2024-06

Perioperative oxygenation-what's the stress?

Larvin, J

10.1016/j.bjao.2024.100277
BJA Open
Elsevier BV

BJA Open

BJA Open, 10 (C): 100277 (2024)

doi: 10.1016/j.bjao.2024.100277
Review Article

REVIEW ARTICLE

Perioperative oxygenation—what's the stress?

Joseph Larvin[1,2], Mark Edwards[1,2], Daniel S. Martin[3], Martin Feelisch[1,2], Michael P. W. Grocott[1,2] and Andrew F. Cumpstey[1,2,*]

[1]Perioperative and Critical Care Theme, NIHR Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, UK, [2]Clinical & Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK and [3]Peninsula Medical School, University of Plymouth, Plymouth, UK

*Corresponding author. Perioperative and Critical Care Theme, NIHR Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, UK. E-mail: a.cumpstey@soton.ac.uk

Summary

Oxygen is the most used drug in anaesthesia. Despite such widespread use, optimal perioperative oxygen administration remains highly controversial because of concerns about the competing harms of both hyperoxia and hypoxia.

Notwithstanding a Cochrane review concluding that routinely administering a fractional inspired oxygen concentration (FiO_2) >0.6 intraoperatively might increase postoperative morbidity and mortality, the World Health Organization (WHO) currently recommends all anaesthetised patients receive 0.8 FiO_2 during and immediately after surgery to reduce surgical site infections. Results from the largest trial available at the time of these two reviews (suggesting long-term survival may be worse with high FiO_2, particularly in patients with malignant disease) were considered 'biologically implausible' by the WHO's Guideline Development Group. In addition, the integrity of some perioperative oxygen studies has been challenged. Resolving these controversies is of fundamental importance to all perioperative clinicians.

This narrative review is based on the inaugural *BJA* William Mapleson lecture delivered by the senior author (AC) at the 2023 annual meeting of the Royal College of Anaesthetists in Birmingham. We present the current evidence for perioperative oxygen administration and contrast this with how oxygen therapy is targeted in other specialties (e.g. intensive care medicine). We will explore whether anaesthetists follow the WHO recommendations and consider how oxygen administration affects the stress response to surgery. We reason that novel clinical trial designs in combination with targeted experimental medicine studies will be required to improve our understanding of how best to optimise individualised perioperative oxygenation—a cornerstone of anaesthesia.

Keywords: hyperoxia; hypoxia; oxidative stress; oxygen therapy; surgical site infections

Oxygen is the most commonly used drug during the perioperative period. For most surgical procedures, oxygen exposure typically begins before the induction of anaesthesia, and in emergency cases patients may already be receiving additional oxygen well in advance of meeting their anaesthetist. Oxygen supplementation normally continues throughout the intraoperative period and after surgery at least into the recovery room. However, titration of perioperative oxygen is often rudimentary at best, and how anaesthetists should balance the benefits and risks of different oxygen concentrations remains unclear.[1]

This narrative review will examine the existing guidelines, evidence, and associated controversies that surround perioperative oxygen therapy and contrast practices in anaesthesia with those of other medical specialties. The current evidence base surrounding the outdated tropes of 'oxygen is good' and 'hypoxia is bad' will be revisited, highlighting the complexities that are missed by a 'one size fits all' approach. This will include a discussion of the mechanistic effects of oxygen at the cellular level, where the potential for causing harm is brought into sharp focus. Finally, we will explore the directions that future work must take if anaesthetists are to

Received: 21 November 2023; **Accepted:** 1 March 2024

attain clarity regarding a subject that is of fundamental importance to all clinicians involved in perioperative patient care.

World Health Organization recommendations and the 30–80% dogma

Oxygen is crucial for optimal cellular and organ function in humans; insufficient oxygen supply can have potentially catastrophic consequences.[2] Under general anaesthesia, pathophysiological changes occur that may impair the body's ability to oxygenate blood, including altered respiratory muscle function, reduced functional residual capacity, development of atelectasis, disturbance of ventilation–perfusion relationships and the development of hypercapnia.[3] The extent to which these occur depends on factors such as the type of anaesthetic, the use of spontaneous or mechanical ventilation, and the duration of the procedure. Traditionally, clinicians' almost exclusive focus has been on the maintenance of oxygen delivery, often through supra-normal oxygenation to achieve a 'safety-margin' and guard against hypoxia.

Over time, the discussion has evolved to encompass potential benefits of different oxygen concentrations, but there remains no clear consensus from the research/perioperative community about the best strategy for oxygen supplementation during surgery.[4] For a drug that is both so widely prescribed and so vital to the care of surgical patients, this is unusual. Part of the reason is the conflicting evidence and controversies that this research area has been embroiled in over the last decade.[5–7] One of the major arguments used to advance the cause for delivering a higher FiO_2 (typically >0.6) intraoperatively has been the potential for this approach to lower the incidence of surgical site infections (SSIs).[8] The scientific premise to this approach is that neutrophils, one of the body's primary defences against bacterial infection, use oxidative killing to combat pathogens.[9] Classical teaching would suggest that increasing FiO_2 should not directly increase convective oxygen flux, other than by a very small amount related to oxygen dissolved in plasma. According to the 'oxygen delivery equation', oxygen delivery, or more correctly oxygen flux, is the product of cardiac output and arterial oxygen content (CaO_2). CaO_2 is defined as the volume of oxygen per volume of blood and is predominantly determined by haemoglobin concentration and oxygen saturation rather than the partial pressure of oxygen (Pa_{O_2}). Moreover, the relationship between FiO_2 and Pa_{O_2} is also dependent on the effectiveness of pulmonary gas exchange (determined by the degree of hypoventilation, diffusion limitation, V/Q mismatching and shunting present).[10] However, studies using both hypoxic and hyperbaric oxygen interventions have demonstrated that NADPH oxidase enzymes driving the 'respiratory burst' (the process that generates superoxide anions [$O_2^{\bullet-}$] and other reactive oxygen species [ROS] to fulfil the antimicrobial function of neutrophils) depend on Pa_{O_2} and not CaO_2.[8,11,12] Therefore, increasing FiO_2 could potentially increase bactericidal respiratory burst activity and reduce SSIs.

Early trials appeared to support this notion. In 2000, Greif and colleagues[13] reported a statistically significant reduction in the rate of SSIs in patients undergoing colorectal surgery administered an FiO_2 of 0.8 compared with an FiO_2 of 0.3 intraoperatively and 2 h after surgery {5.2% (95% confidence interval [CI] 2.4–8.0%) *vs* 11.2% (95% CI 7.3–15.1%), P=0.01}. Further studies soon followed with many also reporting a significant benefit in preventing SSIs when using a higher concentration of oxygen.[14,15] Interestingly, there is no justification for why the FiO_2 values of 0.8 and 0.3 were chosen to represent 'high' and 'low' concentrations of oxygen anywhere in Greif and colleagues' report,[13] and the so-called 'low' (FiO_2=0.3) group still represents a 'liberal' amount of supplemental oxygen when compared with room air (FiO_2=0.21). Yet, these two set FiO_2 values of 0.3 and 0.8 have repeatedly defined the interventional groups used in almost every perioperative oxygen trial conducted since.

In 2016, a World Health Organization (WHO) Guideline Development Group (GDG) (that notably did not include any anaesthetic representation) systematically reviewed the available evidence. This group recommended that adult patients undergoing general anaesthesia with tracheal intubation for surgical procedures should receive an FiO_2 of 0.8 intraoperatively and, if feasible, in the immediate postoperative period for 2–6 h to reduce the risk of SSI.[16]

The WHO *vs* Cochrane controversy and the importance of PROXI

This 2016 WHO recommendation was a stark contradiction to the conclusions published by a Cochrane systematic review just a few months earlier, which concluded that there was 'insufficient evidence to support the routine use of a high fraction of inspired oxygen during anaesthesia and surgery'.[17] The WHO's recommendation also provoked strong reactions from many in this field who criticised the recommendation for being too general and cited several methodological issues with the review; including the omission of additional relevant studies.[7,18,19] The reliability of some of the included studies was also questioned. Specifically, one group had been forced to retract several publications not focussing on oxygen because of research fraud, raising doubts over the data integrity of their oxygen therapy studies.[6,20]

The results of the PROXI trial, still currently the largest randomised trial of perioperative oxygenation to have fully reported, were also questioned by the WHO's 2016 GDG who felt there was no plausible biological mechanism to explain results indicating that long-term survival may be better with normal oxygenation, particularly in patients with malignant disease.[7] This randomised study included 1400 patients undergoing elective or emergency laparotomy in Danish hospitals to receive an FiO_2 of 0.8 or 0.3 during and for 2 h after surgery and found no difference in SSI rates between the two groups (odds ratio [OR] 0.94, 95% CI 0.72–1.22, P=0.64).[21] Thirty-day mortality was noted to be higher in the FiO_2 0.8 group but this was not significant (30 [4.4%] *vs* 20 [2.9%], OR 1.56, 95% CI 0.88–2.77, P=0.15). However, later analysis showed that long-term mortality (median 2.3, range 1.3–3.4 yr) was significantly higher overall in the FiO_2 0.8 group (hazard ratio [HR] 1.30, 95% CI 1.03–1.64, P=0.03), predominantly because of an effect seen in patients undergoing cancer surgery (HR 1.45, 95% CI 1.10–1.90, P=0.009).[22] Further *post hoc* analyses also reported significantly higher incidences of postoperative myocardial infarction (HR 2.86, 95% CI 1.10–7.44, P=0.03) and shorter durations of cancer-free survival (HR 1.19, 95% CI 1.01–1.42, P=0.04) in the FiO_2 0.8 group.[23,24] Other registry studies have also since associated high FiO_2 with a dose-dependent increase in major postoperative respiratory complications (OR 1.99, 95% CI 1.72–2.31, P<0.001) and 30-day mortality (OR 1.97, 95% CI 1.3–2.99, P<0.001).[25]

In 2018, the WHO GDG re-reviewed the evidence and reported separately on both the safety and effectiveness of administering an FiO_2 of 0.8 to reduce SSI in adult patients undergoing general anaesthesia in two simultaneously published systematic reviews.[26,27]

These concluded that no definite signals of harm or benefit could be detected using an FiO_2 of 0.8. There was some evidence a high FiO_2 may be beneficial in patients undergoing general anaesthesia specifically with tracheal intubation, however the certainty of this benefit had become weaker since the 2016 recommendation. Consequently, the wording of the 2018 iteration of the WHO guideline remained unchanged aside from downgrading the strength of the recommendation to a 'conditional recommendation, moderate quality of evidence'[28] (see Fig. 1).

Alongside this development, the Centers for Disease Control and Prevention (CDC) issued a guideline supporting the use of high FiO_2 in intubated surgical patients,[29] whilst other groups, including the British Thoracic Society and the World Federation of Societies of Anaesthesiologists, have continued to advocate a more conservative approach (with the latter also considering the unnecessary added acquisition costs of both oxygen and delivery systems).[30,31] Consequently, guidelines for perioperative oxygen supplementation remain conflicting with no certainty on the approach anaesthetists are choosing to follow in their routine practice (see Fig. 2).

Routine perioperative oxygenation—current anaesthetic practice

In 2017, a large group of anaesthetic trainees conducted a multicentre retrospective observational study in the UK examining the anaesthetic records of 387 patients having surgery requiring arterial cannulation over a 5-day period across 29 participating centres.[32] There was significant variation in the FiO_2 delivered to patients, with the recorded intraoperative FiO_2 ranging from 0.25 to 1.0. Consequently, there was also substantial variation between patients in the Pao_2, the majority of which were above resting physiological values. The median FiO_2 was around 0.5, and this remained consistent across sequential blood gases, with the interquartile range of all recorded arterial blood gas values being 0.4–0.55. The authors concluded that an FiO_2 of ~0.5 represented the standard intraoperative practice for this cohort of patients, alongside a median Pao_2 of 24.7 kPa. These UK results are consistent with wider international practice, as shown in Table 1. A survey of members of the European Society of Anaesthesiology and Intensive Care reported that only 24% of the 798 respondents knew of and followed the WHO's recommendations on perioperative oxygenation.[37]

Although significant variation in practice exists with regards to intraoperative oxygen therapy, the median FiO_2 delivered is consistently found to be ~0.5 internationally. This does not align with any guidelines or recommendations and lies midway between the two FiO_2 values that have been extensively evaluated in trials (0.3 and 0.8), and which now appear to represent relative extremes of what anaesthetists have been shown to deliver in practice.

Oxygen—always a good thing?

The issue of targeting oxygen therapy is not unique to anaesthesia; alongside its use in chronic illness, supplemental oxygen is central to the clinical management of many acutely unwell patients. Approximately 34% of patients in ambulances receive some form of supplemental oxygen, as do around 15% of hospital inpatients in the UK.[38,39] Clear guidelines exist for the management of acutely unwell medical patients, but unlike the perioperative practice of delivering a set FiO_2, more commonly these take the form of targeting a level of oxygenation in the patient (e.g. peripheral oxygen saturation, Spo_2).

However, in 2018 the Improving Oxygen Therapy in Acute Illness (IOTA) systematic review and meta-analysis challenged the assumption that giving more oxygen is always the safest thing to do.[40] This analysis concluded that for acutely ill adults, high-quality evidence shows that liberal oxygen therapy *increases* mortality without improving other outcomes, and supported the use of conservative oxygen therapy. It is difficult to extrapolate these findings to specific groups as the 25 trials included in the analysis encompassed a heterogeneous population of patients. In the perioperative cohort, elective surgical patients were excluded, and emergency surgery cases only represented 1.7% of the total patients analysed. Furthermore, a more recent systematic review and meta-analysis that used trial sequential analysis to account for risk of bias, found no effect from liberal oxygen targets on mortality or other secondary outcomes.[41]

The British Thoracic Society have not issued new guidelines since the publication of the IOTA review although they are due to review their guidelines imminently. Currently though they recommend a target Spo_2 of 94–96% for most acutely ill patients not at risk of hypercapnic respiratory

4.12 Perioperative oxygenation

Recommendation

The panel suggests that adult patients undergoing general anaesthesia with tracheal intubation for surgical procedures should receive an 80% fraction of inspired oxygen (FiO_2) intraoperative- ly and, if feasible, in the immediate postoperative period for 2–6 h to reduce the risk of SSI.
(Conditional recommendation, moderate quality of evidence)

Fig 1. The 2018 recommendation for perioperative oxygenation from the World Health Organization's global guidelines for the prevention of surgical site infections. SSI, surgical site infection.

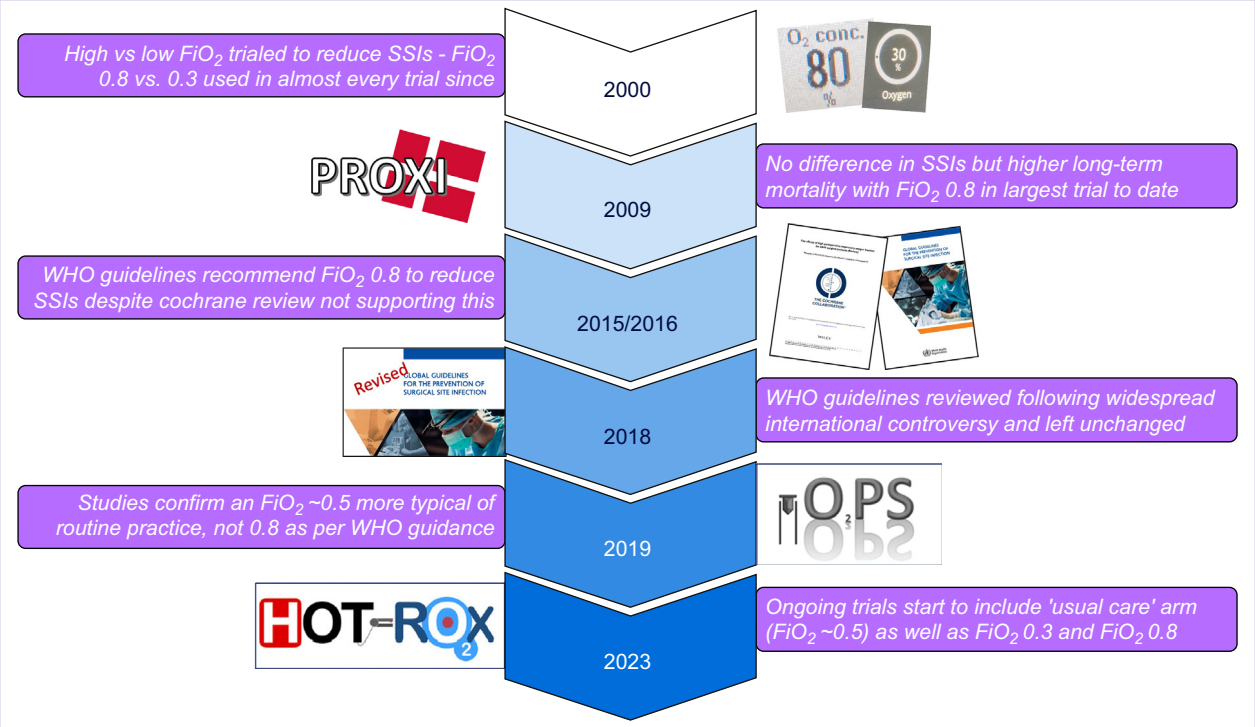

Fig 2. Timeline summarising some of the key events in more than two decades of research investigating the effect intraoperative oxygen administration has on surgical site infections (SSIs). After the first study exploring if 'high' (0.8) FiO_2 might reduce SSI rates compared with 'low' (0.3) FiO_2 reported in 2000, long-term follow-up of patients in the Danish PROXI trial suggested higher rates of adverse outcomes (including higher mortality) with 0.8 FiO_2. The World Health Organization (WHO) recommendations were first published in 2016 and reviewed again in 2018, shortly before several studies reported that anaesthetists often do not follow these recommendations internationally. More recent trials (e.g. the Australasian HOT-ROX) are now including a 'usual care' arm (i.e. FiO_2 around 0.5) and 'high' and 'low' groups.

failure.[30,42] The Thoracic Society of Australia and New Zealand (in guidelines issued more recently) are slightly more conservative, recommending an Spo_2 of 92–96% for most acute medical conditions, and 88–92% for patients with chronic obstructive pulmonary disease (COPD) and other conditions associated with chronic respiratory failure, with supplemental oxygen only to be administered when the Spo_2 is below the lower limit of the appropriate range.[43]

Throughout their training, clinicians are repeatedly taught to reach for the oxygen *first* in situations of uncertainty or in emergencies, and with good reason; brain tissue may have a hypoxia tolerance of <3 min.[44] However, this has led to the rhetoric that 'oxygen is good' and 'hypoxia is bad' becoming so deeply engrained in the mind of healthcare professionals that it can be difficult to challenge these two reductionist statements even though the reality is considerably more nuanced.

Supplemental oxygen may bring benefits beyond preventing hypoxic damage. For example, hyperoxia has received attention as a proposed strategy for reducing postoperative nausea and vomiting (PONV). One proposed mechanism is that hyperoxic conditions may reduce the occurrence of subclinical intestinal ischaemia and the subsequent release of mediators such a serotonin.[45] Another is that hyperoxia may result in a central antinausea effect through reducing the release of dopamine from the carotid bodies.[46] Multiple trials testing these hypotheses have been conducted with conflicting results. Two large systematic reviews and meta-analyses have found no evidence for hyperoxia reducing PONV,[47,48] whereas another found a small benefit for late nausea, in addition to a more pronounced effect on PONV for a subgroup of patients undergoing inhalation anaesthesia without a prophylactic antiemetic.[49] The most recent iteration of the consensus guidelines for the management of PONV do not recommend the use of supplemental oxygen for this purpose.[50]

The 2015 Difficult Airway Society guidelines advocate pre-oxygenating all patients with oxygen 100% before induction and emergence from anaesthesia to build a reserve in the lungs in case of unanticipated airway difficulty.[51] Similarly, administration of warm humidified high-flow nasal oxygen (e.g. transnasal humidified rapid-insufflation ventilatory exchange, THRIVE) has been shown to extend apnoea times significantly and high-flow nasal oxygen devices are now commonly used in many anaesthetic rooms and intensive care units.[52]

One patient group with a larger evidence base is the critically ill. Large retrospective observational studies in Dutch intensive care units reported that in-hospital mortality was strongly associated with both low and high Pao_2 during the first 24 h of intensive care admission.[53] Furthermore, the probability of death increased both with longer duration of hyperoxic exposure and with higher average Pao_2 values

Table 1 Summary of selected studies that describe international typical intra-operative oxygen administration and resulting oxygenation levels in adults during general anaesthesia. IQR, inter-quartile range.

Authors	Year(s) analysed	Location	Method	Study population	Size (*n*)	Administered FiO_2
Staehr-Rye and colleagues[25]	2007–2014	USA (Massachusetts)	Registry study of three hospitals	Non-cardiothoracic surgery with tracheal intubation	73 922	Median FiO_2 0.52 (1st–5th quintile medians 0.31–0.79) Median Spo_2 100% (1st–5th quintile medians 99–100)
LAS VEGAS investigators[33]	2013	International (29 countries)	Prospective, observational study of pulmonary complications	Surgeries not requiring one-lung ventilation or cardiopulmonary bypass	9413	Median FiO_2 0.52 (IQR 0.45–0.70) Median Spo_2 99.0% (IQR 98.0–100.0)
Karalapillai and colleagues[34]	2014–2017	Australia	Retrospective single-centre cohort study	>40 yr of age, major surgery (exclusions included cardiac, intracranial and one lung) anticipated to take >2 h, with tracheal intubation and arterial cannulation	373	Median lowest FiO_2 0.45 (IQR 0.4–0.5) Median highest FiO_2 0.7 (IQR 0.5–0.96) Median pre-emergence Pao_2 25 kPa (IQR 19–32)
Suzuki and colleagues[35]	2015	Japan	Cross-sectional, multicentre study	Surgeries >1 h, requiring mechanical ventilation, and no cardiopulmonary bypass or extracorporeal membrane oxygenation in first hour	1498	Median FiO_2 0.47 (IQR 0.4–0.6) Median Spo_2 100% (IQR 0.4–0.6)
Morkane and colleagues[32]	2017	UK	Retrospective multicentre observational study	Operations not requiring cardiopulmonary bypass and necessitating an arterial cannula, with blood gas monitoring	378 Cases	Median FiO_2 0.50 (IQR 0.41–0.55) Median Pao_2 24.7 kPa (IQR 17.9–30.8)
Frei and colleagues[36]	2020–2021	Australia and New Zealand	Prospective multicentre observational study	Non-cardiothoracic surgery for ASA 3 or 4 patients, anticipated to be ≥120 min and ≥1 postoperative night stay	150 Anaesthetists	Median FiO_2 0.47 (IQR 0.40–0.55) Median Spo_2 98.3% (97.5–99.2)

across the length of stay.[54] Following this, several large pragmatic interventional trials have been conducted. The ICU ROX and HOT ICU studies both showed no difference in mortality with either conservative or higher oxygen targets.[55,56] However, the LOCO$_2$ trial was stopped prematurely after five patients in the conservative oxygen group (target Spo_2 88–92% or Pao_2 55–70 mm Hg) developed mesenteric ischaemia.[57] A large meta-analysis of these interventional trials comparing high *vs* low oxygen targets in ICUs was unable to draw clear conclusions about the effect on all-cause mortality.[58] However, this may have been complicated by the fact that definitions of 'high' and 'low' oxygen targets have become progressively more conservative.[56,57,59] A meta-analysis accounting for this tendency towards more conservative targets reported that the highest oxygen targets were associated with higher mortality at longest follow-up, supporting the presence of a 'U-shaped' effect on mortality as originally suggested by the earlier retrospective reviews.[60,61]

Similar concerns have been raised in other areas of medicine. In patients with a myocardial infarction, hyperoxia has been associated with increased risk of a repeat myocardial infarction and ventricular arrythmia.[62] Hyperoxia also decreases systemic and coronary blood flow and consequently reduces tissue oxygen consumption.[63–65] Current guidelines now advocate treating normoxaemic patients suffering an acute myocardial infarction with air and not supplemental oxygen.[66] Guidelines for neonatal resuscitation also recommend using room air initially as this is associated with a reduction in mortality without any evidence of other harm.[67] Hyperoxia has also been associated with adverse outcomes after out-of-hospital cardiac arrest in adults,[68] and after stroke.[69]

Mechanisms of oxygen toxicity—just oxidative stress?

Hyperoxaemia (i.e. high blood oxygen concentrations) may mediate harm through its systemic vasoconstricting effect (reversed in the pulmonary and placental circulations) and a decrease in an individual's heart rate. These changes are associated with a decrease in cardiac output and a potential reduction in the delivery of oxygenated blood to tissues. However, excessively high FiO_2 may also induce intense inflammation in the lungs, or in cells in other tissue beds, even in the absence of hyperoxaemia (e.g. in patients with acute respiratory distress syndrome [ARDS] who may still have a low Spo_2 despite receiving a high FiO_2).[70] ROS may have an important role in triggering these changes. Oxygen is the 'terminal acceptor' in the mitochondrial electron transport chain (ETC); an essential process for the release of a cell's universal energy currency, adenosine triphosphate (ATP). Here, oxygen is reduced to water, but the efficiency of electron transfer along the ETC is not 100%. Both electron and proton leaks occur physiologically and are responsible for the generation of ROS, specifically the leakage of incompletely reduced oxygen in the form of superoxide anions ($O_2^{\bullet-}$).[71] Superoxide then undergoes spontaneous and enzyme-catalysed dismutation to form hydrogen peroxide (H_2O_2) and oxygen.[72] Although $O_2^{\bullet-}$ and H_2O_2 are the two most abundant ROS and can exert their effects directly, their interactions with metals and other biomolecules can produce additional species with far greater reactivity, including the hydroxyl radical($^{\bullet}OH$) and singlet oxygen ($^1O_2$), see Fig. 3.

The proposed mechanism for oxygen's vasoconstricting effect is the scavenging reaction of superoxide with nitric oxide (NO) to form peroxynitrite ($ONOO^-$), which reduces the bioactivity of NO.[73] This reaction not only reduces the bioavailability of an endogenous vasodilator, but also changes the chemistry of the cellular microenvironment as peroxynitrite is a powerful thiol oxidant that also engages in nitrosation and nitration reactions.[74] In addition, ROS react with protein and non-protein thiols (including glutathione and hydrogen sulfide, H_2S), leading to the formation of various oxidation products. This greater complexity is captured by the 'reactive species interactome' conceptual framework and may contribute to the system-wide effects of COVID-19 and other viral infections, and affect many other bodily functions linked to electron exchange (redox) processes, including immune function, metabolism, and nutrient utilisation.[75,76]

We are still learning about the physiological and pathophysiological roles of ROS, a family of molecules which were initially regarded as solely harmful. The potential consequences of their overproduction include damage to biological structures such as DNA and RNA, the impairment of repair systems for these molecules, lipid peroxidation, direct interference with protein function, and cell death.[77] In addition, ROS have also been implicated in inflammatory processes and disease, including the development of atherosclerosis.[78] However ROS have also been demonstrated to play key messenger roles in intracellular pathways,[79–82] and as described previously, serve an important function in the killing of microbes by phagocytes.[9] Antioxidant systems play a vital role in regulating the concentration of different redox species and it is the balance of these, along with the level of ROS production, which determines the consequences for individual cells and the organism as a whole.[83,84] When conditions result in antioxidant mechanisms becoming overwhelmed, this balance is tipped in favour of the oxidants, causing oxidative stress.[71,85] One factor that dynamically modulates the level of ROS produced is the local oxygen

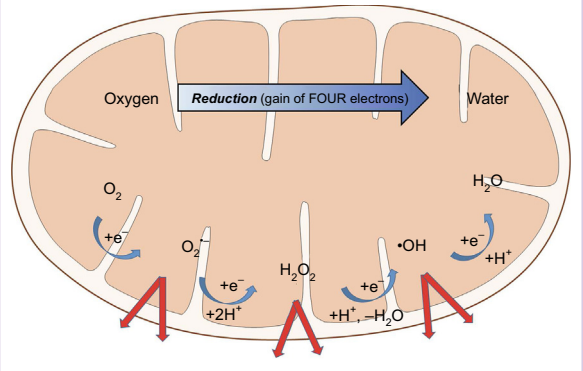

Fig 3. Oxygen is fully reduced to water by gaining four electrons (blue arrows) in the mitochondrial respiratory chain (top line). Incomplete oxygen reduction results in the production of the reactive intermediates superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($^{\bullet}OH$), respectively. These intermediates can go on to react with other cell constituents (red arrows) such as metal ions (e.g. Fe^{2+} in haemoproteins), thiols (e.g. glutathione) or compounds in the cell nucleus (e.g. DNA).

tension. Although decreased oxygen delivery to mitochondria does lead to less oxygen being available to accept electrons, this does not necessarily translate into less ROS generation. Hypoxic conditions can also simultaneously lead to a reduction in the efficiency of electron transfer along the ETC and thereby paradoxically increase ROS production.[86]

Hypoxia—always a bad thing?

Hypoxia describes an insufficiency of oxygen at the tissue level to meet the metabolic demands of individual cells. Unrecognised and uncorrected perioperative hypoxia poses a threat to life. Of Barcroft's four types of hypoxia,[87] hypoxaemic hypoxia (a low Pa_{O_2}), is the form most commonly encountered intraoperatively. Prior to the increased use of pulse-oximetry in the 1980s and the subsequent development of monitoring standards in the 1990s, hypoxaemia was the leading cause of anaesthesia-related mortality.[88] Despite these safety advances, hypoxaemia remains a relatively common occurrence in operating theatres. A retrospective study of 95 407 records from two large centres in the United States looked at episodes of hypoxaemia and severe hypoxaemia during anaesthesia, which were defined as $\geq$2 min of an Sp_{O_2} of <90% and $\leq$85%, respectively.[89] Their findings showed that 6.8% of patients experienced an episode of hypoxaemia, and this was severe for 3.5%, with these episodes lasting $\geq$5 consecutive minutes in 1.6% and 0.8% of patients, respectively. How these transient hypoxaemic episodes correlate to hypoxia at the tissue level remains unclear, as does their clinical impact.

The body's response to hypoxia is multifaceted as illustrated by successful acclimatisation to high altitude.[90] Chemoreception leads to several responses from many body systems, including the respiratory, sympathetic nervous, cardiovascular, and microvascular systems. Each of these responses is dependent on the magnitude and temporality of the triggering exposure. Hypoxia-inducible factors (HIFs) act as intracellular sensors and are crucial to achieving oxygen homeostasis. These transcription factors promote the expression of several hundred other genes including erythropoietin, angiogenic, and vasoactive mediators, and metabolic enzymes that optimise oxygen demand and energetic balance. Under normoxic conditions, destruction of HIFs is mediated by the Von Hippel–Lindau protein (VHL), ubiquitination, and proteolysis. Hypoxia prevents this degradation and allows HIF-activated transcription of these other proteins to occur.[91] When successful, these responses allow acclimatised individuals to function well with remarkably low Pa_{O_2} values (e.g. mean 3.28 kPa, range 2.55–3.93 kPa at 8400 m on Mt Everest), values well below what would usually be considered compatible with survival in a clinical perioperative or critical care context.[92]

Tibetan Sherpas, highly adapted and able to perform exceptionally well under hypobaric hypoxic conditions at high altitude, have evolved mechanisms to enhance tissue oxygen utilisation (i.e. metabolic adaptation) as well as enhancing tissue oxygen delivery.[93] These include reduced skeletal muscle capacity for fatty acid oxidation, improved muscle energetics, and protection against oxidative stress. Lowlanders appear to develop similar responses over prolonged altitude exposures; reducing muscle mitochondrial volume density and downregulating ETC complexes possibly to mitigate against ROS production,[94] with the stress response also appearing to be unique to each individual.[95]

High altitude/hypoxia pre-acclimatisation is already commonly used to improve athletic performance, and its therapeutic potential continues to be explored.[96] In a small randomised double-blind study, 15 sessions of passive intermittent hypoxia (FiO_2 0.10–014), across 3 weeks, compared with normoxia, was shown to increase peak oxygen consumption by +6.2% *vs* −3.0% (P<0.001).[97] Additionally, similar intermittent hypoxic training (IHT) has been shown to reduce blood pressure in hypertensive patients,[98] assist in weight loss (when alongside simultaneous exercise),[99] and enhance glucose homeostasis.[100] More specifically, HIT has been associated with lower fasting glucose concentrations, improved oral glucose tolerance test results, and remission from prediabetes.[101] HIFs are thought to be driving these effects.[102,103]

Other potential therapeutic roles for hypoxia include the treatment of mitochondrial disease such as Leigh syndrome, which results in neurodegeneration and death, often before the age of 3 yr. Compared with controls breathing room air (FiO_2 0.21), mouse models of this condition reared in FiO_2 0.11 at normal atmospheric pressure (normobaric hypoxia) extended their overall median survival from 58 days to 270 days (P<0.0001), whilst rearing these mice in FiO_2 0.55 dramatically reduced survival.[104] This suggests that patients with mitochondrial disease may be highly sensitive to oxygen toxicity, with hypoxia either facilitating repair mechanisms by removing the upstream cause of damage or directly promoting repair mechanisms. Hypoxia may trigger adaptive programs that the disease itself does not, and the altered interaction with other reactive species may also be important.

The above examples together illustrate the folly of a reductionist approach that labels hypoxia universally as 'bad.' The type, magnitude, and duration of hypoxia, in combination with the context in which it is experienced and several patient-specific factors, all are key determinants of its eventual impact, as is the individual sensitivity to the hypoxic exposure.

Steps towards personalising perioperative oxygen therapy?

A one-size-fits-all approach is rarely the answer to patients' problems in modern medicine, and we have known for many decades that individual responses to oxygen administration vary. After World War II, experiments exploring the tolerance to increased (hyperbaric) oxygen tensions showed that the time it took for fit young male participants to show signs of oxygen toxicity (nausea, vertigo, lip twitching, paraesthesia, vomiting, convulsions) ranged from 6 to 96 min.[105] Another recent trial in patients undergoing coronary artery bypass grafting concluded that the response of biventricular systolic variables to an FiO_2 of 0.8 was dependent on their systolic function when receiving an FiO_2 of 0.3.[106] In patients with a poorer left ventricular (LV) global longitudinal strain (GLS) than the derived cut-off receiving an FiO_2 of 0.3, systolic function improved with higher FiO_2 (P<0.01). However, the opposite response occurred in patients with LV GLS better than the derived cut-off whilst receiving an FiO_2 of 0.3.[106]

Identifying and targeting these different responses and sensitivities to oxygen poses a challenge for perioperative physicians. Although a brief 10-min exposure to oxygen 100% (delivered as preoxygenation before a sedative procedure in the emergency department) decreases cardiac output by at least 10% in ~25% of patients, it was not possible for clinicians to identify this 'at risk' subgroup of patients from physical

examination or any patient data.[107] Most pulse oximeters cannot measure hyperoxaemia, by definition the Spo_2 scale stops at 100% and any increase in a patient's oxygenation level beyond this value cannot be detected without invasive and intermittent arterial blood sampling. New biomarkers of oxygen tolerance, sensitivity, and toxicity are urgently needed, along with new technology and monitoring devices to measure them.

As discussed above, although observational studies have demonstrated a dose response to oxygen's effects on bodily functions, few interventional studies have been designed in an optimal way to detect a similar effect. Whilst large pragmatic RCTs carry many methodological advantages, only comparing an arbitrary 'high' (e.g. an FiO_2 of 0.8) to an arbitrary 'low' (typically an FiO_2 of 0.3) allows no assessment of effective titration and neither of these commonly studied FiO_2 levels represent the amount most commonly delivered by the majority of anaesthetists in routine practice. The HOT-ROX trial, developed in Australia and New Zealand, has recently reported its pilot data confirming the feasibility of recruiting and randomising to three different interventional groups (restricted, usual care, or liberal oxygen therapy).[108] However, even if the HOT-ROX trial does eventually produce clear results, this study alone will not tell us definitively how best to optimise perioperative oxygenation for individual patients.[1] The broad inclusions needed by large pragmatic trials to generate adequate power may also inherently ignore individual phenotypes and response signals amongst background noise. Novel trial designs, such as platform trials, offer an opportunity to test multiple different interventions more efficiently and also can allow for different interventions to be added or removed whilst the trial is in progress.[109] Platform trials have become much more familiar since the COVID-19 pandemic, with the Randomised Evolution of COVID-19 Therapy (RECOVERY) and the Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP CAP) trials both allowing many different potential treatments for COVID-19 to be tested remarkably rapidly.[110,111] However, relatively few perioperative studies have used a platform trial design to date. A platform perioperative oxygen trial could offer many advantages over more classical trial designs. For example, it could allow for the FiO_2 values being tested as interventions to be adjusted and refined as the trial progressed. This design could also make it easier for trialists to target different interventional FiO_2 values to specific patient phenotypes for the first time, including patients from under-represented minority groups, such as pregnant women or children, where research in this area is especially lacking.

Conclusions

Supplemental oxygen will continue to be a common and essential treatment in perioperative and intensive care medicine. However, oxygen will remain a limited and finite resource (as was sadly witnessed in many hospitals internationally during the COVID-19 pandemic) that requires large amounts of energy to produce, making decisions about its appropriate use critical to maintaining adequate supplies and ensuring future sustainability. Research into perioperative oxygen needs not only to resolve the uncertainty created by the WHO guideline controversy but also to equip perioperative physicians with simple and effective ways of personalising the treatment they give to individual patients.

Author's contributions

Project conception and design: ME, DSM, MF, MPWG, AFC
Drafting manuscript: JL, AFC
Reviewing and editing manuscript: all authors

Declarations of interest

MPWG has received grant support from: National Institute for Health Research, Bill and Melinda Gates Foundation, National Lottery Fund (UK), NHS England (UK), Edwards Lifesciences, Macmillan Cancer Support (UK). MG has received consulting fees (medical advisory board and trial monitoring) from Edwards Life Sciences, Sphere Medical Ltd, South-West Sensors Ltd. AFC has received oxygen monitoring equipment on loan from Masimo (Irvine, CA, USA) to use in investigator-led trials. All other authors have no conflicts of interest to declare.

Funding

MG is in part funded by the NIHR Senior Investigator Scheme and in part by the NIHR Southampton Biomedical Research Centre. AFC is funded through an NIHR Clinical Lecturer award and has previously received funding through the NIHR Southampton Biomedical Research Centre.

References

1. Martin D, Cumpstey A. Is there clarity on the horizon for peri-operative oxygen therapy? *Anaesthesia* 2024; **79**. 15–7
2. Bickler PE, Feiner JR, Lipnick MS, Batchelder P, MacLeod DB, Severinghaus JW. Effects of acute, profound hypoxia on healthy humans: implications for safety of tests evaluating pulse oximetry or tissue oximetry performance. *Anesth Analg* 2017; **124**: 146
3. Lumb AB. Why do patients need extra oxygen during a general anaesthetic? *BJA Educ* 2019; **19**: 37–9
4. Elfeky A, Chen Y-F, Grove A, et al. Perioperative oxygen therapy: a protocol for an overview of systematic reviews and meta-analyses. *Syst Rev* 2022; **11**: 140
5. Meyhoff CS. Perioperative hyperoxia: why guidelines, research and clinical practice collide. *Br J Anaesth* 2019; **122**: 289–91
6. Myles PS, Carlisle JB, Scarr B. Evidence for compromised data integrity in studies of liberal peri-operative inspired oxygen. *Anaesthesia* 2019; **74**: 573–84
7. Oldman AH, Cumpstey AF, Martin DS, Grocott MPW. Data integrity issues: catalyst for a more robust approach to research on perioperative oxygen therapy? *Perioper Med (Lond)* 2019; **8**: 7
8. Allen DB, Maguire JJ, Mahdavian M, et al. Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. *Arch Surg* 1997; **132**: 991–6
9. Winterbourn CC, Kettle AJ, Hampton MB. Reactive oxygen species and neutrophil function. *Annu Rev Biochem* 2016; **85**: 765–92
10. Cumpstey AF, Grocott MPW. 3. Gas exchange. In: *Oxford Textbook of respiratory critical care*. 1st Edn. Oxford: Oxford University Press; 2023
11. Nisimoto Y, Diebold BA, Cosentino-Gomes D, Lambeth JD. Nox4: a hydrogen peroxide-generating oxygen sensor. *Biochemistry* 2014; **53**: 5111–20

12. Almzaiel AJ, Billington R, Smerdon G, Moody AJ. Effects of hyperbaric oxygen treatment on antimicrobial function and apoptosis of differentiated HL-60 (neutrophil-like) cells. *Life Sci* 2013; **93**: 125–31
13. Greif R, Akça O, Horn EP, Kurz A, Sessler DI, Outcomes Research Group. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 2000; **342**: 161–7
14. Belda FJ, Aguilera L, García de la Asunción J, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. *JAMA* 2005; **294**: 2035–42
15. Myles PS, Leslie K, Chan MTV, et al. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. *Anesthesiology* 2007; **107**: 221–31
16. Allegranzi B, Zayed B, Bischoff P, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016; **16**: e288–303
17. Wetterslev J, Meyhoff CS, Jørgensen LN, Gluud C, Lindschou J, Rasmussen LS. The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. *Cochrane Database Syst Rev* 2015; **2015**: CD008884
18. Volk T, Peters J, Sessler DI. The WHO recommendation for 80% perioperative oxygen is poorly justified. *Anaesthesist* 2017; **66**: 227–9
19. Myles PS, Kurz A. Supplemental oxygen and surgical site infection: getting to the truth. *Br J Anaesth* 2017; **119**: 13–5
20. Schietroma M, Cecilia EM, Sista F, Carlei F, Pessia B, Amicucci G. Retraction notice to "High-concentration supplemental perioperative oxygen and surgical site infection following elective colorectal surgery for rectal cancer: a prospective, randomized, double-blind, controlled, single-site trial" [*Am J Surg* 208 (2014) 719–726]. *Am J Surg* 2018; **215**: 534
21. Meyhoff CS, Wetterslev J, Jorgensen LN, et al. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. *JAMA* 2009; **302**: 1543–50
22. Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial. *Anesth Analg* 2012; **115**: 849–54
23. Fonnes S, Gögenur I, Søndergaard ES, et al. Perioperative hyperoxia — long-term impact on cardiovascular complications after abdominal surgery, a post hoc analysis of the PROXI trial. *Int J Cardiol* 2016; **215**: 238–43
24. Meyhoff CS, Jorgensen LN, Wetterslev J, Siersma VD, Rasmussen LS, PROXI Trial Group. Risk of new or recurrent cancer after a high perioperative inspiratory oxygen fraction during abdominal surgery. *Br J Anaesth* 2014; **113**(Suppl 1): i74–81
25. Staehr-Rye AK, Meyhoff CS, Scheffenbichler FT, et al. High intraoperative inspiratory oxygen fraction and risk of major respiratory complications. *Br J Anaesth* 2017; **119**: 140–9
26. Mattishent K, Thavarajah M, Sinha A, et al. Safety of 80% vs 30–35% fraction of inspired oxygen in patients undergoing surgery: a systematic review and meta-analysis. *Br J Anaesth* 2019; **122**: 311–24
27. Jonge S, Egger M, Latif A, et al. Effectiveness of 80% vs 30–35% fraction of inspired oxygen in patients undergoing surgery: an updated systematic review and meta-analysis. *Br J Anaesth* 2019; **122**: 325–34
28. World Health Organization. *Global guidelines for the prevention of surgical site infection*. Available from: World Health Organization; 2018. https://apps.who.int/iris/handle/10665/277399. [Accessed 9 August 2023]
29. Berríos-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection. *JAMA Surg* 2017; **152**: 784–91. 2017
30. O'Driscoll BR, Howard LS, Earis J, Mak V. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax* 2017; **72**. ii1–90
31. Mellin-Olsen J, McDougall RJ, Cheng D. WHO guidelines to prevent surgical site infections. *Lancet Infect Dis* 2017; **17**: 260–1
32. Morkane CM, McKenna H, Cumpstey AF, et al. Intraoperative oxygenation in adult patients undergoing surgery (iOPS): a retrospective observational study across 29 UK hospitals. *Perioper Med (Lond)* 2018; **7**: 17
33. VEGAS investigators LAS. Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications. *Eur J Anaesthesiol* 2017; **34**: 492–507
34. Karalapillai D, Weinberg L, Peyton PJ, et al. Frequency of hyperoxaemia during and after major surgery. *Anaesth Intensive Care* 2020; **48**: 213–20
35. Suzuki S, Mihara Y, Hikasa Y, et al. Current ventilator and oxygen management during general anesthesia: a multicenter, cross-sectional observational study. *Anesthesiology* 2018; **129**: 67–76
36. Frei DR, Beasley R, Campbell D, et al. Practice patterns and perceptions of Australian and New Zealand anaesthetists towards perioperative oxygen therapy. *Anaesth Intensive Care* 2019; **47**: 288–94
37. Scharffenberg M, Weiss T, Wittenstein J, et al. Practice of oxygen use in anesthesiology – a survey of the European Society of Anaesthesiology and intensive care. *BMC Anesthesiology* 2022; **22**: 350
38. Hale KE, Gavin C, O'Driscoll BR. Audit of oxygen use in emergency ambulances and in a hospital emergency department. *Emerg Med J* 2008; **25**: 773–6
39. O'Driscoll BR, Howard LS, Bucknall C, Welham SA, Davison AG. British Thoracic Society. British Thoracic Society emergency oxygen audits. *Thorax* 2011; **66**: 734–5
40. Chu DK, Kim LH-Y, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018; **391**: 1693–705
41. Barbateskovic M, Schjørring OL, Krauss SR, et al. Higher vs lower oxygenation strategies in acutely ill adults: a systematic review with meta-analysis and trial sequential analysis. *Chest* 2021; **159**: 154–73
42. British Thoracic Society. *Emergency Oxygen. Better lung health for all*. Available from: https://www.brit-thoracic.org.uk/quality-improvement/guidelines/emergency-oxygen/. [Accessed 5 November 2023]
43. Barnett A, Beasley R, Buchan C, et al. Thoracic Society of Australia and New Zealand Position statement on acute oxygen use in adults: 'Swimming between the flags. *Respirology* 2022; **27**: 262–76

44. Leach RM, Treacher DF. Oxygen transport—2. Tissue hypoxia. *BMJ* 1998; **317**: 1370–3
45. Oktedalen O, Lunde OC, Opstad PK, Aabakken L, Kvernebo K. Changes in the gastrointestinal mucosa after long-distance running. *Scand J Gastroenterol* 1992; **27**: 270–4
46. Kober A, Fleischackl R, Scheck T, et al. A randomized controlled trial of oxygen for reducing nausea and vomiting during emergency transport of patients older than 60 years with minor trauma. *Mayo Clin Proc* 2002; **77**: 35–8
47. Orhan-Sungur M, Kranke P, Sessler D, Apfel CC. Does supplemental oxygen reduce postoperative nausea and vomiting? A meta-analysis of randomized controlled trials. *Anesth Analg* 2008; **106**: 1733
48. Markwei MT, Babatunde IO, Kutlu-Yalcin E, et al. Perioperative supplemental oxygen and postoperative nausea and vomiting: subanalysis of a trial, systematic review, and meta-analysis. *Anesthesiology* 2023; **138**: 56–70
49. Hovaguimian F, Lysakowski C, Elia N, Tramèr MR. Effect of intraoperative high inspired oxygen fraction on surgical site infection, postoperative nausea and vomiting, and pulmonary function: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* 2013; **119**: 303–16
50. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2020; **131**: 411
51. Frerk C, Mitchell VS, McNarry, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. *Br J Anaesth* 2015; **115**: 827–48
52. Patel A, Nouraei SAR. Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. *Anaesthesia* 2015; **70**: 323–9
53. de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008; **12**: R156
54. Helmerhorst HJF, Arts DL, Schultz MJ, et al. Metrics of arterial hyperoxia and associated outcomes in critical care. *Crit Care Med* 2017; **45**: 187
55. ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Mackle D, Bellomo R, *et al*. Conservative oxygen therapy during mechanical ventilation in the ICU. *N Engl J Med* 2020; **382**: 989–98
56. Schjørring OL, Klitgaard TL, Perner A, et al. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. *N Engl J Med* 2021; **384**: 1301–11
57. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med* 2020; **382**: 999–1008
58. Klitgaard TL, Schjørring OL, Nielsen FM, et al. Higher versus lower fractions of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit. *Cochrane Database Syst Rev* 2023; **9**: CD012631
59. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the Oxygen-ICU randomized clinical trial. *JAMA* 2016; **316**: 1583–9
60. Cumpstey AF, Oldman AH, Martin DS, Smith A, Grocott MPW. Oxygen targets during mechanical ventilation in the ICU: a systematic review and meta-analysis. *Crit Care Explor* 2022; **4**, e0652
61. Martin DSBs, Grocott MPWM. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. *Crit Care Med* 2013; **41**: 423–32
62. Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment elevation myocardial infarction. *Circulation* 2015; **131**: 2143–50
63. Reinhart K, Bloos F, König F, Bredle D, Hannemann L. Reversible decrease of oxygen consumption by hyperoxia. *Chest* 1991; **99**: 690–4
64. McNulty PH, King N, Scott S, et al. Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. *Am J Physiol Heart Circ Physiol* 2005; **288**: H1057–62
65. Farquhar H, Weatherall M, Wijesinghe M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J* 2009; **158**: 371–7
66. Cabello JB, Burls A, Emparanza JI, Bayliss S, Quinn T. Oxygen therapy for acute myocardial infarction. *Cochrane Database Syst Rev* 2013; **8**: CD007160
67. Tan A, Schulze A, O'Donnell CPF, Davis PG. Air versus oxygen for resuscitation of infants at birth. *Cochrane Database Syst Rev* 2004; **3**: CD002273
68. Kilgannon J, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA* 2010; **303**: 2165–71
69. Rønning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? *Stroke* 1999; **30**: 2033–7
70. Dushianthan A, Bracegirdle L, Cusack R, Cumpstey AF, Postle AD, Grocott MPW. Alveolar hyperoxia and exacerbation of lung injury in critically ill SARS-CoV-2 pneumonia. *Med Sci (Basel)* 2023; **11**: 70
71. Cumpstey A, Feelisch M. Free radicals in inflammation. In: Cavaillon J-M, Singer M, editors. *Inflammation: from molecular and cellular mechanisms to the clinic, 4 volume set*. Hoboken, NJ: Wiley; 2017. p. 695–726
72. Zhao R-Z, Jiang S, Zhang L, Yu Z-B. Mitochondrial electron transport chain, ROS generation and uncoupling (Review) *Int J Mol Med* 2019; **44**: 3–15 (Pubmed ID PMC6559295)
73. Guzik TJ, West NEJ, Pillai R, Taggart DP, Channon KM. Nitric oxide modulates superoxide release and peroxynitrite formation in human blood vessels. *Hypertension* 2002; **39**: 1088–94
74. Piacenza L, Zeida A, Trujillo M, Radi R. The superoxide radical switch in the biology of nitric oxide and peroxynitrite. *Physiol Rev* 2022; **102**: 1881–906
75. Cortese-Krott MM, Koning A, Kuhnle GGC, et al. The reactive species interactome: evolutionary emergence, biological significance, and opportunities for redox metabolomics and personalized medicine. *Antioxid Redox Signal* 2017; **27**: 684–712
76. Cumpstey AF, Clark AD, Santolini J, Jackson AA, Feelisch M. COVID-19: a redox disease—what a stress pandemic can teach us about resilience and what we may learn from the reactive species interactome about its treatment. *Antioxid Redox Signal* 2021; **35**: 1226–68
77. Orrenius S, Gogvadze V, Zhivotovsky B. Mitochondrial oxidative stress: implications for cell death. *Annu Rev Pharmacol Toxicol* 2007; **47**: 143–83

78. Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL. Oxidative stress in atherosclerosis. *Curr Atheroscler Rep* 2017; **19**: 42
79. D'Autréaux B, Toledano MB. ROS as signalling molecules: mechanisms that generate specificity in ROS homeostasis. *Nat Rev Mol Cell Biol* 2007; **8**: 813–24
80. De Giusti VC, Caldiz CI, Ennis IL, Pérez NG, Cingolani HE, Aiello EA. Mitochondrial reactive oxygen species (ROS) as signaling molecules of intracellular pathways triggered by the cardiac renin-angiotensin II-aldosterone system (RAAS). *Front Physiol* 2013; **4**: 126
81. Cortese-Krott MM, Santolini J, Wootton SA, Jackson AA, Feelisch M. The reactive species interactome. In: Sies H, editor. *Oxidative stress – eustress and distress*. London: Academic Press Ltd-Elsevier Science Ltd; 2020. p. 51–64
82. Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nat Rev Mol Cell Biol* 2020; **21**: 363–83
83. Sies H. Oxidative eustress: on constant alert for redox homeostasis. *Redox Biol* 2021; **41**, 101867
84. Feelisch M, Cortese-Krott MM, Santolini J, Wootton SA, Jackson AA. Systems redox biology in health and disease. *EXCLI J* 2022; **21**: 623–46
85. Sies H, editor. *Oxidative stress: eustress and distress*. Walthum: Academic Press; 2019
86. Guzy RD, Schumacker PT. Oxygen sensing by mitochondria at complex III: the paradox of increased reactive oxygen species during hypoxia. *Exp Physiol* 2006; **91**: 807–19
87. Kane AD, Kothmann E, Giussani DA. Detection and response to acute systemic hypoxia. *BJA Educ* 2020; **20**: 58–64
88. Cooper JB, Newbower RS, Long CD, McPeek B. Preventable anesthesia mishaps: a study of human factors. *Anesthesiology* 1978; **49**: 399–406
89. Ehrenfeld JM, Funk LM, Schalkwyk JV, Merry AF, Sandberg WS, Gawande A. The incidence of hypoxemia during surgery: evidence from two institutions. *Can J Anaesth* 2010; **57**: 888–97
90. Martin D, Windsor J. From mountain to bedside: understanding the clinical relevance of human acclimatisation to high-altitude hypoxia. *Postgrad Med J* 2008; **84**: 622–7
91. Kaelin WG, Ratcliffe PJ. Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. *Mol Cell* 2008; **30**: 393–402
92. Grocott MPW, Martin DS, Levett DZH, McMorrow R, Windsor J, Montgomery HE. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 2009; **360**: 140–9
93. Horscroft JA, Kotwica AO, Laner V, et al. Metabolic basis to Sherpa altitude adaptation. *Proc Natl Acad Sci U S A* 2017; **114**: 6382–7
94. Murray AJ, Horscroft JA. Mitochondrial function at extreme high altitude. *J Physiol* 2016; **594**: 1137–49
95. Cumpstey AF, Minnion M, Fernandez BO, et al. Pushing arterial-venous plasma biomarkers to new heights: a model for personalised redox metabolomics? *Redox Biol* 2019; **21**, 101113
96. Burtscher M, Millet GP, Burtscher J. Hypoxia conditioning for high-altitude pre-acclimatization. *J Sci Sport Exerc* 2022; **4**: 331–45
97. Burtscher M, Pachinger O, Ehrenbourg I, et al. Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease. *Int J Cardiol* 2004; **96**: 247–54
98. Lyamina NP, Lyamina SV, Senchiknin VN, Mallet RT, Downey HF, Manukhina EB. Normobaric hypoxia conditioning reduces blood pressure and normalizes nitric oxide synthesis in patients with arterial hypertension. *J Hypertens* 2011; **29**: 2265
99. Kong Z, Zang Y, Hu Y. Normobaric hypoxia training causes more weight loss than normoxia training after a 4-week residential camp for obese young adults. *Sleep Breath* 2014; **18**: 591–7
100. Serebrovska TV, Portnychenko AG, Drevytska TI, et al. Intermittent hypoxia training in prediabetes patients: beneficial effects on glucose homeostasis, hypoxia tolerance and gene expression. *Exp Biol Med (Maywood)* 2017; **242**: 1542–52
101. Fuller NR, Courtney R. A case of remission from prediabetes following intermittent hypoxic training. *Obes Res Clin Pract* 2016; **10**: 487–91
102. Semenza GL. Hypoxia-inducible factors in physiology and medicine. *Cell* 2012; **148**: 399–408
103. Catrina S-B, Zheng X. Hypoxia and hypoxia-inducible factors in diabetes and its complications. *Diabetologia* 2021; **64**: 709–16
104. Ferrari M, Jain IH, Goldberger O, et al. Hypoxia treatment reverses neurodegenerative disease in a mouse model of Leigh syndrome. *Proc Natl Acad Sci U S A* 2017; **114**: E4241–50
105. Donald KW. Oxygen poisoning in man – part 1. *Br Med J* 1947; **1**: 667–72
106. Friess JO, Mikasi J, Baumann R, et al. Hyperoxia-induced deterioration of diastolic function in anaesthetised patients with coronary artery disease – randomised crossover trial. *BJA Open* 2023; **6**, 100135
107. Stolmeijer R, van Ieperen E, Lameijer H, van Beest P, Ter Maaten JC, Ter Avest E. Haemodynamic effects of a 10-min treatment with a high inspired oxygen concentration in the emergency department: a prospective observational study. *BMJ Open* 2022; **12**, e059848
108. Frei DR, Beasley R, Campbell D, et al. A vanguard randomised feasibility trial comparing three regimens of perioperative oxygen therapy on recovery after major surgery. *Anaesthesia* 2023; **78**: 1272–84
109. Myles PS, Yeung J, Beattie WS, Ryan EG, Heritier S, McArthur CJ. Platform trials for anaesthesia and perioperative medicine: a narrative review. *Br J Anaesth* 2023; **130**: 677–86
110. Wise J, Coombes R. Covid-19: the inside story of the RECOVERY trial. *BMJ* 2020; **370**: m2670
111. Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) study. Rationale and design. *Ann Am Thorac Soc* 2020; **17**: 879–91

Handling editor: Phil Hopkins