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Review Article

REVIEW ARTICLE

Effects of perioperative oxygen concentration on oxidative stress in adult surgical patients: a systematic review

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Abstract

Background: The fraction of inspired oxygen (FIO_2) administered during general anaesthesia varies widely despite international recommendations to administer FIO_2 0.8 to all anaesthetised patients to reduce surgical site infections (SSIs). Anaesthetists remain concerned that high FIO_2 administration intraoperatively may increase harm, possibly through increased oxidative damage. In previous systematic reviews associations between FIO_2 and SSIs have been inconsistent, but none have examined how FIO_2 affects perioperative oxidative stress. We aimed to address this uncertainty by reviewing the available literature.
Methods: EMBASE, MEDLINE, and Cochrane databases were searched from inception to March 9, 2020 for RCTs comparing higher with lower perioperative FIO_2 and quantifying oxidative stress in adults undergoing noncardiac surgery. Candidate studies were independently screened by two reviewers and references hand-searched. Methodological quality was assessed using the Cochrane Collaboration Risk of Bias tool.
Results: From 19 438 initial results, seven trials (n=422) were included. Four studies reported markers of oxidative stress during Caesarean section (n=328) and three reported oxidative stress during elective colon surgery (n=94). Risk of bias was low (four studies) to moderate (three studies). Pooled results suggested high FIO_2 was associated with greater malondialdehyde, protein-carbonyl concentrations and reduced xanthine oxidase concentrations, together with reduced antioxidant markers such as superoxide dismutase and total sulfhydryl levels although total antioxidant status was unchanged.
Conclusions: Higher FIO_2 may be associated with elevated oxidative stress during surgery. However, limited studies have specifically reported biomarkers of oxidation. Given the current clinical controversy concerning perioperative oxygen therapy, further research is urgently needed in this area.

Keywords: anaesthesia; hyperoxia; inflammation; oxidative stress; oxygen; perioperative care; surgery

Editor's key points

- International recommendations to routinely administer 80% oxygen (FIO_2 0.8) throughout anaesthesia remain controversial. Systemic, detrimental effects of hyperoxaemia are often thought to be mediated through increased oxidative stress.
- Despite very broad searches, this review could only include seven small single-centre RCTs comparing oxidative stress at higher and lower FIO_2 levels.

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- High intraoperative FIO_2 may be associated with elevated oxidative stress during surgery but further studies are urgently needed to confirm this.

In 2016 the WHO recommended administering a fractional inspired oxygen concentration (FIO_2) of 0.8 to all intubated patients undergoing surgery, in order to reduce instances of surgical site infections (SSIs).[1,2] In the first revision of these guidelines in 2018, this recommendation remained unaltered but its strength was downgraded from 'strong' to 'conditional'.[3] The 2016 recommendation was based on a meta-analysis of 15 RCTs of perioperative oxygen therapy performed by members of the WHO guideline development group,[4] and remain controversial amongst the international anaesthetic community.[5–7] Notably, the findings of the single largest trial available when the 2016 recommendation was Q2 published (the PROXI study, $n=1378$[8]) were deemed biologically implausible by the guideline development group for reasons that remain obscure.[2] *Post hoc* analyses from the PROXI study have suggested that higher FIO_2 in surgical procedure could be associated with higher long-term mortality in patients with cardiac disease, cancer, or both.[9,10] A better understanding of the mechanisms underlying such outcome differences is essential to successfully resolve this debate.

Systemic detrimental effects of oxygen are often thought to be mediated through 'oxidative stress' – an imbalance between the production of highly reactive by-products of metabolism (reactive oxygen species [ROS]) and endogenous antioxidant defence mechanisms.[11–13] ROS are largely formed during oxidative phosphorylation in the mitochondrial electron transport chain, or within neutrophil/macrophages and non-phagocytic cells.[14–16] Interaction of these chemical species with cellular constituents can irreversibly damage lipids, proteins, and DNA; injuring cells and tissue or end organs and Q3 ultimately resulting in cell death through apoptosis or necrosis.[14,15] Oxidative stress can be beneficial (e.g. the innate immune system uses this process to attack and destroy invading pathogens) but can also lead to tissue damage and organ failure.[17,18]

Direct detection of ROS remains a challenge because of their high reactivity and short half-life. Alternative biomarkers are therefore used as indirect measures of ROS activity, for example:

1. Markers of oxidation (after interactions with ROS that alter the cell microenvironment).[19,20]
2. Antioxidants and markers of cellular redox status, which change biochemical status after exposure to redox stress.[21] Q4

Common markers of oxidation include lipid peroxides (e.g. malondialdehyde [MDA], F_2-isoprostanes, and organic hydroperoxide [OHP]), which indicate the levels of cellular lipid oxidation.[19,22] 8-Isoprostane is a lipid peroxidation product of arachidonic, widely utilised by redox scientists.[23] MDA is also formed from peroxidation of fatty acids, used historically to

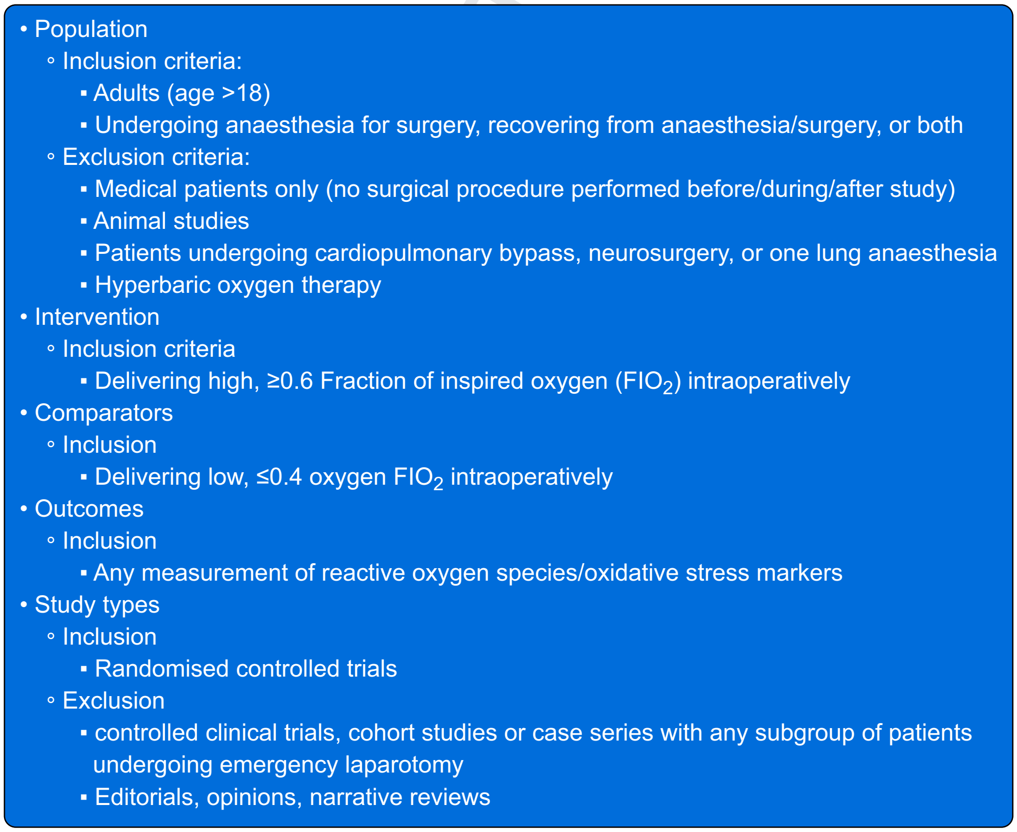
- Population
  - Inclusion criteria:
    - Adults (age >18)
    - Undergoing anaesthesia for surgery, recovering from anaesthesia/surgery, or both
  - Exclusion criteria:
    - Medical patients only (no surgical procedure performed before/during/after study)
    - Animal studies
    - Patients undergoing cardiopulmonary bypass, neurosurgery, or one lung anaesthesia
    - Hyperbaric oxygen therapy
- Intervention
  - Inclusion criteria
    - Delivering high, ≥0.6 Fraction of inspired oxygen (FIO_2) intraoperatively
- Comparators
  - Inclusion
    - Delivering low, ≤0.4 oxygen FIO_2 intraoperatively
- Outcomes
  - Inclusion
    - Any measurement of reactive oxygen species/oxidative stress markers
- Study types
  - Inclusion
    - Randomised controlled trials
  - Exclusion
    - controlled clinical trials, cohort studies or case series with any subgroup of patients undergoing emergency laparotomy
    - Editorials, opinions, narrative reviews

Fig 1. Inclusion and exclusion criteria for studies.

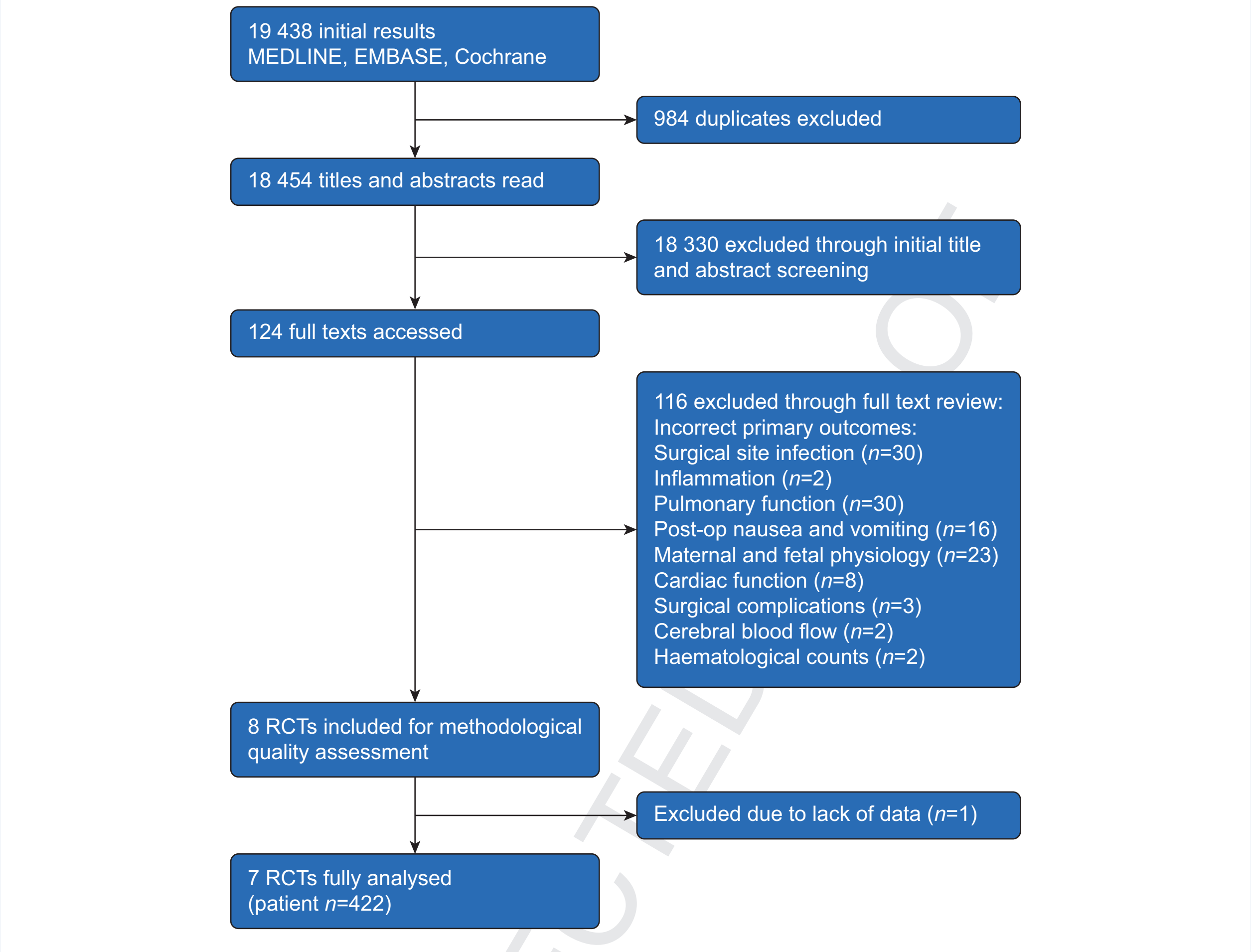

Fig 2. CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials.

detect ROS which degrade lipids to form MDA, which itself is toxic to cells; binding and oxidising DNA causing cross-linking of nucleic acid bases, and reacting with other cellular amine groups.[24] Similarly, protein carbonyl moieties (PCO) or methionine sulfoxide can be measured to reflect levels of cellular protein oxidation,[25] and DNA oxidation can be assessed by measuring concentrations of 8-oxo-2′-deoxyguanosine.

Across the surgical literature, xanthine oxidase (XO), an enzyme which generates ROS, has been widely used by researchers to quantify ischaemic/reperfusion injury in patients perioperatively; with tissue damage thought to be mediated by adenosine diphosphate catabolism, acidosis, and subsequent XO production and neutrophil mediation.[26–28]

Antioxidants act as the cellular counterbalance to oxidation reactions. They can be measured both individually and cumulatively, as their individual effects are additive.[29] Well-studied antioxidant enzymes include superoxide dismutase (SOD), glutathione peroxidase, and catalase. Chain-breaking antioxidants (including vitamin E, thiols, nitric oxide, and ubiquinol) act by attenuating ROS-triggered chain reactions by transferring electrons across aqueous or lipid cellular compartments.[30,31] Thiols, either proteins or non-protein compounds with free sulfhydryl groups, are also a major target of ROS-induced oxidation. Reactive aldehydes (e.g. MDA) can react further with sulfhydryl and amino moieties of proteins and transcription factors to modulate a variety of cell functions and interfere with redox signalling.[32] The ratio of reduced over oxidised glutathione (GSG/GSSG) is a common marker of cellular redox status intracellularly, whereas extracellularly (e.g. in plasma) serum/plasma total free thiols are more convenient markers of oxidative status as serum albumin (with one single free sulfhydryl group) accounts for the majority of thiols and free glutathione concentrations are much lower.[32]

Total antioxidant status (TAS) represents the additive function of antioxidants through a colorimetry assay using a specific test solution. The value produced represents the solution's antioxidant capacity and can act as a figure with which to compare levels of antioxidation across clinical samples.[29,33]

Although anaesthetists are becoming increasingly aware of the role oxidative stress plays in the inflammatory surgical stress response, how intraoperative oxygen affects this remains unclear.[34,35] The aim of this review is to determine whether a lower FIO_2 during general anaesthesia reduces the magnitude of perioperative oxidative stress.

Table 1 Combined results of RCTs reporting on markers of oxidative stress in arterial blood, fetal blood, and bronchial lavage samples. *P<0.05; **P<0.01. EL C/S elective Caesarean section; EM C/S: emergency Caesarean section.

Authors	Patient no.	Control *vs* intervention (FIO$_2$)	Sample	Isoprostane (various)	Organic hydroperoxides (μmol L^{-1})	Malondialdehyde, MDA (various)	Protein carbonyl, PCO (nmol mg^{-1})	Xanthine oxidase, XO (mU mg $protein^{-1}$)
Khaw and colleagues[41]	44	0.21 *vs* 0.6	Maternal arterial	121.8 *vs* 200.6**(μmol L^{-1})	0.14 vs 0.14	0.89 *vs* 1.2** (μmol L^{-1})	–	–
			Umbilical venous	135.3 *vs* 403.0** (μmol L^{-1})	0.15 vs 0.5*	0.47 *vs* 0.78* (μmol L^{-1})	–	–
			Umbilical arterial	122.1 *vs* 215** (μmol L^{-1})	0.18 vs 0.39**	0.4 *vs* 0.4** (μmol L^{-1})	–	–
Khaw and colleagues[42]	125	0.21 *vs* 0.6	Maternal venous	225 *vs* 240.7 (pg ml^{-1})	–	–	–	–
			Umbilical venous	427 *vs* 471 (pg ml^{-1})	–	–	–	–
			Umbilical arterial	457 *vs* 473 (pg ml^{-1})	–	–	–	–
Khaw and colleagues[43]	39	0.3 *vs* 0.5 *vs* 1.0	Maternal arterial	154 *vs* 156 *vs* 158 (pg ml^{-1})	–	–	–	–
			Umbilical venous	480 *vs* 416 *vs* 441 (pg ml^{-1})	–	–	–	–
			Umbilical arterial	410 *vs* 368 *vs* 468 (pg ml^{-1})	–	–	–	–
Koksal and colleagues[44]	40	0.4 *vs* 0.8	Subject arterial	–	–	8.1 *vs* 8.1 (nmol mg^{-1})	5.8 vs 7.5	–
			Subject bronchial lavage	–	–	7.7 *vs* 12.6** (nmol mg^{-1})	10.1 vs 4.5**	–
Ahuja and colleagues[45]	60 (EL C/S)	0.21 *vs* 0.5	Maternal arterial	–	–	6.1 *vs* 6.2 (μmol)	–	–
			Umbilical venous	–	–	5.3 *vs* 4.8 (μmol)	–	–
			Umbilical arterial	–	–	5.4 *vs* 4.3 (μmol)	–	–
	60 (EM C/S)	0.21 *vs* 0.5	Maternal arterial	–	–	6.1 *vs* 6.2 (μmol)	–	–
			Umbilical arterial	–	–	5.1 *vs* 5.5 (μmol)	–	–
			Umbilical venous	–	–	5.4 *vs* 4.8 (μmol)	–	–
Garcia de la Asuncion and colleagues[39]	30	0.3 *vs* 0.8	Subject arterial 1 h after induction	–	–	0.6 *vs* 0.5 (nmol ml^{-1})	–	–
			Subject arterial 6 h postoperatively	–	–	0.65 *vs* 0.4* (nmol ml^{-1})	–	–
Garcia de la Asuncion and colleagues[40]	24	0.3 *vs* 0.8	Subject mucosal	–	–	2.0 *vs* 1.0** (nmol mg^{-1} $protein^{-1}$)		595 *vs* 310*
			Subject arterial	–	–	1.5 *vs* 0.4** (nmol mg^{-1} ml^{-1})		

	Khaw et al. 2002	Garcia de la Asuncion et al. 2007	Khaw et al. 2008	Khaw et al. 2010	Garcia de la Asuncion et al. 2013	Koksal et al. 2016	Ahuja et al. 2018
Random sequence generation	+	?	+	+	+	+	+
Allocation concealment (selection bias)	+	?	+	+	?	+	+
Blinding of participants and personnel (performance bias)	+	?	+	+	?	+	+
Blinding of outcome assessment (detection bias)	?	?	+	+	?	+	+
Complete outcome data (attrition bias)	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+
No other bias	+	?	+	+	+	+	+

Fig 3. Bias grid.

Methods

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[36] and was prospectively registered online at International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD42017078995).

Selection criteria

RCTs, published in English, in adult (aged 18 yr or older) patients undergoing any noncardiac procedure in an operating theatre under general anaesthesia and not requiring one lung ventilation, neurosurgery or hyperbaric oxygen therapy were eligible. All included studies reported biochemical levels of oxidative stress (as agreed by all authors) in response to administration of either a high or low intraoperative FIO_2 (>0.6 *vs* <0.4, or $\geq$20% difference between interventional groups) (Fig. 1).

Search strategy

EMBASE, MEDLINE, and Cochrane databases were searched from inception until March 9, 2020 for keywords relating to ROS, oxidative stress, oxygen, hyperoxia, anaesthesia, and surgery. Full search strategies are detailed in Appendix A. Two authors (AO and AC) independently identified potentially eligible studies by screening all titles and abstracts using Rayyan (systematic review web application[37]). Any disagreements were resolved by discussion with all other authors. Full texts of potentially eligible studies were obtained and reviewed by two authors (AO and AC). Review by other authors was available if consensus could not be reached, but not necessary. Included articles' references were then hand-searched for completeness.

Data extraction and assessment of methodological quality

Data were extracted, placed in an analysis table, and independently cross-checked by two authors (AO and AC). One author (AO) used the Cochrane Collaboration Tool (The Nordic Cochrane Centre, Copenhagen, Denmark) to assess Risk of Bias to assess methodological quality. Studies were scored as high, low, or unclear risk in each of the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, complete outcome data, selective reporting, and other biases. Because of the high level of heterogeneity in the small number of results, a meta-analysis was not performed.

Table 2 Results of RCTs reporting on antioxidant levels in blood and bronchial lavage. *$P<0.05$; **$P<0.01$.

Author	Patient no.	Control vs intervention (FIO_2)	Sample	Superoxide dismutase (nmol mg^{-1})	Non-protein sulfhydryl (nmol mg^{-1})	Protein sulfhydryl (nmol mg^{-1})	Reduced glutathione (μmol ml^{-1})	Oxidised glutathione	Total antioxidant status (mM)
Koksal and colleagues[44]	40	0.4 vs 0.8	Subject arterial	3.6 vs 1.4**	2.56 vs 2.7	3.2 vs 2.6*	–	–	
			Subject bronchial lavage	13.7 vs 13.4**	2.2 vs 1.2**	11.8 vs 6.7**	–	–	
Garcia de la Asuncion and colleagues[39]	30	0.3 vs 0.8	Subject arterial 1 h after induction	–	–	–	0.68 vs 0.58	20 vs 30	
			Subject atrial 6 h postoperatively	–	–	–	0.78 vs 0.7	42 vs 30**	
Garcia de la Asuncion and colleagues[40]	24	0.3 vs 0.8	Subject arterial	–	–	–	–	42 vs 30	
Ahuja and colleagues[45]	60 (EL C/S)	0.21 vs 0.5	Maternal arterial	–	–	–	–	–	1.1 vs 1.1
			Umbilical arterial	–	–	–	–	–	1.2 vs 1.3
			Umbilical venous	–	–	–	–	–	1.3 vs 1.3
	60 (EM C/S)	0.21 vs 0.5	Umbilical arterial	–	–	–	–	–	1.1 vs 1.1
			Umbilical venous	–	–	–	–	–	1.6 vs 1.5

Results

The initial search yielded 19 438 results, of which 984 were duplicates. Overall, 124 were deemed potentially eligible after title and abstract review; however, 116 were excluded on reviewing the full texts, leaving eight eligible studies (Fig. 2). The most common reasons for exclusion were only reporting clinical outcomes and not specifically reporting on biochemical measures. One article was subsequently excluded from the analysis owing to missing data despite attempts to contact the authors.[38] Data from 422 patients in seven studies were included in the final analysis.

Characteristics of included studies

From available data across the seven studies with a total of 422 participants, mean age was 38 (standard deviation [SD], 13.9) yr and weight 66.9 (3.1) kg. Of the six trials reporting participants' sex (n=392 total), only 47 (12%) participants were male. All seven RCTs included in the analysis reported different biomarkers of oxidative stress in surgical patients (Table 1).[39–45] Four studies (three of which were from the same group) reported oxidative stress in maternal and fetal blood samples collected during either elective or emergency Caesarean section.[41–43,45] One trial reported markers of oxidative stress in serum and bronchoalveolar lavage (BAL) samples collected from 40 patients undergoing a hemicolectomy procedure under general anaesthesia,[44] and the final two studies (both from the same group) studied both mucosal and arterial levels of MDA intraoperatively and postoperatively during colon surgery.[39,40]

Risk of bias in included studies

Of the seven studies analysed, four were deemed to have low risk of bias across all domains,[42–45] and three articles were deemed to have a moderate risk of bias because of no reporting on blinding and patient group allocation concealment.[39–41] A risk bias summary grid depicting these results is shown in Figure 3. Combined results are listed in Tables 1 and 2.

Markers of oxidation

MDA was the most commonly reported biomarker of oxidative stress, reported in five of the seven studies.[39–41,44,45] Two studies demonstrated significant increases in MDA with higher FIO_2 in maternal and umbilical serum,[41] and bronchial lavage.[44] Two other studies (from the same group) reported significantly lower mucosal and postoperative arterial MDA concentrations with an FIO_2 of 0.8,[39,40] and neither maternal nor umbilical MDA concentrations changed in the remaining study.[45]

Three separate studies (from the same group) reported maternal and umbilical isoprostane concentrations.[41–43] Although the earliest of these reported significant increases in the higher FIO_2 (=0.6) group,[41] no significant differences were demonstrated in the latter two studies.[42,43]

High FIO_2 was also associated with higher fetal OHP concentrations,[41] lower bronchial PCO concentrations,[44] and lower mucosal XO concentrations[40] in three separate studies.

Antioxidant and cellular redox status

No differences in oxidised and reduced glutathione were demonstrated, either intraoperatively (1 h after induction) or 6 h after surgery, in two separate studies (both FIO_2 0.3 *vs* 0.8) from the same group.[39,40]

Only two RCTs reported on other markers of antioxidant status (Table 2). Koksal and colleagues[44] reported significant decreases in arterial and BAL SOD and PSH, and also BAL non-protein sulfhydryl (NPSH), with lower FIO_2 (0.4 *vs* 0.8) in 40 patients having colorectal surgery, and Ahuja and colleagues[45] reported no changes in TAS between control (FIO_2 0.21) and intervention (FIO_2 0.5) and in maternal arterial, fetal arterial, or fetal venous blood during elective and emergency Caesarean section.

Discussion

Evidence from this systematic review suggests that higher intraoperative FIO_2 could be associated with increased perioperative oxidative stress. Evidence from 138 patients across four studies demonstrated increased biomarkers of oxidative stress in serum and alveolar samples collected from patients receiving high FIO_2.[39–41,44] However, the number and size of all of these studies was small, and considerable uncertainty remains about which redox pathways might be most affected by intraoperative oxygen administration.

Oxygen is one of the most commonly administered perioperative drugs, yet paradoxically the debate about how much oxygen patients should receive whilst undergoing surgery remains highly controversial. Even though studies and publications frequently state that hyperoxia increases levels of oxidative stress during surgery, direct mechanistic evidence during the perioperative period appears limited. We believe this to be the first systematic review reporting oxidative stress in response to different FIO_2s during surgery and our findings show few (all small single-centre) trials have explored this during surgery to date. This is even more interesting given one of most contentious aspects of this debate amongst anaesthetists is that the WHO's guideline development group considered the PROXI trial's findings to be 'mechanistically implausible'.[2] This is surprising given that excess oxygen administration is well documented to be associated with a lack of benefit or increased harm in a variety of related clinical settings, including acute illness,[46] critical illness,[47,48] cardiac disease,[49] post resuscitation,[50] stroke,[51] and traumatic brain injury.[52–54] High FIO_2 is also thought to cause acute cardiopulmonary complications including pulmonary oedema, atelectasis, and fibrosis in the critical care setting.[55,56]

Similarly redox biomarkers have increasingly been associated with adverse clinical outcomes in a range of clinical conditions. High cysteine/glutathione ratios are associated with increased mortality in coronary artery disease.[57] Total free thiol concentrations were tightly inversely correlated both with all-cause mortality in renal transplant patients, and with adverse features in patients with chronic heart failure.[58,59] A pro-oxidant change in the free thiol ratio has also been demonstrated in patients with active malignancy,[60] myocardial infarction,[61] atrial fibrillation,[62] chronic obstructive pulmonary disease,[63] and asthma.[64] Many risk factors known to increase perioperative risk have also been associated with thiol oxidation, including ageing, smoking, alcohol abuse, and obesity.[65] It is also plausible that ROS produced under hyperoxic conditions may contribute to cellular carcinogenesis, damage DNA, and impair DNA polymerase activity, negatively affecting DNA synthesis and repair.[66,67]

Significant increases in MDA (used as a serum and tissue marker in four of the seven included trials) were observed across neonatal cord blood, arterial, bronchial, and colon mucosal samples given high FIO_2. MDA and isoprostane represent the final oxidation products of polyunsaturated fatty acids, suggesting FIO_2 might affect lipid membrane composition during surgery. Interestingly, serum MDA concentrations showed no change between different FIO_2 levels (0.4 and 0.8) in one study, but did increase within BAL and arterial samples, suggesting most oxidative stress may occur within the pulmonary vasculature.[44] ROS induced hyperoxia-induced acute lung injury, a state of increased permeability of the alveolar/vascular interface and endothelial disruption (also mediated by interleukins, cytokines, and chemokines) is well described,[68] and direct disruption of type 2 epithelial cells by oxidative and inflammatory mediators promotes cellular apoptotic and necrotic pathways.[69]

In contrast, during elective C-section, isoprostane and MDA concentrations in both maternal and umbilical serum increased up to two-fold with FIO_2 0.6,[41] supporting other research showing that redox mediators can cross the placenta.[70] However, MDA concentrations did not change in a second study where mothers received FIO_2 of 0.21 or 0.5 during both elective and emergency operations,[45] possibly because of either the lower FIO_2 or shorter duration (<10 *vs* >52 min) of oxygen exposure. Oxidative stress has been implicated in multiple obstetric complications including preterm labour, maternal vascular disease, and miscarriage, with ROS formation causing lipid peroxidation, membrane disruption of placental tissue, and dysregulation of fetal growth and development.[71–73] It is worth noting that all participants in the trials conducted by Khaw and colleagues[41–43] received spinal (regional) anaesthesia alone, so these results may not be directly comparable with patients undergoing endotracheal intubation and general anaesthesia.

Only one trial reported XO expression, an enzyme family known to directly generate ROS,[40] suggesting that inspiring high FIO_2 may attenuate XO activity at a tissue level and reduce ROS production. Given that urate, a common product of XO activity, is also one of the main constituents of many assays used to measure total antioxidant capacity,[74] other measures of antioxidant activity might also be expected to respond similarly to hyperoxia. Lack of consistency as to how antioxidant status is reported makes direct comparison challenging – two studies only reported oxidised and reduced glutathione concentrations,[39,40] whereas two other trials reported alternative markers of activity including SOD, NPSH, PSH, and TAS.[44,45] In one of these latter trials, SOD expression and both NPSH and PSH concentrations were significantly reduced with high FIO_2 administration,[44] suggesting that lower concentrations of oxygen may stimulate a greater antioxidant response or that excess oxygen might 'consume' cellular antioxidant capacity. In contrast, the other trial reported no significant differences in TAS,[45] suggesting oxidative stress was not associated with reciprocal anti-oxidation responses in these procedures performed under regional (as opposed to general) anaesthesia.

Hyperoxia-induced vasoconstriction is recognised to increase afterload and reduce cardiac output,[75,76] as well as reduce coronary blood flow.[77] Moreover, high flow oxygen administration is no longer routinely used to manage myocardial infarction.[49,78] A meta-analysis looking at all *in vivo* and *ex vivo* animal studies of oxygen-induced vasoconstriction concluded that vasoconstriction was directly proportional to the degree of oxygen exposure, and greatest within the vascular smooth muscle.[79] High FIO_2 may also contribute to peripheral and coronary vasoconstriction during anaesthesia, increasing tissue ischaemia.

Our analysis is limited by the quantity and quality of research conducted in this area. Of the seven studies identified in the current systematic review, only four studies were deemed to have low risk of reporting bias in all domains (Fig. 3). Furthermore, a high proportion of participants were young females as four of the seven included studies only recruited participants having Caesarean section procedures. It is not known how perioperative redox changes might differ between obstetric and non-obstetric surgery, but redox markers are known to vary with age, sex, body habitus and pregnancy.[35] Another limitation that has hampered progress in this field is the lack of a conceptual framework for what oxidative stress actually means *in vivo*. Many different readouts have been proposed and are currently being used as indicators of the involvement of ROS in clinical setting without a clear understanding what any of these analytes actually ‘mark’ or how these different ‘readouts of cellular activity’ may interact with each other.[80]

Taken together, our findings evidence a striking lack of high-quality research exploring the cellular consequences of perioperative oxygen administration. Historically, perioperative oxygen research has focused on the effects of hyperoxia on SSI rates as well as nausea and vomiting.[81–83] However, larger trials (such as PROXI) and meta-analyses demonstrate that the presumed association between hyper-oxygenation and reduction in SSI rates is uncertain,[8,84] and there remains strong evidence to suggest that ROS formation increases perioperative tissue inflammation.[35] Understanding whether oxygen causes shifts in the production of ROS and antioxidants has considerable implications for clinical practice, and further work is urgently needed to explore these mechanisms that underlie so many current practices in perioperative medicine.

Authors’ contributions

Conception: all authors
Design: all authors
Data collection: AHO, AC
Writing of manuscript: AHO, AC
Editing of manuscript: all authors

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Declarations of interest

DM has received honoraria for speaking and consultancy work from Siemens Healthineers and Edwards Lifesciences, and is a director of Oxygen Control Systems Ltd. MPWG serves on the medical advisory board of Sphere Medical Ltd. and is a director of Oxygen Control Systems Ltd. He has received honoraria for speaking and/or travel expenses from BOC Medical (Linde Group), Edwards Lifesciences, and Cortex GmBH. MPWG leads the Xtreme Everest Oxygen Research Consortium and the Fit-4-Surgery research collaboration. Some of this work was undertaken at University Southampton NHS Foundation Trust—University of Southampton NIHR Southampton Biomedical Research Centre. MPWG serves as the UK NIHR CRN national specialty group lead for Anaesthesia Perioperative Medicine and Pain and is an elected council member of the Royal College of Anaesthetists and president of the Critical Care Medicine Section of the Royal Society of Medicine. All other authors declare that they have no conflicts of interests.

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NIHR Southampton Biomedical Research Centre (to AHO and AC). Q7

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.09.050.

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