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REVIEW ARTICLE/BRIEF REVIEW

The impact of hyperoxia on outcomes after cardiac surgery: a systematic review and narrative synthesis

Répercussions de l'hyperoxie sur les résultats après une chirurgie cardiaque : revue systématique et synthèse narrative

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Abstract

Purpose *Historically, cardiac surgery patients have often been managed with supraphysiologic intraoperative oxygen levels to protect against the risks of cellular hypoxia inherent in the un-physiologic nature of surgery and cardiopulmonary bypass. This may result in excessive reactive oxygen species generation and exacerbation of ischemia-reperfusion injury. In this review, we synthesize all available data from randomized controlled trials (RCTs) to investigate the impact that hyperoxia has on postoperative organ dysfunction, length of stay, and mortality during adult cardiac surgery.*

Source *We searched Medline, Embase, Scopus, and Cochrane Central Register of Controlled Trials databases using a high-sensitivity strategy for RCTs that compared oxygenation strategies for adult cardiac surgery. Our primary outcome was postoperative organ dysfunction defined by postoperative increases in myocardial enzymes, acute kidney injury, and neurologic dysfunction. Secondary outcomes were mortality, ventilator days, and length of stay in the hospital and intensive care unit.*

Principal findings *We identified 12 RCTs that met our inclusion criteria. Risk of bias was unclear to high in all but one trial. Significant heterogeneity in timing of the treatment period and the oxygenation levels targeted was evident and precluded meta-analysis. The large majority of trials found no difference between hyperoxia and normoxia for any outcome. Two trials reported reduced postoperative myocardial enzymes and one trial reported reduced mechanical ventilation time in the normoxia group.*

Conclusions *Hyperoxia had minimal impact on organ dysfunction, length of stay, and mortality in adult cardiac surgery. The current evidence base is small, heterogeneous, and at risk of bias.*

Trial registration *International Prospective Register of Systematic Reviews (PROSPERO) (CRD42017074712). Registered 17 August 2017.*

Résumé

Objectif *Historiquement, les patients de chirurgies cardiaques ? ont souvent été gérés avec une oxygénothérapie peropératoire supraphysiologique pour*

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protéger contre le risque d'hypoxie cellulaire inhérent à la nature non physiologique de la chirurgie et de la circulation extracorporelle. Ceci peut entraîner la formation de dérivés réactifs de l'oxygène et l'exacerbation des lésions d'ischémie-reperfusion. Dans cette synthèse, nous avons résumé toutes les données disponibles provenant d'essais contrôlés randomisés (ECR) pour étudier l'impact de l'hyperoxie sur les troubles fonctionnels postopératoires des organes, la durée de séjour et la mortalité au cours de la chirurgie cardiaque de l'adulte.

Source *Nous avons fait des recherches dans les bases de données MEDLINE, Embase, Scopus et dans le Registre central Cochrane des essais contrôlés en utilisant une stratégie de grande sensibilité pour trouver les ECR comparant les stratégies d'oxygénation au cours de la chirurgie cardiaque de l'adulte. Notre principal critère d'évaluation était le dysfonctionnement postopératoire des organes défini par une augmentation postopératoire des enzymes myocardiques, une lésion rénale aiguë et une atteinte neurologique. Les critères d'évaluation secondaires étaient la mortalité, le nombre de jours de ventilation et la durée de séjour en unité de soins intensifs et à l'hôpital.*

Constatations principales *Nous avons identifié 12 essais cliniques randomisés qui satisfaisaient nos critères d'inclusion. Le risque de biais allait d'indéterminé à élevé dans 11 des 12 essais. Une hétérogénéité significative dans l'horaire de la période de traitement et des taux d'oxygénation visés a été évidente et a empêché une méta-analyse. Dans leur grande majorité, aucune différence sur les critères d'évaluation n'a été trouvée dans les essais entre l'hyperoxie et la normoxie. Deux essais ont décrit une baisse des enzymes myocardiques en post opératoire et un essai a décrit une baisse de la durée de la ventilation mécanique dans le groupe normoxie.*

Conclusions *L'hyperoxie a eu des répercussions minimes sur le dysfonctionnement des organes, la durée de séjour et la mortalité au cours de la chirurgie cardiaque de l'adulte. La base actuelle des données probantes est limitée, hétérogène et sujette à des biais.*

Enregistrement de l'essai clinique *International Prospective Register of Systematic Reviews (PROSPERO) (CRD42017074712). Enregistré le 17 août 2017.*

Each year, more than 1.25 million patients worldwide undergo cardiac surgery utilizing cardiopulmonary bypass (CPB).[1] The associated morbidity and mortality remain relatively high despite advances in surgical technique and anesthetic management.[1-3] One of the principal goals in the perioperative care of the cardiac surgery patient is to maintain end-organ perfusion and tissue oxygenation. With this aim in mind, it has been common practice to provide supraphysiologic levels of oxygen to patients while on CPB to protect against the risks of cellular hypoxia inherent in the un-physiologic nature of surgery and CPB. Hyperoxia during CPB may also reduce gas microembolism and improve the oxidative killing function of neutrophils.[4-6] The use of hyperoxia as an ischemic-preconditioning stimulus for cerebral and myocardial protection has also been described.[7,8]

Despite these potential benefits, there is an evolving understanding that hyperoxia may also have harmful systemic consequences.[9] The proposed harm from hyperoxia in the setting of cardiac surgery using CPB can be broadly divided as arising from three separate but interrelated mechanisms. These mechanisms are hyperoxia-related cardiovascular dysregulation, direct tissue injury from increased production of reactive oxygen species (ROS), and enhancement of ischemia-reperfusion injury.[9-12]

High partial pressures of oxygen have multiple direct effects on the heart and peripheral vasculature. Oxygen has a direct vasoconstrictive effect that leads to an increase in systemic vascular resistance as well as an increased coronary vascular resistance.[10,13,14] Hyperoxic conditions also lead to an impairment of diastolic dysfunction by altering calcium handling in the myocyte sarcoplasmic reticulum.[15] These direct effects have the potential to result in impaired coronary and systemic perfusion during cardiac surgery. Hyperoxic conditions also result in the increased and incomplete reduction of oxygen leading to formation of the superoxide radical.[4] Superoxide dismutases convert superoxide to hydrogen peroxide, which can go on to form a group of highly reactive oxygen-containing compounds known as ROS.

During cardiac surgery utilizing CPB, reperfusion of ischemic myocardium occurs after release of the aortic cross-clamp. The reperfusion phase is characterized by enhanced production of ROS, dysregulation of intracellular and mitochondrial calcium, microvascular dysfunction, and a hyperactive immune response.[16] This detrimental constellation of events is known as ischemia-reperfusion injury and is believed to be exacerbated by hyperoxic conditions.[4,17]

There are compelling arguments both for and against the use of hyperoxia in cardiac surgery. The aim of this systematic review is to identify, critically appraise, and synthesize the highest quality evidence to inform clinical practice and identify unanswered questions for future trials. Our primary objective was to determine the impact of hyperoxic *vs* normoxic oxygenation strategies on postoperative organ dysfunction, length of stay, and mortality during adult cardiac surgery with CPB.

Methods

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 17 August 2017 (CRD42017074712, http://www.crd.york.ac.uk/prospero/display_record.php?RecordID=74712). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed while writing this review.[18]

Eligibility criteria

We included randomized trials in humans $\geq$ 18 yr of age who underwent cardiac surgery, with at least 80% of patients undergoing CPB. This allowed for inclusion of trials that may have a small subset of patients that underwent off-pump cardiac surgery.

Only randomized controlled trials (RCTs) were considered for inclusion. In considering RCTs, we allowed for any intervention that targeted a specific partial pressure of oxygen (PaO_2), or specified the delivered fraction of inspired oxygen (F_iO_2), at any point during the patient's time in the operating room. We included any comparator PaO_2 target or F_iO_2. Given that there is no universally accepted definition of hyperoxia,[19] we did not pre-specify thresholds for hyperoxic or normoxic F_iO_2 or PaO_2 targets, but instead relied on the individual study definitions.[1,17]

The primary outcome examined was postoperative organ dysfunction defined by: 1) postoperative increases in myocardial enzymes (creatine kinase [CK] and/or troponin), 2) acute kidney injury (AKI), and 3) neurologic dysfunction. The definition of AKI and neurologic dysfunction was in accordance with the individual study report definitions. Secondary outcomes included mortality at the longest follow-up, days on a ventilator, as well as hospital and intensive care unit (ICU) length of stay.

Information sources and search

A systematic search of the literature identified potentially relevant studies. The initial bibliographic database search strategy was designed by a professional librarian using Ovid Medline and was peer-reviewed by an independent librarian using the Peer Review of Electronic Search Strategies (PRESS) guidelines.[20] Searches of the following bibliographic databases, from inception to present, were conducted on 26 June 2017 and then updated on 22 November 2017: Medline (Ovid), Embase (Ovid), Scopus (Elsevier), and the Cochrane Central Register of Controlled Trials (Wiley). Results were limited to English language publications. Animal studies, commentaries, editorials, letters, and historical articles were excluded. See the Appendix for the complete search strategy using Medline, which was subsequently adapted for the other databases. A search of the grey literature to identify unpublished studies was also conducted in clincialtrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), and Open Grey on 26 June 2017 and again on 22 November 2017.

The electronic search was further supplemented with a hand search of conference abstracts presented in the past three years from the American Society of Anesthesiologists, the European Society of Anaesthesiology, the Canadian Anesthesiologists' Society, the Society of Thoracic Surgeons, The American Association for Thoracic Surgery, The European Society of Thoracic Surgeons, and the Society of Critical Care Medicine. The reference lists of included articles were also mined for additional citations.

We included all English language reports regardless of their age or publication status. Both abstracts and full manuscripts were included. When only an abstract was available, we contacted the authors to request a full manuscript. All authors of completed trials identified through clinicaltrials.gov or ICTRP were contacted and asked to provide a manuscript for review.

Study selection

Titles and abstracts of the reports identified by our search were screened independently by two reviewers (J.H. and C.L.). Full texts were obtained for all relevant reports and were again independently screened for inclusion. Discrepancies between the two reviewer's decisions were resolved by consensus discussion and consultation with a third reviewer (H.G.).

Data collection and processing

We developed a standardized data extraction form that was tested and revised by a single reviewer (J.H.). The form was then applied independently in duplicate by two reviewers (J.H. and C.L.) to all the included reports. The forms were reviewed and discrepancies resolved by consensus discussion.

Data extracted from the reports included first author and citation, study period, and funding source. Demographic details of the included patients in each trial were collected including age, body mass index, and sex. Information regarding the surgical procedures performed in each study included type of cardiac surgery performed, procedure urgency, CPB time, and aortic cross-clamp time. Details of the intervention and comparator in each trial were recorded, including the PaO_2 levels or delivered F_iO_2, as well as the timing of the intervention. Finally, data were collected for all three primary and four secondary outcomes. This included

information on how outcomes were defined by study authors, when outcomes were assessed, what assays were used, and from which sites blood samples were taken. If postoperative myocardial enzyme levels were sampled at multiple time points, we included their maximum value in our data set. We preferentially reported data for enzymes sampled from peripheral venous and arterial sites over those collected from coronary sinus blood.

Risk of bias

Risk of bias in the included studies was assessed using the Cochrane Risk of Bias Tool.[21] Each report was assessed at the study level for risk of bias in seven domains including: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each study was evaluated independently by two reviewers (J.H. and C.L.). Disagreement between the two reviewer's assessments was resolved by consensus discussion and consultation with a third reviewer (A.A.). Overall risk of bias for an individual study was considered high if there was a high risk of bias in any of the individual domains. If there were no domains at high risk of bias, but one or more domains had an unclear risk, the overall risk of bias was rated unclear. Only if all the domains were at low risk of bias was the study assessed as having a low risk of bias overall.

Synthesis of results

We intended to perform a meta-analysis for outcome if there was sufficient clinical and statistical homogeneity; the methods for a meta-analysis were outlined prospectively in our protocol. After all included trials had been reviewed, we determined that there was too much clinical heterogeneity to conduct a sound meta-analysis. In lieu of a meta-analysis, a narrative synthesis was performed. Further, since we did not conduct a meta-analysis, we were unable to formally investigate publication bias.

Results

Study characteristics

Our initial database search identified 4,421 items (Fig. 1). Following screening, we identified 11 RCTs that met our

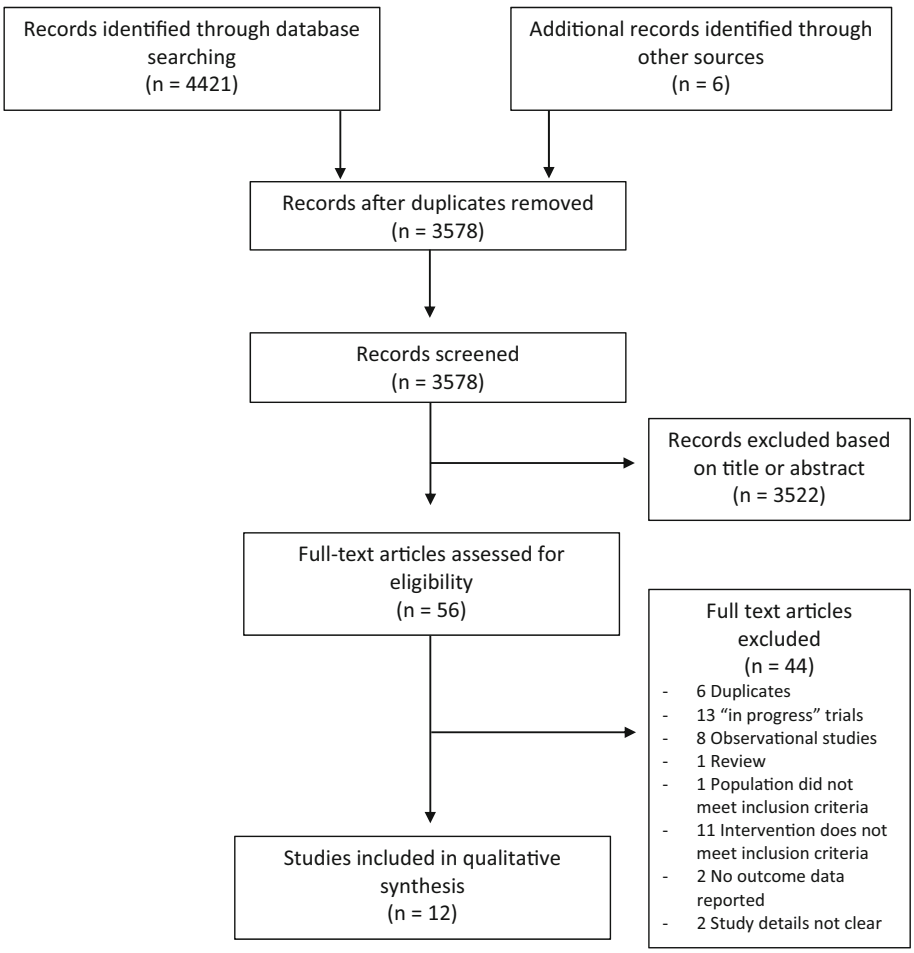

Fig. 1 Study selection flow diagram

inclusion criteria. An additional trial was identified by hand searching the reference lists of the included RCTs, leaving us with a total of 12 RCTs for inclusion.[22] Hand screening of conference abstracts did not identify any additional RCTs that were eligible for inclusion. Authors of an English abstract from a Korean-language manuscript were contacted for an English manuscript, but did not reply.[23] There was sufficient detail in the abstract alone to allow for inclusion in our review. In two trials identified in our database search, details of the study intervention were reported with insufficient depth to be evaluated as part of our review and were not included.[24,25] The authors were contacted for clarification, but we did not receive a response.

The 12 included RCTs were published between 1991 and 2016 (Table 1). Only five of the reports described how the trials were funded.[1,8,9,26,27] None of these trials were industry supported. The average age of patients included in trial intervention groups ranged from 47 to 68 years (Table 1). The majority of patients were male in the treatment and control arms of all but one included trial (Table 1).

All of the RCTs included only patients scheduled for elective surgery. Nine of the trials included patients for coronary artery bypass grafting (CABG) only; one trial included patients for isolated valvular surgery only; two trials included patients for CABG, isolated valvular, as well as combined procedures (Table 1). Mean (standard deviation [SD]) CPB times were reported in ten trials and ranged from 63 (26) to 156 (10) min.[1,9,22,23,26-31] Mean (SD) aortic cross clamp times were reported in ten trials and ranged from 43 (12) to 112 (43) min.[1,8,9,22-24,26,28,29,31]

There was marked heterogeneity in the timing of the study intervention in these trials. There were five distinct time periods over which the oxygenation strategy being evaluated was applied. These included the pre-CPB period, during CPB, during the reperfusion phase (i.e., after aortic cross-clamp removal), during rewarming, and during the postoperative ICU period. The 12 included RCTs applied their intervention over six distinct combinations of these time periods (Table 1).

The specific oxygenation strategy used in the normoxia and hyperoxia arms of each study also varied substantially. Six trials used specific PaO_2 targets, five trials prescribed a set F_iO_2, and one trial used a combination of PaO_2 and pulse oximetry (SpO_2) targets (Table 1). There were also significant differences in authors' choices of oxygenation thresholds for their normoxic and hyperoxic treatment arms (Figs. 2 and 3).

The resulting heterogeneity from the differences in timing of the study intervention as well as the varying oxygenation strategies precluded us from conducting a meta-analysis.

Risk of bias

Risk of bias assessment using the Cochrane Risk of Bias Tools is presented in Fig. 4. Only one report described methods of sequence generation and allocation concealment that were rigorous and detailed enough to be at low risk of bias.[1] In seven studies the risk of bias was unclear. Four studies were at high risk of bias for selective reporting.[22,26,30,32] These studies reported on outcomes that were not detailed in a protocol or their methods section. Reporting quality was generally poor.

Primary outcomes

Five trials reported on postoperative CK levels (Table 2). One trial found that mean (SD) post-CPB coronary sinus blood CK levels were 293 (21) $U{\cdot}L^{-1}$ when patients had a PaO_2 target of 140 mmHg on CPB and 672 (130) $U{\cdot}L^{-1}$ when a PaO_2 of 400 mmHg was targeted ($P = 0.002$).[30] The other four trials reported on the CK-MB subtype in arterial blood and found no significant difference in postoperative levels between groups.[8,9,28,29]

Six trials included postoperative troponin levels as a reported outcome (Table 2). One trial found that the maximum postoperative troponin was significantly higher in the hyperoxia group.[29] Five trials found no significant difference between postoperative troponins in the hyperoxic and near-physiologic groups.[1,8,9,23,26]

The occurrence of postoperative AKI was examined in three trials (Table 2). The definitions of AKI in the various reports varied.[33,34] One trial used the Kidney Disease: Improving Global Outcomes AKI Work Group guidelines (KDIGO), while the other two trials reported on "renal failure" and "renal complications' without further details.[1,31,32] One trial found that 8.3% of patients on CPB with a PaO_2 of 190-300 mmHg had postoperative renal failure whereas 4.2% of patients exposed to a PaO_2 of 75-112 mmHg had renal failure.[31] A P value was not reported. One trial found no significant difference in postoperative AKI in hyperoxic and near-physiologic groups (using KDIGO criteria); another had no postoperative renal complications in either group.[1,32]

Neurologic dysfunction was examined in two trials (Table 2). In a trial comparing CPB with a PaO_2 of 190-300 mmHg to 75-112 mmHg, 4.2% of patients in the hyperoxic group had a cerebrovascular accident compared

Table 1 Descriptive characteristics of trials included in the review

Trial	*n*	Age	Male sex	Population	Timing of intervention	Oxygenation strategy (N/H)	Outcomes reported
Belboul *et al.*,[31] 1991	N: 24 H: 24	N: 61 (7) H: 62 (4) [mean, SD]	N: 21/24 (88%) H: 19/24 (79%)	elective CABG	CPB	N: PaO_2 75-112 mmHg H: PaO_2 190-300 mmHg	AKI, neuro, mortality, vent time
Ihnke *et al.*,[30] 1998	N: 20 H: 20	N: 63 (2) H: 61(2) [mean, SD]	N: 17/20 (85%) H: 16/20 (80%)	elective CABG	CPB	N: PaO_2 140 mmHg H: PaO_2 400 mmHg	CK, vent time, ICU LOS, Hosp. LOS
Pizov *et al.*,[27] 2000	N: 15 H: 15	NR	NR	elective CABG	Pre-CPB, CPB	N: F_IO_2 0.5 pre CPB and F_iO_2 0.5 CPAP on CPB H: F_IO_2 1.0 pre CPB and F_iO_2 1.0 CPAP during CPB	Vent time
Kim *et al.*,[23] 2001	N: 15 H: 15	N: 49.87 (5.35) H: 46.93 (5.76) [mean, SE]	N: 7/15 (47%) H: 8/15 (53%)	elective CABG, valve, combined	CPB	N: PaO_2 120 mmHg H: PaO_2 400 mmHg	Troponin
Inoue *et al.*,[29] 2002	N: 10 H: 10	N: 65.0 (2) H: 65.6 (1.7) [mean, SE]	N: 6/10 (60%) H: 6/10 (60%)	elective CABG	reperfusion	N: PaO_2 200-250 mmHg H: PaO_2 450-550 mmHg	CK/Troponin
Abdel-Rahman *et al.*,[22] 2003	N: 10 H: 9	N: 68.4 (55.8-76.4) H: 64.4 (54.4-76.2) [mean, range]	NR	elective CABG	reperfusion	N: PaO_2 50-70 mmHg H: $PaO_2 > 250$ mmHg	mortality
Karu *et al.*,[8] 2007	N: 20 H: 20	N: 64 (9) H: 60 (7) [mean, SD]	N: 12/20 (60%) H: 16/20 (80%)	elective CABG	Pre-CPB	N: F_IO_2 0.4 H: F_IO_2 0.96	CK/Troponin
Toraman *et al.*,[32] 2007	N: 30 H1: 30 H2: 30	NR	NR	elective CABG	CPB initiation to rewarming	N: F_IO_2 0.35-0.45 H1: F_IO_2 0.4-0.5 H2: F_IO_2 0.4-0.6	AKI, neuro, mortality, ICU LOS, Hosp. LOS
Lee *et al.*,[28] 2010	N: 28 H: 28	N: 55.8 (11) H: 53.6 (10) [mean, SD]	N: 14/28 (50%) H: 17/28 (61%)	elective single valve	reperfusion	N: F_iO_2 0.5 H: F_iO_2 0.7	CK, vent time, ICU LOS, Hosp. LOS
Karu *et al.*,[26] 2012	N: 19 H: 20	N: 65 (8) H: 66 (11) [mean, SD]	N: 12/19 (63%) H: 16/20 (74%)	elective CABG	Pre-CPB	N: F_IO_2 0.4 H: F_IO_2 0.96	Troponin, mortality
McGuinness *et al.*,[1] 2016	N: 150 H: 148	N: 65.8 (20-88) H: 65.3 (30-90) [mean, range]	N: 108/150 (72%) H: 110/150 (73%)	elective CABG, valve, combined	Pre-CPB, CPB	N: SpO_2 target 92-95% pre-CPB, PaO_2 75-90 mmHg on CPB H: F_IO_2 titrated for $SpO_2 \geq 99\%$	Troponin, AKI, mortality, vent time, ICU LOS, Hosp. LOS

Table 1 continued

Trial	*n*	Age	Male sex	Population	Timing of intervention	Oxygenation strategy (N/H)	Outcomes reported
Smit *et al.*,[9] 2016	N: 25 H: 25	N: 68 (66-61) H: 66 (67-71) [median, IQR]	N: 25/25 (100%) H: 25/25 (100%)	elective CABG	Pre-CPB, CPB, post-op	N: PaO_2 130-150 mmHg on CPB and 80-100 mmHg in ICU H: PaO_2 200-220 on CPB and 130-150 mmHg in ICU *	CK/Troponin, mortality, vent time, ICU LOS

AKI = acute kidney injury; CABG = coronary artery bypass graft; CK = creatine kinase; CPAP = continuous positive airway pressure; CPB = cardiopulmonary bypass; F_IO_2 = fraction of inspired oxygen; H = hyperoxia group; ICU = intensive care unit;

IQR = interquartile range; LOS = length of stay; N = normoxia group; NR = not reported; PaO_2 = partial pressure of oxygen; SD = standard deviation; SPO_2 = peripheral capillary oxygen

*Smit *et al.*[9] Also delivered an $\mathbf{F_I}O_2$ in the hyperoxia group after intubation and before cardiopulmonary bypass, while in the normoxia group a $F_IO_2 < 0.4$ was delivered

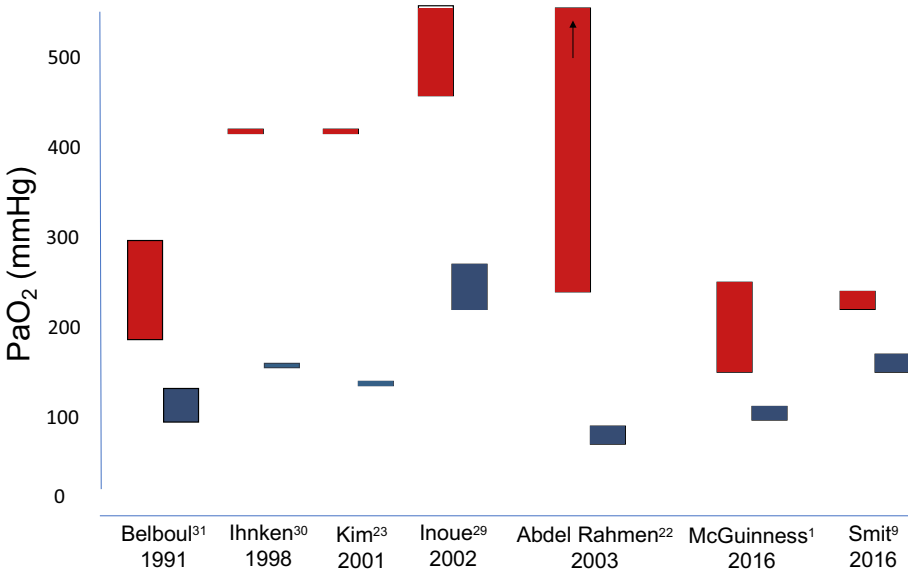

Fig. 2 The ranges of partial pressure of oxygen (PaO_2) targets used in the individual trials included in our systematic review. Red boxes represent hyperoxic treatment groups and blue boxes represent normoxic

with 0% in the near-physiologic group (no *P* value reported).[31] In another trial there was no postoperative neurologic dysfunction reported across any groups.[32]

Secondary outcomes

Postoperative mechanical ventilation time was included as an outcome in six trials (Table 2). In one trial patients who were exposed to a PaO_2 of 75-112 mmHg on CPB were ventilated for a mean (SD) of 5.3 (1.8) hr, while those with a PaO_2 of 190-300 mmHg required 7.2 (2.5) hr of mechanical ventilation ($P < 0.01$).[31] The other five trials reported no difference between groups.[1,9,27,28,30]

Five RCTs examined length of stay in the ICU and four examined length of stay in the hospital (Table 2). The oxygenation strategy had no impact on either outcome in any study. There was no difference in mortality between groups in any of the six RCTs that included it as an outcome (Table 2).

Discussion

The level of oxygen that patients should be exposed to during cardiac surgery is an important clinical question that has been asked by investigators for over two decades. What makes this question so intriguing is the simplicity of the intervention, the complexity of its multisystem effects, and the potential to make a real difference to clinically important outcomes.[35,36] Our systematic review aimed to assess the impact that hyperoxia during adult cardiac surgery has on postoperative organ dysfunction, length of stay, and mortality by synthesizing the evidence from all

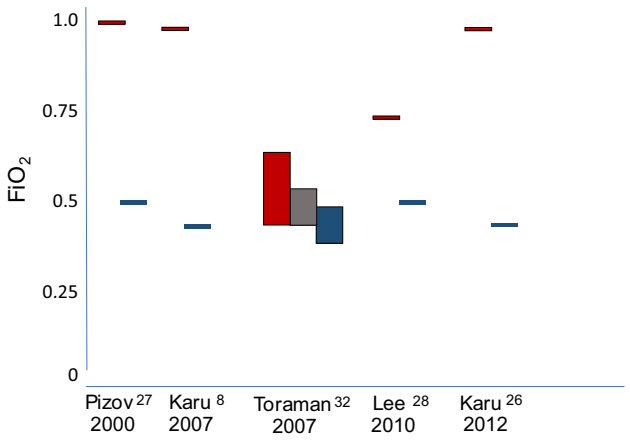

Fig. 3 The ranges of fraction of inspired oxygen (F_IO_2) prescribed to the normoxic and hyperoxic treatment groups in individual trials included in our systematic review. Red boxes represent hyperoxic groups and blue boxes represent normoxic. Toraman *et al.*[32] included three treatment groups

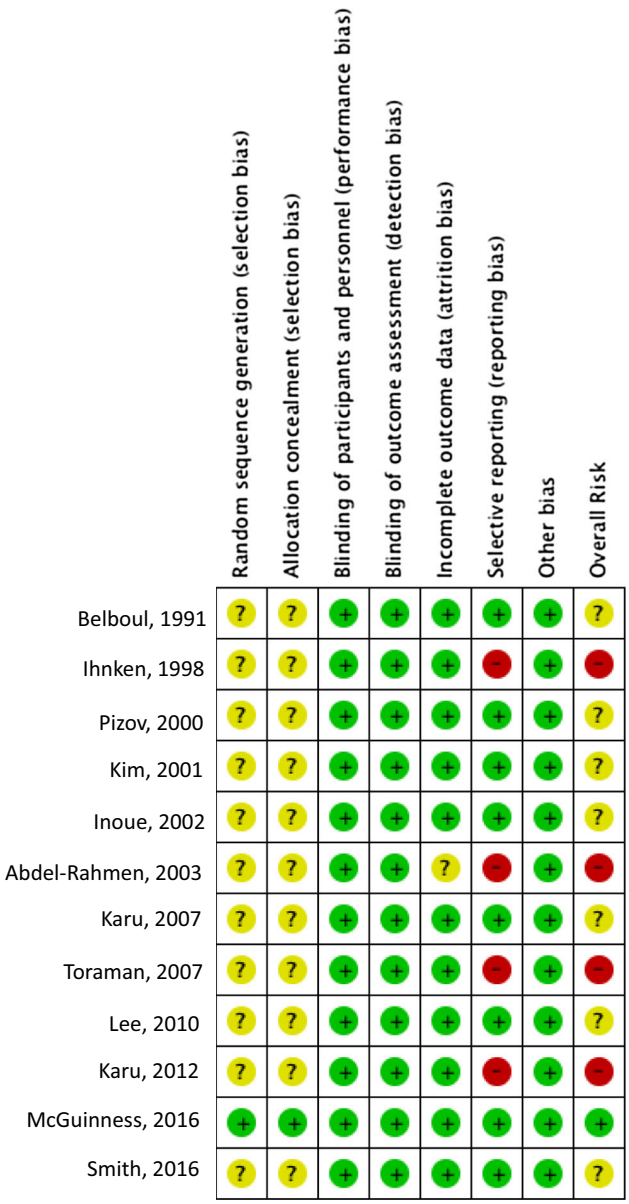

Fig. 4 Risk of bias summary. Each study was assessed at the report level using the Cochrane Risk of Bias Tool. Assessments were done in duplicate by two blinded reviewers. Discrepancies were resolved by consensus and consultation with a third reviewer. Seven unique domains were assessed. Green circles represent a low risk of bias, yellow represent an unclear risk of bias, and red represent a high risk of bias. The overall assessment was based on the highest risk assessment in any individual domain

available RCTs to date. We were unable to perform a meta-analysis because of the significant clinical heterogeneity in the included trials and instead provide this narrative synthesis.

We chose to examine postoperative organ dysfunction as our primary outcome because the impact of hyperoxia during CPB on ROS production and ischemia-reperfusion injury is best detected at the individual organ level. Although it could be argued that postoperative myocardial enzyme levels are not a particularly patient-centred outcome, we believe that it is an important marker of myocardial injury.[37] Additionally, postoperative myocardial enzyme levels are the most commonly studied outcome in this field and therefore inclusion of these results allowed us to synthesize the most comprehensive summary of the current evidence. We anticipated that report definitions and timing of data collection for neurologic dysfunction, AKI, and rise in myocardial enzymes would be heterogeneous. Therefore, we chose to summarize individual report definitions rather than dictate our own *a priori*. Mortality, days on a ventilator, and length of stay (ICU and hospital) were also included as secondary outcomes, ensuring that all outcomes important to individual patients were addressed.

The RCTs that met the inclusion criteria for our review spanned over two decades (1991 to 2016).[1,9,31] There was significant heterogeneity in study design, particularly in two key areas: the timeline over which the oxygenation strategy being studied was employed and the degree of hyperoxia or normoxia participants were exposed to. Additionally, some trials subjected participants to a constant F_IO_2 whereas others adjusted F_IO_2 to meet a PaO_2 target.

An important limitation to interpreting this literature is that the PaO_2 targets were so disparate across studies that the normoxic targets in some trials were higher than the hyperoxic targets in others (Figs. 2 and 3). One explanation for this is that there are no established guidelines for specific PaO_2 targets on bypass and clinical practice is highly variable.[38] The results of our review suggest that there is no agreement in the literature as to what conditions

Table 2 Results of included trials

Trial	CK	Troponin	AKI	Neurological dysfunction	Mortality	Ventilator time (hr)	ICU LOS	Hospital LOS (days)
Belboul, *et al.*[31] 1991	NR	NR	N: 1/24 (4.2%) H: 2/24 (8.3%) P = NR	N: 0/24 (0%) H: 1/24 (4.2%) P = NR	N: 0/24 (0%) H: 0/24 (0%) P = NR	N: 5.3 (1.8) H: 7.2 (2.5) Mean, (SD) $P < 0.01$	NR	NR
Ihnken *et al.*[30] 1998	Post-CPB ^ N: 293 U·L^{-1} (21) H: 672 U·L^{-1} (130) Mean, (SD) P = 0.002	NR	NR	NR	NR	N: 14 (1) H: 22 (8) Mean, (SD) P = 0.2	N: 1.6 d (0.2) H: 1.9 d (0.1) Mean, (SD) P = 0.08	N: 8.6 (0.3) H: 9.6 (0.5) Mean, (SD) P = 0.06
Pizov *et al.*[27]2000	NR	NR	NR	NR	NR	N: 10.4 (3.3) H: 12.3 (5.5) Mean, (SD) P = 0.36	NR	NR
Kim *et al.*[23] 2001	NR	Post-CPB ^ * N: 0.5 μg·L^{-1} H: 0.6 μg·L^{-1} P = NR	NR	NR	NR	NR	NR	NR
Inoue *et al.*[29] 2002	Maximum postoperative * N: 52 μg·L H: 82 μg·L^{-1} Mean $P > 0.05$	Maximum Postoperative * N: 1.2 μg·L^{-1} H: 2.8 μg·L^{-1} Mean $P < 0.05$	NR	NR	NR	NR	NR	NR
Abdel-Rahmnn *et al.*[22] 2003	NR	NR	NR	NR	N: 0/10 (0%) H: 0/9 (0%) P = NR	NR	NR	NR
Karu *et al.*[8] 2007	POD#1 N: 51.5 μg·L^{-1} (28.0-74.7) H: 40.3 μg·L^{-1} (31.8-55.8) Median, [IQR] $P > 0.05$**	POD#1 N: 17 μg·L^{-1} (7.7-25.5) H: 11.7 μg·L^{-1} (6.88-15.7) Median, [IQR] $P > 0.05$**	NR	NR	NR	NR	NR	NR
Toraman *et al.*[32] 2007	NR	NR	N: 0/30 (0%) H1: 0/30 (0%) H2: 0/30 (0%) P = NR	N: 0/30 (0%) H1: 0/30 (0%) H2: 0/30 (0%) P = NR	N: 0/30 (0%) H1: 0/30 (0%) H2: 0/30 (0%) P = *NR*	NR	N: 22.1 hr (7.1) H1: 21.9 hr (5.9) H2: 20.9 hr (6.6) Mean, (SD)	N: 5.2 (2.2) H1: 5.5 (2.9) H2: 5.3 (2.7) Mean, (SD)

Table 2 continued

Trial	CK	Troponin	AKI	Neurological dysfunction	Mortality	Ventilator time (hr)	ICU LOS	Hospital LOS (days)
Lee *et al.*[28] 2010	POD#1 N: 73.8 $\mu g \cdot L^{-1}$ (92.8) H: 51.9 $\mu g \cdot L^{-1}$ (40.4) Mean, (SD) $P = 0.266$	NR	NR	NR	NR	N: 16.2 (7.9) H: 13.4 (6.3) Mean, (SD) $P = 0.149$	N: 2.9 d (0.8) H: 3.1 d (1.4) Mean, (SD) $P = 0.409$	N: 11.2 (3.1) H: 11.5 (5.0) Mean, (SD) $P = 0.780$
Karu *et al.*[26] 2012	NR	POD#1 N: 0.44 $\mu g \cdot L^{1}$ (0.26-0.55) H: 0.45 $\mu g \cdot L^{-1}$ (0.37-0.71) Median, [IQR] $P > 0.05$**	NR	NR	N: 0/19 (0%) H: 0/20 (0%) $P =$ NR	NR	NR	NR
McGuinness *et al.*[1] 2016	NR	Maximum Postoperative N: 0.535 $\mu g \cdot L^{-1}$ (0.354-0.892) H: 0.641 $\mu g \cdot L^{-1}$ (0.345-0.103) Median, [IQR] $P = 0.23$	N: 108/150 (72%) H: 98/148 (66.2%) $P = 0.28$	NR	N: 5/150 (3.3%) H: 4/148 (2.7%) $P = 0.75$	N: 7.2 (5.3-16.6) H: 7.2 (5.0-13.0) Median, [IQR] $P = 0.35$	N: 22.8 hr (20.6-48.5) H: 23.3 hr (19.7-47.3) Median, [IQR] $P = 0.75$	N: 9.0 (7.1-13) H: 8.9 (6.7-13.5) Median, [IQR] $P = 0.65$
Smit *et al.*[9] 2016	Maximum Postoperative N: 24.9 $\mu g \cdot L^{-1}$ (18.4-31.5) H: 25.8 $\mu g \cdot L^{-1}$ (21.0-32.3) Median, [IQR] $P = 0.528$	Maximum Postoperative N: 0.42 $\mu g \cdot L^{-1}$ (0.26-0.49) H: 0.35 $\mu g \cdot L^{-1}$ (0.30-0.46) Median, [IQR] $P = 0.923$	NR	NR	N: 0/25 (0%) H: 0/25 (0%) $P =$ NR	N: 4.3 (3.1-6.2) H: 4.1 (3.2-5.0) Median, [IQR] $P = 0.383$	N: 22.5 hr (19.5-24.5) H: 22 hr (19-24) Median, [IQR] $P = 1.000$	NR

AKI = acute kidney injury; CK = creatine kinase; CPB = cardiopulmonary bypass; H = Hyperoxia group; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; N = Normoxia group; NR = not reported; POD = postoperative day; SD = standard deviation

* Data from figure

** no *P* value reported, significance ($P < 0.05$) stated in text

^ Samples from coronary sinus blood, all other reported results from peripheral venous or arterial blood

should be considered normoxic or hyperoxic during cardiac surgery. That said, a trend towards lower PaO_2 targets in the two most recent RCTs may be indicative of a recent change in clinical practice towards more conservative oxygenation strategies based on evidence from the myocardial infarction and cardiac arrest literature suggesting that high oxygen levels during reperfusion after ischemia may have deleterious effects.[39-42] Real-time continuous in-line PaO_2 monitoring has only recently been widely available, which may explain why some investigators chose to prescribe a specific F_iO_2 to their intervention groups rather than set PaO_2 targets. This variation in study design further made it impossible to proceed with a rigorous meta-analysis of trial data.

The majority of trials found no difference in postoperative organ dysfunction between groups treated with hyperoxic and normoxic strategies during cardiac surgery. One small trial of 20 patients undergoing elective CABG found that the peak postoperative troponin levels were higher in patients who were exposed to a hyperoxic strategy during reperfusion.[29] Notably, there was no difference in the peak CK-MBs between groups in this same trial. Another trial of 40 patients having elective CABG surgery found post-CPB CK levels were higher in

the coronary sinus blood of patients who had a higher PaO_2 target during CPB.[30] Only two trials have shown a statistically significant result for any of our primary outcomes. Together these two positive trials only contained 60 of the 741 patients studied in trials that reported on at least one of the primary outcomes.

There was no difference between the hyperoxic and normoxic intervention groups for all secondary outcomes in all but one trial. One RCT found that patients exposed to a higher PaO_2 on CPB spent a longer time on the ventilator postoperatively.[31] No trials found that the oxygenation strategy used during cardiac surgery had a significant impact on mortality or length of stay.

Risk of bias, as assessed using the Cochrane Risk of Bias Tool, was low only in one trial.[1] Four studies had a high risk of bias because they reported on outcomes that were not described in their protocol or methods.[22,26,30,32] Seven studies had an unclear risk of bias, primarily because they did not report on their methods of sequence generation or allocation concealment with enough detail to satisfy the Cochrane criteria for low risk of bias.[8,9,23,28,29,31] That said, the primary and secondary outcomes included in our review –-were hard outcomes unlikely to be impacted by lack of blinding of participants, personnel, and outcome assessors.[43] Therefore, we did not require strict blinding to obtain a low risk of bias assessment for these domains. It would be helpful if authors of future trials would closely adhere to the CONSORT statement while writing their reports to provide better clarity for risk of bias assessment.[44] Our search strategy and inclusion criteria were limited to English-language reports, which may have introduced a review-level selection bias.

It is unclear why avoidance of hyperoxia in cardiac surgery has not translated into improved clinical outcomes. It is a complex question with an answer that is perhaps too nuanced to be elucidated by any of the trials published to date. If the central harm of hyperoxia is due to enhanced ROS production resulting in exacerbation of ischemia reperfusion injury, then its clinical impact must be consistent with the timing and proportional to the actual degree of ischemia. Trials such as those published by McGuinness *et al.*—by far the largest included in this review—that delivered near-physiologic oxygen levels may have actually aggravated the occurrence of CPB-related ischemia by exposing patients to the relatively lower oxygen levels during time periods of poor tissue perfusion.[1] It follows then that those in the arm that received hyperoxia could have reduced ischemic injury during CPB and therefore reduced ischemia-reperfusion injury in the post-reperfusion period.[1] If there is reduced ischemia in the first place (i.e., in the hyperoxia group, which was originally hypothesized to be injurious), there is less basis for ischemia-reperfusion injury and the amount of oxygen that the patient receives during reperfusion becomes less relevant.

An additional reason for the lack of impact of hyperoxia avoidance on clinical outcomes may be that the treatment separation achieved between hyperoxic and normoxic groups in some trials was quite narrow or non-existent. The largest of the trials by McGuinness *et al.* failed to achieve treatment separation in the pre- and post-CPB intervention periods.[1] This might be explained by the trial's pragmatic design and anesthesiologists who were uncomfortable targeting a near-physiologic PaO_2 while patients were not on CPB. Clinicians and trialists should be reassured by the results of the other most recently published trial by Smit *et al.*[9] This group achieved excellent treatment separation between the normoxic and hyperoxic groups in all phases of their study and had no hypoxic events ($PaO_2 < 55$ mmHg).[9]

We speculate that the ideal strategy may be to exploit temporal variation in PaO_2 during cardiac surgery to improve clinical outcomes. That is, avoidance of hyperoxia is likely to be of most benefit during the reperfusion phase after resumption of pulsatile flow to ischemic tissue beds. On the other hand, use of hyperoxia during periods of poor tissue perfusion might be beneficial compared with normoxia. Thus, future trials could target hyperoxia in the pre-bypass period and while on CPB to limit ischemia and then target normoxia during reperfusion to reduce exacerbation of subsequent ROS-mediated reperfusion injury. There are currently at least four registered trials in progress that would have met inclusion for this review and will enhance our understanding of the topic when complete.[45-48] Nevertheless, none of these trials employ oxygenation targets that vary at critical points during the procedure to minimize both tissue hypoxia and ischemia-reperfusion injury.

Conclusions

Compared with normoxic strategies, the impact of hyperoxia on postoperative organ dysfunction, length of stay, and mortality in adult cardiac surgery patients appears to have been minimal, though the evidence base is highly heterogeneous (with marked variability in study design) and is also at risk of bias. There is no universal consensus on what represents a truly hyperoxic PaO_2 during cardiac surgery. Clinical equipoise exists for future trials to expose patients to a wide range of oxygenation strategies. Further rigorously designed RCTs with meticulous reporting are needed to inform decision-making.

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Conflicts of interest None declared.

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Author contributions *Jeffrey Heinrichs*, *Hilary P. Grocott*, and *Ahmed Abou-Setta* designed the review and wrote the protocol. *Ahmed Abou-Setta* provided methodologic advice. *Christine Neilson* designed and executed the search. *Jeffrey Heinrichs* and *Carly Lodewyks* acquired the data. *Jeffrey Heinrichs*, *Carly Lodewyks*, and *Hilary P. Grocott* analyzed and interpreted the data. *Jeffrey Heinrichs* drafted the manuscript. *Hilary P. Grocott* supervised the review and served as a content expert. All authors critically revised the article for important intellectual content.

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APPENDIX Search Strategy for Medline (Ovid)

Ovid MEDLINE(R) Epub Ahead of Print, In-Process, & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Date searched: 26 June 2017

1	Hyperoxia/	3215
2	Oxygen/	154591
3	(hyperoxia or hyperoxias or hyperoxic or hyperox?emia or hyperoxygenat*).ti,ab,kf.	8900
4	(normoxemia or normoxia).ti,ab,kf.	7847
5	(oxygen adj5 ("partial pressure" or fraction or tension)).ti,ab,kf.	20327
6	((oxygen or oxygenation) adj2 strategy).ti,ab,kf.	111
7	or/1-6	175013
8	cardiopulmonary bypass/	22748
9	(((Cardiopulmonary or "Cardio pulmonary" or "heart lung" or heartlung) adj3 bypass*) or CPB).ti,ab,kf.	31454
10	8 or 9	38064
11	7 and 10	1636
12	11 not (exp animals/not humans/)	1226
13	Comment/	693182
14	Editorial/	443105
15	News/	183664
16	(letter not (letter and randomized controlled trial)).pt.	971042
17	historical article/	348446
18	or/13-17	2084513
19	12 not 18	1174
20	limit 19 to English language	1086

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