Forum

WHO Needs High FIO$_2$?

Ozan Akca[1], Lorenzo Ball[2], F. Javier Belda[3], Peter Biro[4], Andrea Cortegiani[5], Arieh Eden[6], Carlos Ferrando[3], Luciano Gattinoni[7], Zeev Goldik[6], Cesare Gregoretti[5], Thomas Hachenberg[8], Göran Hedenstierna[9], Harriet W. Hopf[10], Thomas K. Hunt[11], Paolo Pelosi[2], Motaz Qadan[12], Daniel I. Sessler[13], Marina Soro[3], Mert Şentürk[14]

[1]Department of Anesthesiology and Perioperative Medicine, Neuroscience ICU, University of Louisville, Kentucky, USA
[2]IRCCS AOU San Martino-IST, Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy
[3]Department of Anesthesiology and Critical Care, Hospital Clinico Universitario, University of Valencia, Valencia, Spain
[4]Institute of Anesthesiology, University Hospital Zurich, Switzerland
[5]Department of Biopathology and Medical Biotechnologies (DIBIMED), Section of Anesthesia, Analgesia, Intensive Care and Emergency. Policlinico Paolo Giaccone. University of Palermo, Italy
[6]Department of Anesthesiology, Critical Care and Pain Medicine, Lady Davis Carmel Medical Center, Haifa, Israel
[7]Department of Anesthesiology Emergency & Intensive Care Medicine, Gottingen University, Gottingen, Germany
[8]Department of Anaesthesiology and Intensive Care Medicine, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany
[9]Clinical Physiology, Uppsala University, Sweden
[10]Department of Anesthesiology, University of Utah, Salt Lake City, UT, USA
[11]Division of General Surgery, University of California, San Francisco, USA
[12]Massachusetts General Hospital, Department of Surgery, Harvard University, Massachusetts, USA
[13]Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio, USA
[14]Department of Anaesthesiology and Reanimation, İstanbul University İstanbul School of Medicine, İstanbul, Turkey
Listed according to the surnames.

World Health Organization and the *United States Center for Disease Control* have recently recommended the use of 0.8 FIO$_2$ in all adult surgical patients undergoing general anaesthesia, to prevent surgical site infections. This recommendation has arisen several discussions: As a matter of fact, there are numerous studies with different results about the effect of FIO$_2$ on surgical site infection. Moreover, the clinical effects of FIO$_2$ are not limited to infection control.

We asked some prominent authors about their comments regarding the recent recommendations

Introduction

Joseph Priestley, (one of) the discoverer(s) of oxygen, has quoted: "… though pure dephlogistated air might be very useful as a medicine, it might not be so proper for us in the usual healthy state of the body; for, as a candle burns out much faster in dephlogistated than in common air, so we might live out too fast, and the animal powers be too soon exhausted in the pure king of air. A moralist would say that the air which nature has provided for us is as good as we deserve…".

Members of the WHO Guidelines Development Group recently attempted to provide worldwide "evidence-based recommendations" for the prevention of surgical site infections (SSI) by stating: "Adult patients undergoing general anaesthesia with endotracheal intubation for surgical procedures should receive 80% fraction of inspired oxygen intraoperatively and, if feasible, in the immediate postoperative period for 2–6 h".

Pro's & Con's of different levels of FIO$_2$ during the intraoperative (and somehow "peri"operative) period have been a very hot topic in our discipline. However, whether there is any obvious rule in terms of "evidence-based medicine", is hard to claim.

We asked some prominent authors about their comments regarding the recent recommendation. Although this text is based on "expert-opinion"s, the reader has to take in account that the authors of this text are the ones who have published the majority of high-impact studies, which obtained/lead to the "evidence" in this topic.

The contributions are in alphabetical order regarding the surnames of the authors.

Mert Şentürk

Ozan Akca:

Who needs high FIO_2? Question is simple and the answer is easy. Hypoxic patient needs oxygen.

How can we deliver that needed oxygen? Oxygen delivery (DO_2) depends on two things: cardiac output (CO) and arterial oxygen content (CaO_2).

$$DO_2 = CO \times CaO_2$$

Although the equation relies on pump function and a good level of hemoglobin (as the main oxygen carrier), tissue oxygen delivery is influenced by many other factors, first one being FIO_2, highlighting importance of free oxygen (1, 2). Incremental FIO_2 increases arterial oxygen tensions, which results in higher tissue oxygen delivery linearly within the clinical range (2). Additionally, hypothermia-related vasoconstriction (3), pain-related sympathetic response,(4) intravascular volume status, (2, 5) and carbon dioxide partial pressures (6) also alter tissue oxygenation. The latter factors mechanistically mostly rely more on local-regional tissue perfusion.

Now, let's get back to the question: "WHO needs high FIO_2?". In fact, the question appears to criticize the World Health Organization's (WHO) global guidelines for surgical site infection (SSI) prevention (7). WHO's recommendation says that adult patients undergoing general endotracheal anesthesia to receive FIO_2 of 0.80 intraoperatively and -if feasible- in the immediate postoperative period for 2-6 hours. Category was ranked as "strong", and the evidence level was marked as "moderate quality".

Recently, the Centers for Disease Control (CDC) published their guidelines for prevention of SSI (8). CDC acknowledged other organizations' recommendations, and came up with a slightly different approach. Although they did not recommend an optimal level, duration, and delivery method of FIO_2 for SSI prevention, they suggested administration of increased FIO_2 intra-operatively and in the immediate postoperative period for patients with normal pulmonary function undergoing general anesthesia. They added the maintenance of perioperative normothermia and adequate volume replacement as required items for optimum tissue oxygen delivery (Category IA–strong recommendation; moderate-quality evidence.). These additional requirements partially address what I mentioned above for better tissue oxygen delivery.

At this point, one may think that during the preparation of these guidelines, neither WHO nor CDC took the time the dig into the Oxygen Controversy or had the most recent meta-analysis (9) to influence their recommendations. Statistically, it's hard to ignore the controversy of supplemental oxygen / high FIO_2 use and SSI, but instead of focusing on the details of these analyses, I suggest understanding the methodological differences between the *so-called* controversial data (1, 10). There are many unanswered questions in spite of published large trials presenting thousands of patients' data, years of scientific effort, and millions of research dollars invested:

- Why and when one may need high FIO_2 perioperatively?
- What is the normal level of oxygenation of surgical tissues and organs-of-interest and how can we maintain those normals?
- How can we deliver high FIO_2 to the tissues-of-interest? Is it easy?
- and finally, if we can deliver that required oxygen to the tissue, can we expect better surgical outcomes?

Now, back to Joseph Priestley: "…*though pure dephlogistated air might be very useful as a medicine, it might not be so proper for us in the usual healthy state of the body…*". True statement, but can we really summarize the "perioperative abdominal surgery in a high risk patient" as "*healthy state of the body*"? One would also wonder what Priestley knew about "*surgical stress*". Answers are "no" and "not much", respectively; otherwise the whole field of "perioperative medicine" would be obsolete.

About 50 years ago, Dr. Thomas Hunt managed to measure tissue oxygen tensions and started researching importance of oxygenation in the experimental surgical setting (11-13). Some years later, Drs. Hunt and Hopf established a landmark perioperative physiology, and reported tissue oxygen tension as the main predictor of surgical wound infections (14). When subcutaneous tissue oxygen tensions stay above 60-80mmHg -which happens when $PaO_2>300$ mmHg (2) SSI happens less frequently than expected. So, it's very likely that in most of the recent high FIO_2 and SSI outcomes studies, provided supplemental oxygen was not delivered sufficiently to the tissues, because their reported PaO_2 levels were not that high (10, 15-17). In fact, until now, there has been only one study where we know that optimum level of oxygen delivered to tissue (i.e. tissue $PO_2>60$ mmHg), (1) and that's still the only study, where we showed when high FIO_2 delivered to tissue, SSI was prevented (1). If oxygen is not even delivered, how can we expect it to protect the tissue of concern?

In summary: first, the very question is a valid question, "who needs high FIO2?". Second, the very first hypothesis "*maintenance of tissue oxygenation improves surgical outcomes*" is still open and desperately needs to be further studied, possibly even beyond the context of high FIO_2. …And third…interpreting evidence is harder than it looks and it can even be tricky for global institutes.

* * *

Lorenzo Ball and Paolo Pelosi:

It is our opinion that answering this question is rather easy: high FIO_2 should be used in patients that are in need for it,

namely those in which lower oxygen delivery fails to maintain oxygenation within safety margins. In the operating room, guidelines recommend to target oxygenation to a peripheral oxygen saturation (SpO$_2$) ≥ 92%, (18) nonetheless a recent large observational study reported that most surgical patients receive FIO$_2$ between 0.4 and 0.8, resulting in saturation values ≥ 96% in nearly all cases (19). Based on this report, one could conclude that most of the surgical patients already receive 'high' FIO$_2$, possibly resulting in supra-physiological oxygenation. Over the last decades, several authors have investigated the effects of hyperoxia, achieved with the deliberate administration of higher FIO$_2$, to improve the efficiency of neutrophil oxidative burst at the surgical wound site and to reduce the incidence of SSIs (20). However, studies investigating the use of different FIO$_2$ levels should comprise several end-points, to reflect the complexity of the effects of oxygen on different organs' function. The guidelines recently published on behalf of the *WHO Guidelines Development Group*, (21) recommend the use of 0.8 FIO$_2$ in the whole intra- and post-operative period in all surgical patients to reduce the incidence of SSIs. This recommendation, that the WHO grades as 'strong' and based on 'moderate' evidence quality, received criticisms from researchers in anaesthesiology (22, 23). In fact, the studies included in the meta-analysis on which the recommendation is based are heterogeneous in design and aims, include studies with potentially clamorous confounding factors such as the use of inhaled nitrous oxide (24). A much more complete Cochrane review of the literature, published one year before the WHO guideline, concluded that evidence does not support the routine use of FIO$_2$ higher than 0.6 during anaesthesia and surgery, while the risk of adverse events including mortality could even be increased with higher versus lower FIO$_2$ (25). A partial exception could be represented by the induction phase, when higher FIO$_2$ could allow a longer time to perform the intubation manoeuvre, which could be crucial in unexpected difficult intubation or in the uncommon but life-threatening 'can't-ventilate, can't-intubate' scenario (26). Nonetheless, also at induction higher FIO$_2$ could have detrimental effects, therefore during pre-oxygenation FIO$_2$ higher than 0.7-0.8 should be avoided, and positive-pressure non-invasive ventilation (NPPV) could be considered in selected cases. The WHO guideline extends the recommendation of administering high FIO$_2$ also in the post-operative period. It is our opinion that, also in this case, oxygen administration should be based on clinical need and pathophysiological reasoning rather than on a routine basis. Post-operative de-saturation is a common complication, that could be secondary to the development of postoperative atelectasis or several other mechanisms (18, 27). Recently, an easy method has been proposed to surgical patients for postoperative atelectasis, consisting in measuring the SpO$_2$ during a 5-minutes room air breathing test: a SpO$_2$ ≤96% had a high sensitivity and specificity for atelectasis (28). Based on this test, the clinician could opt for the most appropriate treatment, including oxygen administration and FIO$_2$ titration or NPPV.

* * *

F. Javier Belda, Carlos Ferrando, Marina Soro:

In line with recent guidelines, we do recommend perioperative FIO$_2$ of 80% in major abdominal surgery because of several reasons:

1. No anesthesiologist doubts that there are circumstances where short periods of hyperoxia may actually increase patient safety, e.g. during the induction of anaesthesia and for intubation in ICU patients to delay the onset of hypoxemia during apnea (29). In fact, various maneuvers have been proposed to extend the effect of preoxygenation, including the use of high-flow nasal oxygen (30-32).

2. Several meta-analysis have shown that the administration of high FIO$_2$ (0.8) compared to lower (0.3) seems to reduce surgical site infection (33). The effect might be due to an increase in partial pressure of tissue oxygen PtsO$_2$ because an increase in partial pressure of arterial oxygen (PaO$_2$), which in turn increases the bacterycidal capacity of neutrophils and reduces local oxydative stress as we have recently shown (34, 35).

A recent meta-analysis (36) which gathered more than 7000 patients showed a favourable effect of high FIO$_2$ only in the sensitivity analysis but at the same time it showed a very significant effect in the subgroup of patients undergoing colorectal surgery (RR: 0.53; 95% CI: 0.37-0.74; p=0.0003). The last meta-analysis stil insist in the beneficial effect on SSI in colorectal surgery in spite of the lack of clear effect in other types of surgery (37). New evidence of the beneficial effect are continuously published (38).

3. The use of supplemental oxygen is widespread in cardiac surgery patients, during and after cardiopulmonary bypass. Its protective effects with this strategy on the myocardium have been reviewed elsewhere (39). However, in a recent prospective trial during cardiac surgery a lower FIO$_2$ had no worse outcomes when compared to the higher concentrations that are commonly used in this setting (40). Finally, in a cohort of 83.000 patients after cardiac surgery, no association of hyperoxia with mortality was found (41).

4. What is mostly clear is that this perioperative high FIO$_2$ have no adverse effect. This has been shown in most of the studies (and in the referred meta-analysis). For example, the PROXI study, the most important study against FIO$_2$ 80% did not find differences in the incidence of atelectasis, pneumonia, respiratory failure or death (10). This may be hypothetically due the use of a FIO$_2$ up to 0.8 for shorts periods of time does not increases the production of free radicals when used within a lung protective strategy.

5. Finally, without bibliographic references, it is clear that the WHO cannot recommend harmful things. We feel that the WHOGD Group (authors of the guidelines (21)) as the rest of physicians in the world, do follow strictly the non-maleficence ethical principle included in the Hippocratic Oath "first do not harm". Although they may accept that high FIO_2 cannot be beneficial for all type of surgeries, they underline its sound physiological mechanism that may be beneficial for subgroups, together with the high safety demonstrated for high FIO_2 for this short perioperative period.

From our point of view, two main issues must be underlined:

1. Readers need to detect and reject biased information. It is a pity that recognized forums (Cochrane database) have published very biased information regarding this issue most likely because of the authors' own bias (25). Just an example; in the author´s conclusions of Cochrane review is stated that high FIO_2 may increase long term mortality and this is based on a single study (42) that has been recently refused in a much higher population (43).

2. Researchers should promote new studies of high quality. However, these studies do not have to be undertaken before solving what is the best strategy for managing the lung perioperatively. Perioperative effects of FIO_2 can only be disclosed in a study where an optimized ventilation strategy is applied before, during and after operation. We have started a multicentre study on this issue that will show the real effect of high FIO_2 in the perioperative period.

In summary, we feel that the WHO has just outlined that high FIO_2 during anesthesia may have many potential benefits, without any inportant adverse effects. Well done!

* * *

Peter Biro:

The bitter truth is, that my conversion was not caused by rational reasoning and becoming convinced by evidence-based information; the routine use of 80% oxygen in adults has simply been directed by the department's director a decade ago. So the only virtue I can claim in this respect is that I was a polite follower to higher orders and only later became convinced about the rightfulness of this change. Those of us, who have learned and began to practice anesthesia in the eighties, were taught to apply rather low oxygen concentrations during anesthesia, mostly around 30%. The arguments of our teachers were fourfold. 1) The lower the oxygen concentration is set, the more nitrous oxide we can administer and the latter is a weak agent that should be given as highly concentrated as possible. 2) High oxygen concentrations might produce more so called "resorption atelectasis". 3) Longer lasting respiration or ventilation with high oxygen concentrations might degrade surfactant and be therefore harmful to the lungs; some even speak of "oxygen toxicity". Finally 4) man anyway is used to the atmospheric concentration of

21% and can live well with it, even in higher altitudes. Besides, we then already knew that newborn babies and young infants might even become blind if treated with too much oxygen, although it was never clear to us where the critical thresholds for oxygen concentration and the child's age was to be located. In the retrospect and guided by more recent knowledge and experience, one has to view the old statements with some scepticism. The argument favouring nitrous oxide delivery that should not be limited by the competing oxygen can be viewed as obsolete, since nitrous oxide in most places faded away from cylinders and supply systems to history books. The "resorption atelectasis" argument is to a certain extent justified, since it is true that in contrast to the ambient air's nitrogen, oxygen is easily and fast resorbed, thus leaving less volume to expand alveoli (44). However, this static view on the issue might be contradicted by positive pressure ventilation, which may counterbalance alveolar collapse. That oxygen toxicity exists as a medical problem has been recognized in multiple settings. Damages on the central nervous system toxicity may be caused by exposure to high oxygen partial pressures (as in hyperbaric oxygenation) (45), while pulmonary and ocular toxicity may be caused by longer exposure to high oxygen levels at atmospheric pressure conditions (46). However, these conditions might not be present in usual anesthesia ventilation with 80% oxygen concentration. Therefore, the toxicity issue can be put aside, at least in patients with otherwise healthy lungs. The final argument for a low oxygen concentration that under normal conditions the humans can live well with far less oxygen seems to be a bit of the tough guy admiration kind. Artificial ventilation in supine position is anything else than something normal or physiologic, so this view might fit for navy seals but not for more or less sick people undergoing surgery. The proven effect on suppression of postoperative infections supports the 80% proponents, in particular in cases of existing or possible contamination during specific surgical interventions. This is even more relevant in patients with a decreased immune competence. For these reasons, I vote "yes" for the routine use of 80% oxygen during anesthesia ventilation of adults.

* * *

Andrea Cortegiani and Cesare Gregoretti:

Supplemental or "extra" oxygen is one of the most widely used therapies for people admitted to the hospital (47). The importance of oxygen therapy for many patients with heart and chronic lung diseases is universally recognized (48). Very recently the Members of the WHO Guidelines Development Group recommend that adult intubated patients undergoing general anesthesia for surgical procedures should receive an 80% fraction of inspired oxygen (FIO_2) intraoperatively and, if feasible, in the immediate postoperative period for 2–6 h, to reduce the risk of surgical site infection (SSI) (21). They produced this statement after performing a systematic review and meta-analysis including 11 randomized controlled trials

comparing perioperative administration of 80% FIO$_2$ compared to 30-35% FIO$_2$. There was moderate grade evidence that hyperoxia significantly reduced SSI (OR 0.72, 95% CI 0.55-0.94). However, we believe that some other aspects of oxygen supplementation should be taken into account apart from its effect on SSI.

Since the first case in which oxygen was actually employed as remedy, in 1783 as reported by Caillens, what is important in term of oxygenation is a never ended story. As a matter of fact, most guidelines do not yet recommend dose titration to accomplish normoxaemia as assessed by invasively or noninvasively obtained end-points such as the level of oxygen and carbon dioxide (47). Moreover, the effects of oxygen level may vary widely according to metrics used and exposure time (49). Hyperoxia causes complex effects on several physiologic functions. It may affect alveolar ventilation/perfusion (Va/Q) (50), may reverse hypoxic vasoconstriction (51, 52), may induce pulmonary toxicity (53, 54) and it may reduce tissue blood flow due to vasoconstriction (55). Although a high partial pressure of oxygen in the blood achieved through the administration of high-concentration oxygen may reduce cytokine production by leukocytes (56), it can also produce structural changes within alveolar macrophages, with an impairment of their antimicrobial activity and a reduction in the production of inflammatory cytokines in response to stimulation (57). On the other hand, it may produce a time-dependent pro-inflammatory pulmonary response (58). There is a growing body of evidence questioning the effect of hyperoxia in many critical care settings; in some cases, there is evidence of harmful effects (e.g. post-resuscitation care, acute coronary syndrome) whereas in others the effect is controversial (traumatic brain injury, sepsis) (59-61). Interestingly, many trials addressing the effect of hyperoxia are still ongoing (61).

Regarding in general critically ill patients, there is also evidence of harm. A large observational cohort study enrolling 14.441 patients showed a higher mortality and fewer ventilators free days associated with increasing arterial PaO$_2$ and exposure time (49). Girardis and colleagues have recently addressed the effect of oxygen supplementation, in comparison to a conservative protocol, in a randomized trial enrolling 480 critically ill patients admitted to a single intensive care unit (62). There was a significant difference in mortality (relative risk 0.57 [95% CI, 0.37-0.90]), less shock episodes, liver failure, and new blood-stream infection. However, it was a single-center study stopped after the enrollment of approximately two-thirds of the planned sample due to slow recruitment.

We believe that, although the data on favorable effects of the use of high FIO$_2$ during and after general anesthesia in terms of SSI are solid, its widespread use may lead to underestimate the side effects of hyperoxia on organs and physiological functions. As for many other decisions in Anesthesiology, a "case-by-case" approach seems to be the best option for FIO$_2$ selection.

Arieh Eden and Zeev Goldik:

At present there are conflicting recommendations for the use of high concentration oxygen therapy during the perioperative period for the prevention of surgical site infections. While the WHO guidelines recommend the use of this therapy based on analysis of current data (21) a recently published Cochrane analysis failed to show any benefit from this treatment (25).

The biological basis for the use of high concentration of oxygen for the prevention of wound infection is that hyperoxia enhances oxidative killing by neutrophils. On the other hand, it has been shown that hyperoxia is associated with increased mortality in various groups of critically ill patients, probably due to increased oxidative stress (63). The PROXI study, which evaluated perioperative high concentration of oxygen in more than 1000 patients found a slight decrease in surgical wound infection (10). This smaller effect in the prevention of wound infection compared to other similar studies could be partially explained by the shorter duration of the intervention (two hours of post-operative high oxygen concentration compared to six in several other studies). However, further analysis revealed that the risk for acute coronary syndrome and myocardial infarction was twice as high in the high oxygen group (64), and even more disturbingly, that long-term follow-up of (evaluated in over 99% of the initial cohort) 3.9 years (median) revealed an increase in mortality of nearly 30%, as well as reduced cancer free survival (65).

In the light of this literature it appears unjustified to recommend the use of high inspiratory oxygen concentration in the perioperative period until a large scale long term study is performed to evaluate the safety and efficacy of this treatment.

* * *

Luciano Gattinoni:

Members of the WHO Guidelines Development Group strongly recommended the perioperative administration of 80% oxygen to prevent infections of the surgical site. The biological rationale of such intervention is that the neutrophils use the oxidative killing as a primary weapon against bacteria, and that several years ago it has been shown that the risk of wound infection was inversely proportioned to the tissue oxygenation. More precisely, Hopf et al. (14) related the increased risk of infection to the lower subcutaneous pO$_2$ (14). The jump from the biological observations to the oxygen supplementation in clinical practice was almost immediate and led to several randomized trials testing higher vs lower FIO$_2$ during anesthesia. The members of WHO chose some of these trials to bolster their strong recommendation, omitting, however, other trials showing the lack of benefit of supplemental oxygen. Volk et al. carefully reviewed this issue by reanalyzing in details the available evidence (9). Their conclusion was that the WHO recommendation of 80% perioperative oxygen is poorly justified.

Actually, the variability of the results observed during these trials is likely due to the fact that what matters is not the arterial oxygen tension, which clearly increases with FIO_2, but the tissue oxygen tension, which depends not only on the arterial oxygen tension, but also on perfusion and on the oxygen consumption. These factors may largely vary in different tissues, at different temperature, pH, microcirculation, etc. That supplemental oxygen is just a tool to improve neutrophils efficiency appears a rather naive vision of the problem.

Indeed, supplemental oxygen beside theoretically improving the neutrophils oxidative capability, affects the whole body. In the lung it has been observed decreased mucociliar transport, inflammatory reaction, focal pulmonary edema, interstitial fibrosis and reabsorption atelectasis. In the cardiocirculatory system, higher oxygen tension decreases cardiac output and stroke volume with increased peripheral vascular resistances and coronary artery vasoconstriction (66-69). The peripheral vasoconstriction, in particular, may explain the possible gap between high PaO_2 and low tissue oxygen tension.

Therefore, the putative benefit of 80% FIO_2 on decreasing the risk of wound infection has to be balanced with the negative effects of the overall increased oxidative stress (70). If, as the simplest approach, we list the advantages of increased PaO_2 in normal men with the disadvantages of high FIO_2 on lung tissue and of high PaO_2 in the whole body system, the recommendation of WHO appears highly questionable. Before blindly adopting it, risks and benefits of high FIO_2 must be carefully evaluated and balanced.

* * *

Thomas Hachenberg:

The guidelines recently published by the *World Health Organization (21)* and the *United States Center for Disease Control (8)* recommend the use of 0.8 FIO_2 in all adult surgical patients undergoing general anaesthesia. The rationale for 80% inspired oxygen intraoperatively and also for 2 to 6 hours postoperatively is to decrease the risk of surgical site infection (SSI). For several reasons this recommendation is poorly substantiated and one would caution against unjustified implementation into clinical practice. The guidelines are based on a meta-analysis including very heterogeneous studies, which is a weak scientific and statistical approach. Meta-analysis should not serve as a substitute of prospective randomized double blind trials with clearly defined endpoints and sufficient sample size. In fact a recent analysis has demonstrated that subsequent randomized trials could not confirm the conclusions of a majority of earlier meta-analysis studies (71). Ironically the WHO and CDC guidelines rely on a meta-analysis after large clinical trials have failed to demonstrate an advantageous effect of perioperative 80% oxygen (10, 17). One may also ask whether studies published in 2000 or earlier reflect present clinical practice, particularly in colorectal or thoracic surgery. More importantly different patient groups were not included into many of these studies due to predefined exclusion criteria. For example patients with advanced peripheral arterial occlusion disease, chronic obstructive lung disease GOLD IV or congestive heart failure NYHA class IV were not included into any of the FIO_2 trials, however these patients are by no means excluded from anaesthesia and surgery in clinical practice. It is unclear whether these patients benefit from supplemental oxygen or whether the risk of postoperative complications unrelated to SSI is actually increased.

I am also concerned that potentially harmful effects of oxygen have not been sufficiently addressed in the WHO and CDC guidelines, although data from different clinical studies suggest that hyperoxia may have detrimental effects. For example supplemental oxygen has been considered as standard therapy for all patients who present with acute coronary syndrome, regardless of arterial oxyhaemoglobin saturation (SpO_2) (72). Likewise oxygen treatment has been used after ischaemic stroke, cardiac arrest, in septic patients or traumatic brain injury. However the efficacy of supranormal PaO_2 in patients with acute myocardial infarction is questionable. In a prospective randomised study supplemental oxygen therapy in patients with ST-elevation-myocardial infarction but without hypoxia was associated with an elevated mean peak creatine kinase and larger myocardial infarct size assessed at 6 months (60). In cardiac surgical patients intraoperative hyperoxia was associated with an increased prevalence of postoperative delirium, suggesting that supranormal PaO_2 may have adverse cerebral effects (73). A retrospective study on adult patients with nontraumatic cardiac arrest (n=6.326) and cardiopulmonary resuscitation within 24 hours prior to ICU arrival found that 18% presented with hyperoxia, 19% with normoxia and 63% with hypoxia. The hyperoxia group had significantly higher in-hospital mortality compared with the normoxia group and the hypoxia group (74). Although the role of oxygen on outcome is still unclear after resuscitation the data may indicate that hyperoxia *per se* is not as harmless as previously thought. Concerns about unjustified use of an increased FIO_2 are supported by preliminary data from a single-centre study suggesting that in critically ill patients a PaO_2 between 70 and 100 mmHg or arterial oxyhaemoglobin saturation (SpO_2) between 94% and 98% was associated with lower ICU mortality (62). In summary different specialties modify their clinical practice in favour of normoxia rather than of hyperoxia.

Finally, in a subgroup of patients even short periods of hyperoxia may induce or aggravate organ injury. For example cisplatin, one of the most widely-used chemotherapeutic agents against various malignancies may generate reactive oxygen species, which impair cellular antioxidant defence system, causing oxidative stress and cell injury, particularly in the kidney and the heart (75). In addition decreased renal function due to cisplatin may also aggravate bleomycin pulmonary toxicity (76). Although they represent a minority

among surgical cases, the risk of SSI is considerably increased due to a compromised immune system. Should we really expose these patients to high FIO$_2$ during general anaesthesia and in the postoperative period? In any case supplemental oxygen should be carefully considered for risk benefit ratio in patients with cytotoxic agents known to cause pulmonary or cardiac toxicity.

Obviously supplemental oxygen is indicated in hypoxic patients by improving oxygen delivery, maintaining cellular function and metabolism and preserving organ function. However it is unclear whether normoxic patients really benefit from supplemental oxygen. Unless large prospective randomised clinical trials clearly demonstrate an advantage of hyperoxia in the perioperative period - e.g. the ongoing study NCT01777568-Clinical Trials.gov (Supplemental oxygen in colorectal surgery: a quality improvement project) - the WHO and CDC guidelines seem to be poorly justified (9).

* * *

Göran Hedenstierna:

The world health organization (WHO) presented guidelines recommending the use of hyperoxic gas (80% O$_2$) during anesthesia and, if feasible, for 2-6 hours post operatively (21). One can argue against these guidelines, perhaps for several reasons, but I will limit my critical attitude to two issues.

Firstly, the scientific basis is not at all well founded. The guidelines are based on a meta-analysis and could be a final and conclusive document if there are no more studies coming out after the publication of the guidelines. However, studies on perioperative hyperoxia continue to be published that are at variance with the guidelines (17), and more are to come. We shall not accept guidelines that have weak scientific or statistical support, if any, and that are of very temporary validity, if any. The scientific basis is already more or less obsolete and new guidelines may be completely different. The present WHO guidelines are thus not at all timely, rather a comment in an ongoing debate.

Secondly, the use of hyperoxic gas may initiate a number of events on a macroscopic as well as on a microscopic level. Macroscopically, atelectasis will be more easily produced during anesthesia and postoperatively when breathing hyperoxic gas (77, 78). Thus, atelectasis is caused by absorption of alveolar gas, and oxygen is the gas that is absorbed the fastest since it is being consumed in the body. Alveolar nitrogen is hardly absorbed at all and acts as a scaffold, preventing collapse. Reducing the nitrogen in the alveoli speeds up the lung collapse and by continuing the hyperoxia in the postoperative period makes atelectasis to last for a longer period. Atelectasis may be a locus of inflammation. Microscopically, the production or release of reactive oxygen species by using hyperoxic gas is most likely harmful to the patient (79). Studies in different experimental animals show considerable decrease in survival

by using hyperoxic gas (80). So far few human studies have been conducted and they are difficult to interpret because of several simultaneous biological processes. However, recently two studies have appeared on intensive care patients, relating survival to arterial oxygenation. They showed increased mortality in those who had high oxygen tension (PaO$_2$) or saturation (SaO$_2$) when comparing patients with similar severity of disease (62) and when relating the mortality to the magnitude and duration of hyperoxia (49). One can always discuss whether the patient selection has been identical in the groups (62) and if a retrospective study, although on a huge material (close to 15000 patients), can be considered free from bias (49). Moreover, these results are from severely sick patients and not from patients undergoing scheduled surgery. However, the results suggest rather strongly that hyperoxic gas is not good but more likely harmful and even deadly.

So, in summary the guidelines of using hyperoxic gas perioperatively is more harmful than helpful. It may even be said, to put it provocatively, that hyperoxia is for the doctor, not for the patient.

* * *

Harriet W. Hopf:

At first glance, the two largest randomized controlled trials that specifically evaluated the use of high inspired oxygen perioperatively in patients at high risk for surgical site infection Greif et al. (1), in colon surgery patients and Meyhoff et al. (10), in abdominal surgery patients, yielded conflicting results, calling into question the potential value of high-inspired oxygen. Greif et al. (1) demonstrated a 50% reduction in surgical site infection (SSI) rate (11.2% vs 5.2%, p=0.01), while Meyhoff et al. (10), in the PROXI trial, demonstrated no difference (19.1% vs. 20.1%), using effectively the same high-inspired oxygen protocol: 80% vs. 30% intraoperatively and for the first 2 hours postoperatively. This presumes that the two trials investigated the same hypothesis. In reality, they did not, and the outcomes are somewhat predictable, given the differences in study aims and design. For the study by Greif et al. (1), the study question could be stated: In patients who are managed to reduce sympathetic nervous system (SNS) activation and increase wound perfusion, does administration of high-inspired oxygen increase wound oxygen tension (P$_w$O$_2$) and decrease SSI? For the PROXI trial, it could be stated: Does administration of high-inspired oxygen, in the context of severely limited fluid administration, decrease SSI?

Starting in the 1960s, Dr. Thomas K. Hunt and other investigators used animal, volunteer, and patient studies (81) to investigate the role of oxygen in wound healing. The basic science is clear: oxygen is required at a high partial pressure for wound immunity (threshold ~ 40 mmHg) (20), collagen deposition (threshold ~25 mmHg) (82), neovascularization (83), and epithilization (84). In 1997, before the widespread

adoption of intraoperative patient warming, Hopf et al. (14) demonstrated a high rate of wound hypoxia in postoperative surgical patients, with SSI rate inversely proportional to postoperative P_wO_2. Animal, volunteer and patient studies demonstrated the crucial role of the SNS in controlling wound perfusion and P_wO_2 (81) and the effectiveness of thermal management (3), pain control (4), and adequate fluid administration (5) in maintaining P_wO_2. In well-perfused, healthy volunteers, perfusion dependent high-inspired oxygen approximately doubles P_wO_2, from ~65 to ~100-130 mmHg (81) Notably, Gottrup et al. (2) demonstrated in a dog model that hypovolemia progressively reduced both P_wO_2 and the response to 100% oxygen, with a nadir at ~20 mmHg; after 20% blood volume removal, the response to oxygen was eliminated; reinfusion returned P_wO_2 to normal.

A major strength of the Greif study (1) was the measurement of P_wO_2 intraoperatively and in the Post-Anesthesia Care Unit (PACU). P_wO_2 in the 80% oxygen group was approximately doubled during the operation (109±43 vs. 59±15, p<0.001) and ~50% higher in the PACU (73±25 vs. 54±25, p<0.001). Mechanistically, this provides an explanation for the reduction in SSI. Unfortunately, no other study has measured P_wO_2 to verify that the increased inspired oxygen was actually delivered to the wound. The PROXI study (10) mandated extremely limited fluid administration, less than even that of so-called restricted fluid studies (85). Although the PROXI study did not measure P_wO_2, based on the P_wO_2 literature, it is reasonable to assume that the lack of effect of high-inspired oxygen in that study stemmed, at least in part, from inadequate wound perfusion that reduced delivery of oxygen to the wound.

Thus, the first concern of an anesthesiologist should be to minimize SNS activation in order to optimize wound perfusion and oxygenation (86). Given the lack of evidence of harm from high-inspired oxygen (25), it is reasonable to add high-inspired oxygen to magnify the impact of maintaining adequate wound perfusion in patients at high risk for SSI (e.g., open abdominal surgery), or in whom SSI, though uncommon, is devastating (e.g., total joint replacement). While absorption atelectasis is a potential concern, it can be mitigated by maintaining inspired oxygen at ~80% and applying PEEP of 5-10 cmH$_2$O (86). This is reflected in the recent recommendations from WHO (7) and CDC (8), which are reasonable and measured. Future studies should incorporate P_wO_2 measurements to elucidate outcomes in relation to whether the high-inspired oxygen effectively reached the wound.

* * *

Thomas K. Hunt:

At the time I retired, I was asking for perioperative supplemental oxygen at every reasonable indication, and my anesthesiologist colleagues were willing. I would still do so now. Here is why:

1) Irrefutable science has long-since verified that wounds are protected from infection by innate immunity and, accordingly, is solidly based on the availability of oxygen at almost every step. Chemotaxis, toll receptor identification, phagocytic killing, angiogenesis, etc. are all effective in proportion to the available oxygen. There is no dissent.

2) Once hemostasis is obtained, wound tissue oxygen (PwO_2) falls far below arterial, and is held low due largely to sympathetic nervous vasoconstriction that is exceptionally active in the fatty tissues and fascia, which are the most common sites of SSI (2). Vessels in these tissues actively constrict in response to catecholamine release due to hypothermia, pain, and low blood volume (3, 4). However, these limitations can be mitigated. We have often witnessed a suboptimal PwO_2 rise significantly in response to increasing fluid administration, enhancing pain control, and/or warming (and upon removing pheochromocytomas) while we have been measuring it in operative patients who were thought to be doing well by usual standards (5, 14, 87, 88).

3) These experiences, made it obvious to us that foundational clinical trials would require designs featuring warming subjects to euthermia (37^{0}C), administration of generous fluids (estimated at least 15 ml electrolyte/kg/hr plus the usual replacement for losses), and patient-controlled pain management protocols as reasonable intraoperative targets for maximizing PwO_2 (87). Our colleagues, Kurz and Sessler (89) accepted these estimates in their landmark paper of 1996 in which they convincingly proved the value of euthermia to limit SSIs. Greif and Akca (1) then performed the single most revealing trial to date by testing 80% oxygen inhalation vs. 30% oxygen using the Kurz protocol plus measurements of PwO_2 in a significant number of subjects, thus demonstrating that 80% oxygen breathing under these conditions is sufficient to raise PwO_2 and proving that this protocol is suitable for clinical trials (1). In doing so, they provided substantial evidence that increasing PwO_2 will reduce the frequency of SSIs. Belda, using a similar protocol, found the same result, but did not measure PwO_2 (16). These events reignited traditional disbelief that I had encountered when I showed that increasing arterial PO$_2$ could actually increase interstitial PO$_2$ without need for an increase in hemoglobin and also a reflexive and exaggerated fear of oxygen toxicity (90).

PROXI in Denmark (10) then performed a negative trial featuring 1400 subjects, fluid restriction, and loose thermal control without even once measuring PwO_2 and seemed eager to seize on a minor break in the Greif trial to disqualify their analysis (25). PROXI has subsequently sought evidence of harm in that trial, but has failed to find it. Furthermore, PROXI has apparently never measured a wound PO$_2$ (PwO_2)– although some of the investigators were trained on how to-, and are, therefore, unqualified to make any judgment with regard to SSI, because they have provided no evidence that their protocol sufficed to increase oxygen in the wound in

a significant number of subjects as would have better suited their contrarian position.

4) Whereas the more than fifteen published "trials" fall nicely into two groups: those that held essentially to the Greif-Akca protocol and report significant reductions of SSI and the remainder that did not and found no effect.

5) My personal conclusion is: Perioperative hyperoxia can reduce SSI if conditions are adequate. Questions remain. Time, I suspect, will tell.

* * *

Motaz Qadan:

This is a topic that has continued to fuel a debate spanning 2 decades. The following commentary represents my personal opinion. I believe that the question at hand has been comprehensively addressed but not definitively answered, due to the large body of conflicting data. The reason for the discrepancy in outcomes exists due to significant heterogeneity in studies that have examined the role of supplemental oxygen, unpredictability of outcomes among patients enrolled (no applicable airline analogies), and implementation of arbitrary, or arguably flawed, statistical principles that have served to fuel the controversy.

As scientists examining the role of supplemental oxygen, one could argue that we have failed medical practice in our lack of cohesiveness and consensus on this topic. While the application of scientific rigor and debate is encouraged, poor adherence to uniform trial design has resulted in undecipherable outcomes, and should serve as the ultimate learning lesson for the medical community.

In the first study on the topic, Greif and colleagues examined the role of supplemental oxygen in a well-designed, rigorously implemented, meticulously analyzed, and well-written randomized-controlled trial that established benefit from the administration of 80% oxygen to 250 patients, compared with 250 patients who did not receive supplemental oxygen (30% oxygen) (1). However, as is sometimes the case (more often with negative trials), results were not broadly accepted. This led to the design and implementation, followed by, arguably, the inappropriate discontinuation of the Pryor study, which became the fulcrum for rejection of the supplemental oxygen theory (91). Based on the results of this incomplete study alone, the role of supplemental oxygen became heavily disputed, despite all additional level I and meta-analyzed data confirming Greif's findings (92).

Eventually, the Meyhoff PROXI trial followed, 9 years after the Greif study, and showed no discernible difference between the 80% and 30% oxygen arms on surgical site infection rates (10). Unfortunately, several spin-off publications followed from the same data set in the form of post-hoc analyses in attempts to answer questions for which the original trial was not designed. Disappointingly, scathing findings

regarding the role of supplemental oxygen were reported, although some of these have since been, fortunately, debunked (e.g. mortality associated with supplemental oxygen among cancer patients) (42, 43).

In attempting to define the role of supplemental oxygen on surgical site infection, I have previously stated that there are more opinions, editorials, and commentaries on this topic than there are actual data! Nonetheless, it is my personal belief that (protective) oxygen sinks exist in the human body, such as endothelial cells, which modify oxygen utilization and subsequent transmission to end-organs and capillaries, as eloquently described by Tsai et al. (93). As such, 'excess' inspired oxygen may not be fully transmitted to capillaries at the wound, for example. Therefore, the benefit from supplemental oxygen may be smaller than anticipated. However, in certain procedures, such as colorectal surgery, anaerobic organisms prevail. As such, even a small increase in wound oxygen tension may result in benefit, which has indeed been confirmed among patients undergoing colorectal surgery. In addition, basic scientific data exist to support enhancement of innate immunologic mechanisms associated with the use of supplemental oxygen (20, 56).

At this time, it should be noted that data support that administration of supplemental oxygen to anesthetized patients is safe in the acute perioperative period (88). Furthermore, the liberal use of oxygen routinely occurs during surgery. Oxygen is also cheap, widely available, and administration is not supported by industry or associated with any financial incentive. Above all, benefit from supplemental administration appears to be logical in principle.

Therefore, I believe that supplemental oxygen administration is justified, despite the extensive controversy that exists in the literature today. I am uncertain as to how this debate can be more definitively concluded.

* * *

Daniel I. Sessler:

Surgical site infections remain an important cause of patient morbidity and mortality. All wounds become contaminated, and whether contamination progresses to clinical infection is determined by antibiotic administration and host defense. The most important defense against bacterial infection is oxidative killing by neutrophils. The process depends on molecular oxygen and the reaction rate depends on *tissue* oxygen over the entire clinical range. The easiest way to increase tissue oxygen is to provide supplemental inspired oxygen which increases tissue oxygen from about 50 mmHg to about 100 mmHg. (1) The increase is potentially clinically important because infections are common at the lower partial pressure and rare at the higher one (14).

Even a few minutes of 100% inspired oxygen, as used during induction of nearly every general anesthetic, causes atelecta-

sis (94) which can be reversed with a recruitment maneuver (95) or positive end-expiratory pressure (98). However, 80% inspired oxygen does not cause atelectasis (88) and, despite an initial report, (42) does not increase long-term mortality. (43) Supplemental perioperative oxygen thus appears to be safe, although harm has been demonstrated in other contexts. But lack of harm does not justify recommendations for use.

In recent months, both the World Health Organization (21) and the United States Center for Disease Control (8) have issued guidelines recommending that adults having general anaesthesia should be given 80% inspired oxygen intraoperatively and, when feasible, also for 2-6 hours thereafter to reduce the risk of surgical site infection. These recommendations fail to consider divergent results of available trials, that recent large trials have uniformly failed to demonstrate benefit, (10, 17) and that a meta-analysis of available trials shows that supplemental oxygen does not significantly reduce the risk of surgical site infection (9). The results of a large trial will soon provide definitive evidence of whether supplemental oxygen reduces surgical site infection (NCT01777568). Curiously, the World Health Organization recommendation specifically includes regional anesthesia, although not a single study of supplemental oxygen during regional anesthesia identified any benefit (97-100).

References

1. Greif R, Akça O, Horn E-P, 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. [CrossRef]

2. Gottrup F, Firmin R, Rabkin J, Halliday BJ, Hunt TK. Directly measured tissue oxygen tension and arterial oxygen tension assess tissue perfusion. Crit Care Med 1987; 15: 1030-6. [CrossRef]

3. Sheffield CW, Sessler DI, Hopf HW, Schroeder M, Moayeri A, Hunt TK, et al. Centrally and locally mediated thermoregulatory responses alter subcutaneous oxygen tension. Wound Repair Regen 1996; 4: 339-45. [CrossRef]

4. Akça O, Melischek M, Scheck T, Hellwagner K, Arkiliç C, Kurz A, et al. Postoperative pain and subcutaneous oxygen tension. Lancet 1999; 354: 41-2. [CrossRef]

5. Arkilic CF, Taguchi A, Sharma N, Ratnaraj J, Sessler DI, Read TE, et al. Supplemental perioperative fluid administration increases tissue oxygen pressure. Surgery 2003; 133: 49-55. [CrossRef]

6. Akça O, Doufas A, Morioka N, Iscoe S, Fisher J, Sessler D. Hypercapnia Improves Tissue Oxygenation. Anesthesiology 2002; 97: 801-6. [CrossRef]

7. Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F, 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-e303.

8. Berrios-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection. JAMA Surg 2017 May 3. doi: 10.1001/jamasurg.2017.0904. [Epub ahead of print] [CrossRef]

9. Volk T, Peters J, Sessler DI. The WHO recommendation for 80% perioperative oxygen is poorly justified. Anaesthesist 2017; 66: 227-9. [CrossRef]

10. Meyhoff CS, Wetterslev J, Jorgensen LN, Henneberg SW, Hogdall C, Lundvall L, 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. [CrossRef]

11. Hunt TK. A New Method of Determining Tissue Oxygen Tension. Lancet 1964; 2: 1370-1. [CrossRef]

12. Hunt TK, Dunphy JE. Effects of increasing oxygen supply to healing wounds. Br J Surg 1969; 56: 705.

13. Hunt TK, Linsey M, Sonne M, Jawetz E. Oxygen tension and wound infection. Surg Forum 1972; 23: 47-9.

14. Hopf HW, Hunt TK, West JM, Blomquist P, Goodson WH, 3rd, Jensen JA, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. Arch Surg 1997; 132: 997-1004; discussion 1005.

15. Akca O, Kurz A, Fleischmann E, Buggy D, Herbst F, Stocchi L, et al. Hypercapnia and surgical site infection: a randomized trial. Br J Anaesth 2013; 111: 759-67. [CrossRef]

16. Belda FJ, Aguilera L, Garcia de la Asuncion J, Alberti J, Vicente R, Ferrandiz L, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. JAMA 2005; 294: 2035-42. [CrossRef]

17. Kurz A, Fleischmann E, Sessler DI, Buggy DJ, Apfel C, Akca O, et al. Effects of supplemental oxygen and dexamethasone on surgical site infection: a factorial randomized trialdouble dagger. Br J Anaesth 2015; 115: 434-43. [CrossRef]

18. Güldner A, Kiss T, Serpa Neto A, Hemmes SN, Canet J, Spieth PM, et al. Intraoperative Protective Mechanical Ventilation for Prevention of Postoperative Pulmonary Complications A Comprehensive Review of the Role of Tidal Volume, Positive End-expiratory Pressure, and Lung Recruitment Maneuvers. Anesthesiology 2015; 123: 692-713. [CrossRef]

19. Kroell W, Metzler H, Struber G, Wegscheider T, Gombotz H, Hiesmayr M, et al. The LAS VEGAS investigators for the PROVE Network, the Clinical Trial Network of the European Society of Anaesthesiology. Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications: An observational study in 29 countries. Eur J Anaesthesiol 2017; 34: 492-507. [CrossRef]

20. Allen DB, Maguire JJ, Mahdavian M, Wicke C, Marcocci L, Scheuenstuhl H, et al. Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. Arch Surg 1997; 132: 991-6. [CrossRef]

21. Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F, et al. WHO Guidelines Development Group. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis 2016; 16: e288-e303.

22. Ball L, Lumb AB, Pelosi P. Intraoperative fraction of inspired oxygen: bringing back the focus on patient outcome. Br J Anaesth 2017; 119: 16-8. [CrossRef]

23. Hedenstierna G, Perchiazzi G, Meyhoff CS, Larsson A. Who Can Make Sense of the WHO Guidelines to Prevent Surgical Site Infection? Anesthesiology 2017; 126: 771-3.

24. Myles PS, Leslie K, Chan MTV, Forbes A, Paech MJ, Peyton P, et al. Avoidance of Nitrous Oxide for Patients Undergoing Major Surgery: A Randomized Controlled Trial. Anesthesiology 2007; 107: 221-31. [CrossRef]

25. 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; (6): CD008884.

26. De Jong A, Futier E, Millot A, Coisel Y, Jung B, Chanques G, et al. How to preoxygenate in operative room: healthy subjects and situations 'at risk'. Ann Fr Anesth Reanim 2014; 33: 457-61. [CrossRef]

27. Ball L, Bos LD, Pelosi P. High-flow nasal cannula in the postoperative period: is positive pressure the phantom of the OPERA trial? Intensive Care Med 2017; 43: 119-21.

28. Ferrando C, Romero C, Tusman G, Suarez-Sipmann F, Canet J, Dosdá R, et al. The accuracy of postoperative, non-invasive Air-Test to diagnose atelectasis in healthy patients after surgery: a prospective, diagnostic pilot study. BMJ Open 2017; 7: e015560.

29. Nimmagadda U, Salem MR, Crystal GJ. Preoxygenation: Physiologic Basis, Benefits, and Potential Risks. Anesth Analg 2017; 124: 507-17. [CrossRef]

30. Ang KS, Green A, Ramaswamy KK, Frerk C. Preoxygenation using the Optiflow™ system. Br J Anaesth 2017; 118: 463-4. [CrossRef]

31. Ricard JD. Hazards of intubation in the ICU: role of nasal high flow oxygen therapy for preoxygenation and apneic oxygenation to prevent desaturation. Minerva Anestesiol 2016; 82: 1098-106.

32. Slinger PD. Is There Anything New About Preoxygenation? Duh, Yeah! Anesth Analg 2017; 124: 388-9.

33. 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. [CrossRef]

34. García de la Asunción J, Belda FJ, Greif R, Barber G, Viña J, Sastre J. Inspired supplemental oxygen reduces markers of oxidative stress during elective colon surgery. Br J Surg 2007; 94: 475-7. [CrossRef]

35. García-de-la-Asunción J, Barber G, Rus D, Perez-Griera J, Belda FJ, Martí F, et al. Hyperoxia during colon surgery is associated with a reduction of xanthine oxidase activity and oxidative stress in colonic mucosa. Redox Rep 2011; 16: 121-8. [CrossRef]

36. Wang H, Hong S, Liu Y, Duan Y, Yin H. High inspired oxygen versus low inspired oxygen for reducing surgical site infection: a meta-analysis. Int Wound J 2017; 14: 46-52. [CrossRef]

37. Yang W, Liu Y, Zhang Y, Zhao QH, He SF. Effect of intra-operative high inspired oxygen fraction on surgical site infection: a meta-analysis of randomized controlled trials. J Hosp Infect 2016; 93: 329-38. [CrossRef]

38. Vallabha T, Karjol U, Kalyanappagol V, Sindgikar V, Nidoni R, Biradar H, et al. Rational Hyperoxia in the Perioperative Period: a Safe and Effective Tool in the Reduction of SSI. Indian J Surg 2016; 78: 27-31. [CrossRef]

39. Ferrando C, Soro M, Belda FJ. Protection strategies during cardiopulmonary bypass: ventilation, anesthetics and oxygen. Curr Opin Anaesthesiol 2015; 28: 73-80. [CrossRef]

40. Smit B, Smulders YM, de Waard MC, Boer C, Vonk AB, Veerhoek D, et al. Moderate hyperoxic versus near-physiological oxygen targets during and after coronary artery bypass surgery: a randomised controlled trial. Crit Care 2016; 20: 55. [CrossRef]

41. Sutton AD, Bailey M, Bellomo R, Eastwood GM, Pilcher DV. The association between early arterial oxygenation in the ICU and mortality following cardiac surgery. Anaesth Intensive Care 2014; 42: 730-5.

42. Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS; PROXI Trial Group. 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. [CrossRef]

43. Podolyak A, Sessler DI, Reiterer C, Fleischmann E, Akça O, Mascha EJ, et al. Perioperative Supplemental Oxygen Does Not Worsen Long-Term Mortality of Colorectal Surgery Patients. Anesth Analg 2016; 122: 1907-11. [CrossRef]

44. White GC. Basic Clinical Lab Competencies for Respiratory Care. 4th ed. New York: Delmar Cengage Learning; 2002.p.230.

45. Bitterman N. CNS oxygen toxicity. Undersea Hyperb Med 2004; 31: 63-72.

46. Clark JM, Lambertsen CJ. Pulmonary oxygen toxicity: a review. Pharmacol Rev 1971; 23: 37-133.

47. Sjoberg F, Singer M. The medical use of oxygen: a time for critical reappraisal. J Intern Med 2013; 274: 505-28. [CrossRef]

48. Jindal SK, Agarwal R. Long-term oxygen therapy. Expert Rev Respir Med 2012; 6: 639-49. [CrossRef]

49. Helmerhorst HJF, Arts DL, Schultz MJ, van der Voort PHJ, Abu-Hanna A, de Jonge E, et al. Metrics of Arterial Hyperoxia and Associated Outcomes in Critical Care. Crit Care Med 2017; 45: 187-95. [CrossRef]

50. Dussault C, Gontier E, Verret C, Soret M, Boussuges A, Hedenstierna G, et al. Hyperoxia and hypergravity are independent risk factors of atelectasis in healthy sitting humans: a pulmonary ultrasound and SPECT/CT study. J Appl Physiol (1985) 2016; 121: 66-77. [CrossRef]

51. Sommer N, Dietrich A, Schermuly RT, Ghofrani HA, Gudermann T, Schulz R, et al. Regulation of hypoxic pulmonary vasoconstriction: basic mechanisms. Eur Respir J 2008; 32: 1639-51. [CrossRef]

52. Naeije R, Brimioulle S. Physiology in medicine: importance of hypoxic pulmonary vasoconstriction in maintaining arterial oxygenation during acute respiratory failure. Crit Care 2001; 5: 67-71. [CrossRef]

53. Nash G, Blennerhassett JB, Pontoppidan H. Pulmonary lesions associated with oxygen therapy and artifical ventilation. N Engl J Med 1967; 276: 368-74. [CrossRef]

54. Sinclair SE, Altemeier WA, Matute-Bello G, Chi EY. Augmented lung injury due to interaction between hyperoxia and mechanical ventilation. Crit Care Med 2004; 32: 2496-501. [CrossRef]

55. Duling BR. Microvascular responses to alterations in oxygen tension. Circ Res 1972; 31: 481-9. [CrossRef]

56. Qadan M, Battista C, Gardner SA, Anderson G, Akca O, Polk HCJ. Oxygen and surgical site infection: a study of underlying immunologic mechanisms. Anesthesiology 2010; 113: 369-77. [CrossRef]

57. O'Reilly PJ, Hickman-Davis JM, Davis IC, Matalon S. Hyperoxia impairs antibacterial function of macrophages through effects on actin. Am J Respir Cell Mol Biol 2003; 28: 443-50. [CrossRef]

58. Helmerhorst HJF, Schouten LRA, Wagenaar GTM, Juffermans NP, Roelofs JJTH, Schultz MJ, et al. Hyperoxia provokes a time- and dose-dependent inflammatory response in mechanically ventilated mice, irrespective of tidal volumes. Intensive Care Med Exp 2017; 5: 27. [CrossRef]

59. Vincent JL, Taccone FS, He X. Harmful Effects of Hyperoxia in Postcardiac Arrest, Sepsis, Traumatic Brain Injury, or Stroke: The Importance of Individualized Oxygen Therapy in Critically Ill Patients. Can Respir J 2017; 2017: 2834956. [CrossRef]

60. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE et al. Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. Circulation 2015; 131: 2143-50. [CrossRef]

61. Eastwood GM, Young PJ, Bellomo R. The impact of oxygen and carbon dioxide management on outcome after cardiac arrest. Curr Opin Crit Care 2014; 20: 266-72. [CrossRef]

62. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, 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. [CrossRef]

63. Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. Crit Care 2014; 18: 711. [CrossRef]

64. Fonnes S, Gögenur I, Søndergaard ES, Siersma VD, Jorgensen LN, Wetterslev J, 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. [CrossRef]

65. 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-i81.

66. Milone SD, Newton GE, Parker JD. Hemodynamic and biochemical effects of 100% oxygen breathing in humans. Can J Physiol Pharmacol 1999; 77: 124-30. [CrossRef]

67. Lodato RF. Decreased O2 consumption and cardiac output during normobaric hyperoxia in conscious dogs. J Appl Physiol (1985) 1989; 67: 1551-9.

68. Farquhar H, Weatherall M, Wijesinghe M, Perrin K, Ranchord A, Simmonds M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. Am Heart J 2009; 158: 371-7. [CrossRef]

69. McNulty PH, King N, Scott S, Hartman G, McCann J, Kozak M, 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.

70. Asfar P, Singer M, Radermacher P. Understanding the benefits and harms of oxygen therapy: response to comments by Akca. Intensive Care Med 2015; 41: 1875. [CrossRef]

71. Sivakumar H, Peyton PJ. Poor agreement in significant findings between meta-analyses and subsequent large randomized trials in perioperative medicine. Br J Anaesth 2016; 117: 431-41. [CrossRef]

72. Shuvy M, Atar D, Gabriel Steg P, Halvorsen S, Jolly S, Yusuf S, et al. Oxygen therapy in acute coronary syndrome: are the benefits worth the risk? Eur Heart J 2013; 34: 1630-5.

73. Lopez MG, Pandharipande P, Morse J, Shotwell MS, Milne GL, Pretorius M, et al. Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery. Free Radic Biol Med 2017; 103: 192-8. [CrossRef]

74. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 2010; 303: 2165-71. [CrossRef]

75. Dugbartey GJ, Peppone LJ, de Graaf IA. An integrative view of cisplatin-induced renal and cardiac toxicities: Molecular mechanisms, current treatment challenges and potential protective measures. Toxicology 2016; 371: 58-66. [CrossRef]

76. Sleijfer S, van der Mark TW, Schraffordt Koops H, Mulder NH. Enhanced effects of bleomycin on pulmonary function disturbances in patients with decreased renal function due to cisplatin. Eur J Cancer 1996; 32A: 550-2.

77. Hedenstierna G, Rothen HU. Respiratory function during anesthesia: effects on gas exchange. Compr Physiol 2012; 2: 69-96. [CrossRef]

78. Edmark L, Auner U, Enlund M, Ostberg E, Hedenstierna G. Oxygen concentration and characteristics of progressive atelectasis formation during anaesthesia. Acta Anaesthesiol Scand 2011; 55: 75-81. [CrossRef]

79. Pagano A, Barazzone-Argiroffo C. Alveolar cell death in hyperoxia-induced lung injury. Ann N Y Acad Sci 2003; 1010: 405-16. [CrossRef]

80. Matute-Bello G, Frevert CW, Martin TR. Animal models of acute lung injury. Am J Physiol Lung Cell Mol Physiol 2008; 295: L379-99.

81. Hopf HW. Development of subcutaneous wound oxygen measurement in humans: contributions of Thomas K Hunt, MD. Wound Repair Regen 2003; 11: 424-30. [CrossRef]

82. Jonsson K, Jensen JA, Goodson WH 3rd, Scheuenstuhl H, West J, Hopf HW, et al. Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients. Ann Surg 1991; 214: 605-13. [CrossRef]

83. Hopf HW, Gibson JJ, Angeles AP, Constant JS, Feng JJ, Rollins MD, et al. Hyperoxia and angiogenesis. Wound Repair Regen 2005; 13: 558-64. [CrossRef]

84. Medawar PS. The behavior of mammalian skin epithelium under strictly anaerobic conditions. Q J Microsc Sci 1947; 88: 27-37.

85. Brandstrup B, Tønnesen H, Beier-Holgersen R. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg 2003; 238: 641-8. [CrossRef]

86. Hopf HW, Cochran A, Ueno C, Morrissey C. Inflammation, Wound Healing, and Infection. In: Barash P, Cullen B, Stoelting R, Cahalan M, Stock C, editors. Clinical Anesthesia 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2017.p.183-203.

87. Hopf HW, Viele M, Watson JJ, Feiner J, Weiskopf R, Hunt TK, et al. Subcutaneous perfusion and oxygen during acute severe isovolemic hemodilution in healthy volunteers. Arch Surg 2000; 135: 1443-9. [CrossRef]

88. Akca O, Podolsky A, Eisenhuber E, Panzer O, Hetz H, Lampl K, et al. Comparable postoperative pulmonary atelectasis in patients given 30% or 80% oxygen during and 2 hours after colon resection. Anesthesiology 1999; 91: 991-8. [CrossRef]

89. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med 1996; 334: 1209-15. [CrossRef]

90. Feiner JR, Finlay-Morreale HE, Toy P, Lieberman JA, Viele MK, Hopf HW, et al. High oxygen partial pressure decreases anemia-induced heart rate increase equivalent to transfusion. Anesthesiology 2011; 115: 492-8. [CrossRef]

91. Pryor KO, Fahey TJ, 3rd, Lien CA, Goldstein PA. Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population: a randomized controlled trial. JAMA 2004; 291: 79-87. [CrossRef]

92. Qadan M, Akca O, Mahid SS, Hornung CA, Polk HC, Jr. Perioperative supplemental oxygen therapy and surgical site infection: a meta-analysis of randomized controlled trials. Arch Surg 2009; 144: 359-66; discussion 66-7.

93. Tsai AG, Johnson PC, Intaglietta M. Oxygen gradients in the microcirculation. Physiol Rev 2003; 83: 933-63. [CrossRef]

94. Edmark L, Kostova-Aherdan K, Enlund M, Hedenstierna G. Optimal oxygen concentration during induction of general anesthesia. Anesthesiology 2003; 98: 28-33. [CrossRef]

95. Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G. Reexpansion of atelectasis during general anaesthesia may have a prolonged effect. Acta Anaesthesiol Scand 1995; 39: 118-25. [CrossRef]

96. Rusca M, Proietti S, Schnyder P, Frascarolo P, Hedenstierna G, Spahn DR, et al. Prevention of atelectasis formation during induction of general anesthesia. Anesth Analg 2003; 97: 1835-9. [CrossRef]

97. Gardella C, Goltra LB, Laschansky E, Drolette L, Magaret A, Chadwick HS, et al. High-concentration supplemental perioperative oxygen to reduce the incidence of postcesarean surgical site infection: a randomized controlled trial. Obstet Gynecol 2008; 112: 545-52. [CrossRef]

98. Scifres CM, Leighton BL, Fogertey PJ, Macones GA, Stamilio DM. Supplemental oxygen for the prevention of postcesarean infectious morbidity: a randomized controlled trial. Am J Obstet Gynecol 2011; 205: 267 e1-9.

99. Duggal N, Poddatoori V, Noroozkhani S, Siddik-Ahmad RI, Caughey AB. Perioperative oxygen supplementation and surgical site infection after cesarean delivery: a randomized trial. Obstet Gynecol 2013; 122: 79-84. [CrossRef]

100. Williams NL, Glover MM, Crisp C, Acton AL, McKenna DS. Randomized controlled trial of the effect of 30% versus 80% fraction of inspired oxygen on cesarean delivery surgical site infection. Am J Perinatol 2013; 30: 781-6. [CrossRef]