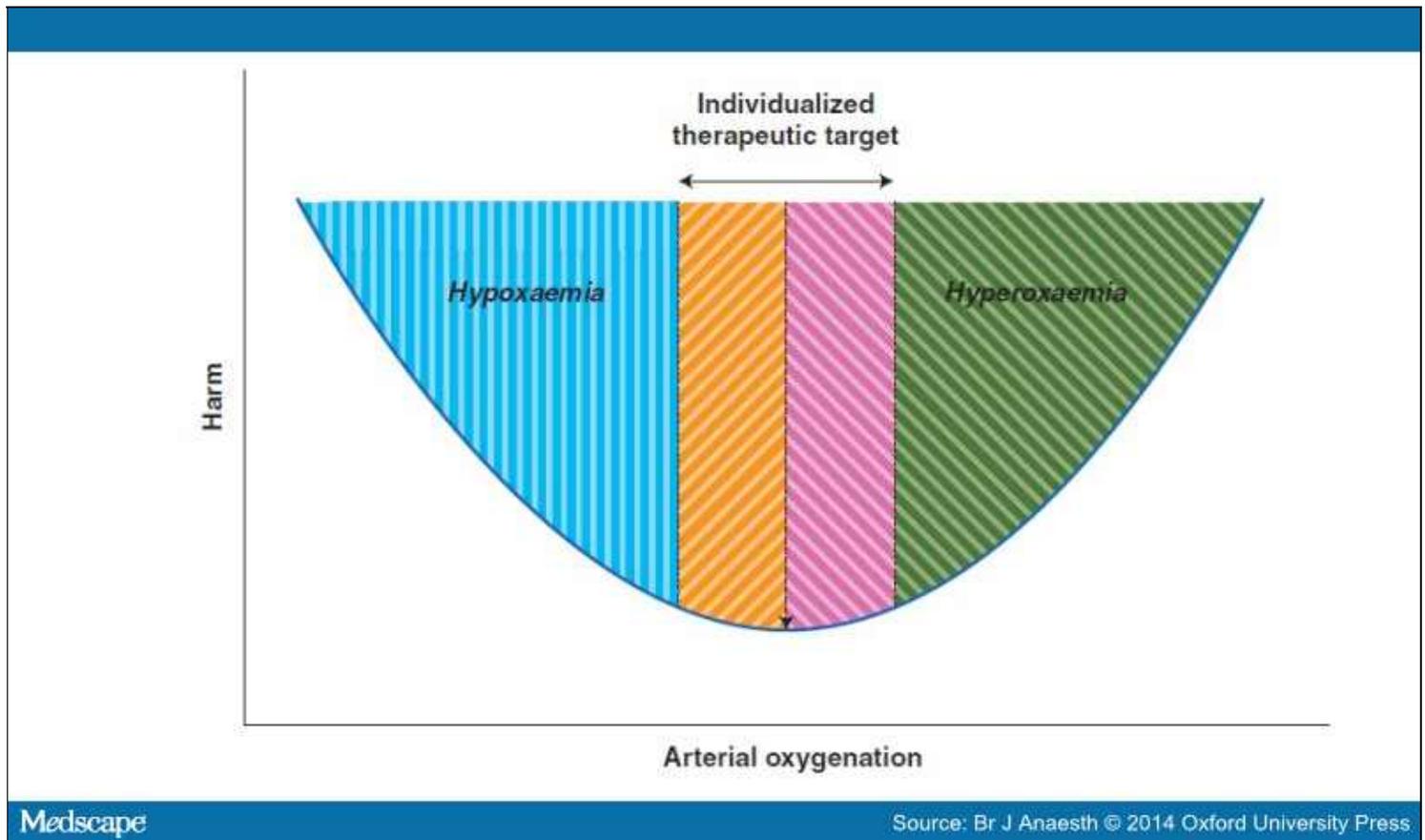
We have proposed two related, and potentially synergistic, therapeutic strategies: 'Precise control of arterial oxygenation' (PCAO) (Fig. 1) and 'Permissive hypoxaemia' (PH) (Fig. 2). The aim of PCAO is to achieve tight control of blood oxygen levels through targeting arterial oxygen partial pressure (

 $P_{a_{O_2}}$ 

) or arterial haemoglobin oxygen saturation (

 $S_{a_{O_2}}$ 

) to individualized values, with the avoidance of significant variation from these levels. PH describes the acceptance of levels of arterial oxygenation lower than conventionally tolerated in patients in order to minimize the harms of high-concentration oxygen therapy and aggressive mechanical ventilation and has previously been proposed by others.<sup>[27,28]</sup> Used together, these strategies may lead to a more controlled (and considered) use of oxygen and have the potential to provide significant patient benefit.



**Figure 1.**

A conceptual diagram of the precise control of arterial oxygenation model. An individualized oxygenation target (

 $P_{a_{O_2}}$ 

or

$SaO_2$

) is selected for a patient (dashed, arrowed line in the centre of the curve) dependent on the clinical situation. Tight margins around the target form the desired therapeutic oxygenation range (thin dashed lines). Harm may occur if oxygenation falls outside of this selected range. Adapted from Martin and Grocott,<sup>15</sup> with permission from Wolters Kluwer Health.

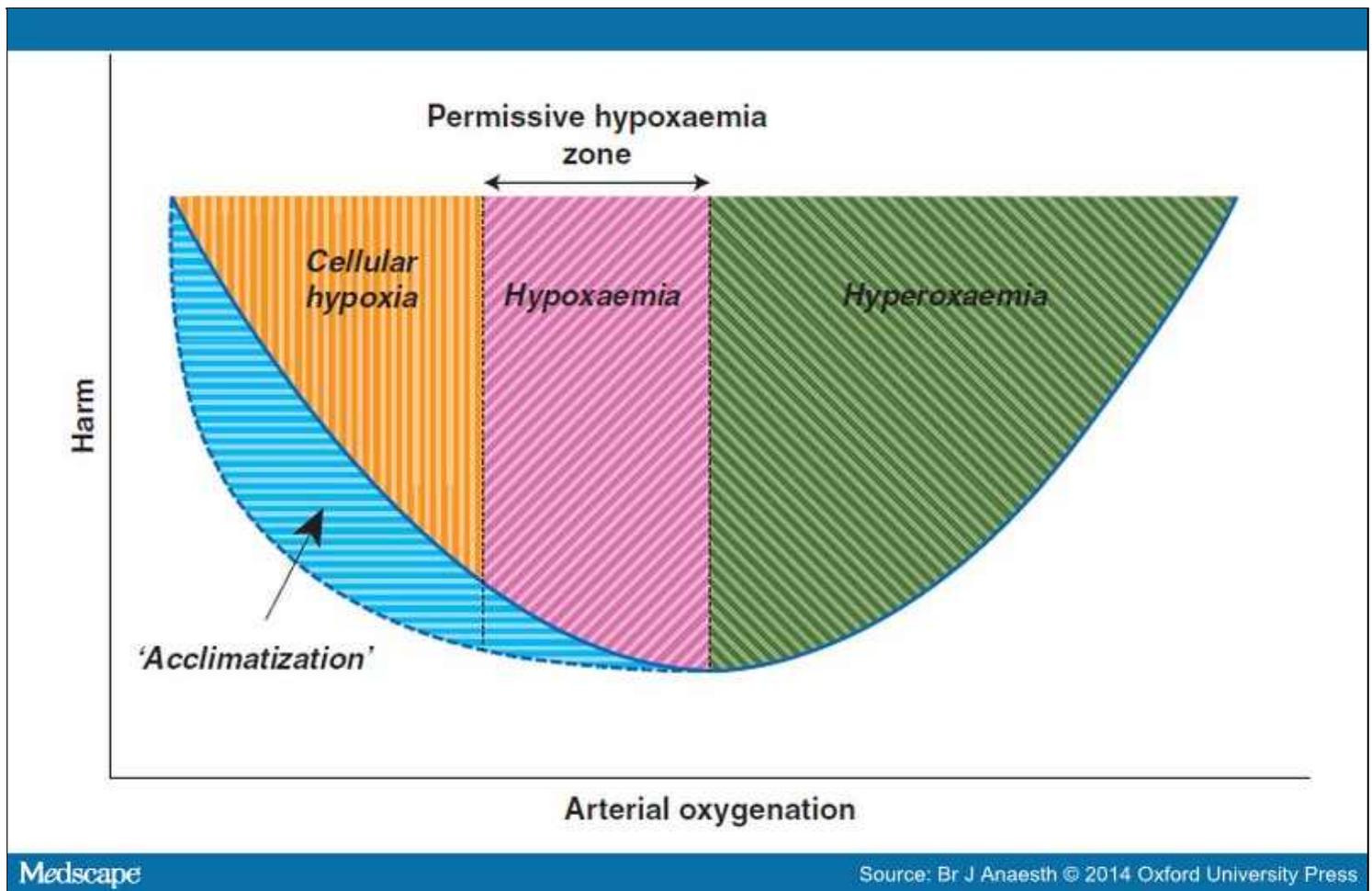


Figure 2.

A diagram demonstrating the potential reduction in harm when permissive hypoxaemia is used in conjunction with the precise control of arterial oxygenation model. Moving the therapeutic target range for oxygenation (area between thin dashed lines) to the left on this conceptual diagram has the potential for reducing harm in selected critically ill patients. This occurs through a combination of physiological tolerance of hypoxaemia (acclimatization) and the avoidance of interventions that pursue normoxaemia (which frequently lead to hyperoxaemia). Cellular adaptation to hypoxia may occur during sustained hypoxaemia, as occurs during prolonged ascent to high altitude, and may permit survival without increased harm. Adapted from Martin and Grocott,<sup>15</sup> with permission from Wolters Kluwer Health.

The concept of PCAO is analogous to our approach with other therapies that are titrated against a defined outcome (e.g. monitoring of plasma glucose during administration of i.v. insulin). The case that prescription of a patient-specific oxygenation target range (e.g. '

$PaO_2$

of 8–10 kPa',

$SaO_2$

of 88–92%) should be standard for all patients is consistent with current clinical guidelines.<sup>[29]</sup> PH is more speculative, and the risk of harm greater. Evaluation of the safety and feasibility of PH and identification of target oxygenation values and biomarkers of susceptibility and response will be needed before larger studies are contemplated. Well-designed high-quality clinical trials will be needed to assess efficacy and effectiveness, including cost-effectiveness, of the implementation of PCAO and PH, and to identify target oxygenation values and determinants of treatment effect in different patient groups.

Several work-streams will be required to develop the tools to deliver PCAO and PH safely and effectively. These include identification and development of biomarkers predicting tolerance of hypoxia and hyperoxia, biomarkers of hypoxic (and hyperoxic) harm to guide ongoing therapy, and the development of effective monitors of cellular hypoxia. The development of servo-controlled oxygen delivery devices may assist in achieving PCAO.<sup>[30]</sup> Early work identifying human biomarkers of hypoxic adaptation has been conducted in healthy volunteers exposed to environmental hypoxia at high altitude,<sup>[31]</sup> but clinical studies are only just beginning.

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## Current Clinical Guidelines

The importance of avoiding hyperoxaemia is recognized within the British Thoracic Society (BTS) guidelines on oxygen therapy.<sup>[29]</sup> These recommendations focus on the harm of inhibition of ventilation by oxygen in susceptible patients with chronic obstructive pulmonary disease (COPD), while arguably underplaying the direct harms of hyperoxaemia mediated through oxidative stress and cardiovascular effects. However, they provide a sensible middle ground based on currently available data. It may be that in time, we come to treat most patients in the same way as we now treat patients with COPD who are at risk of ventilatory failure. Consistent with the recommendations, a recent RCT in COPD demonstrated a survival benefit for patients treated with controlled oxygen therapy in comparison with those given unrestricted oxygen.<sup>[32]</sup> Intriguingly, the mortality benefit in this study seems disproportionately large, given the effect on rates of mechanical ventilation, suggesting that alternative mechanisms of harm from hyperoxia may be important in this patient group as well.

In conclusion, oxygen is essential for the survival of all higher animals, including humans. Oxygen therapy is widespread and essential in the care of acutely ill patients and as part of perioperative care. However, the assumption that unlimited oxygen therapy is without harm merits challenge; it may be possible to have too much of a good thing.<sup>[33]</sup> Data from a variety of clinical situations where anaesthetists deliver care suggest that unrestricted, and/or high concentration, oxygen therapy may be harmful and suggest the need for a fundamental re-evaluation of therapeutic goals. We should aim to get the right amount of oxygen to the right patient at the right time: the mantra of individualized (or stratified) medicine.

PH and PCAO are rational candidate strategies that we believe are likely to improve clinical outcomes. The clinical and cost-effectiveness of these strategies is uncertain and requires careful evaluation. While implementation of PCAO is consistent with current clinical guidelines and unlikely to be associated with harm, implementation of PH is more speculative (and potentially harmful) and evaluation of the safety and feasibility of this approach in perioperative and critical care settings is needed before clinical trials are contemplated. Development of biomarkers of susceptibility and tolerance of hypoxia and hyperoxia, including monitors of cellular oxygenation and oxidative stress, will be needed to underpin these studies. Addressing these challenges should be a research priority for our community.

In the meantime, current recommendations for oxygen therapy are a useful guide for clinicians at the bedside. The laudable goal of improving patient outcomes through carefully targeted administration of oxygen offers opportunities for innovation in devices, diagnostics, and therapies.

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#### **Authors' contributions**

D.S.M.: concept and writing of manuscript; M.P.W.G.: concept and writing of manuscript.

#### **Declaration of interest**

None declared.

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