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WHAT'S NEW IN INTENSIVE CARE

Oxygen toxicity in major emergency surgery—anything new?

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There is a liberal use of oxygen in anaesthesia and intensive care. The rationale is to create high levels of oxygen tension in arterial blood that, together with satisfactory tissue perfusion, should prevent hypoxemic events at a cellular level. Patients undergoing major and emergency surgery are at particular risk of low tissue perfusion. Thus, hyperoxia may appear a reasonable thinking and has received support in guidelines by the World Health Organisation, WHO, with a recently published update after criticism of the initial document [1]. The updated version suggests to use 80% oxygen in intubated patients undergoing surgery and for some hours afterwards in an attempt to reduce postoperative surgical site infections. However, the criticism of the WHO guidelines remains as emphasised in a new editorial view by our group, where we conclude that "suggesting hyperoxia has very little scientific support and it may instead be erroneous and possibly harmful" [2].

The reason to argue against the WHO guidelines can be illustrated by two recent large studies that are not included in the WHO meta-analyses. Thus, one study based on a retrospective analysis of administrative data from almost 74,000 patients undergoing non-cardiothoracic surgery found an increased frequency of pulmonary complications with hyperoxia [3]. The other study had a prospective design with more than 5700 patients undergoing major abdominal surgery and found no benefit by hyperoxia for wound complications [4]. To these two 80,000-patient studies can be added studies that found the risk of harm in abdominal surgery to involve significantly increased long-term mortality [5], shorter time to cancer recurrence or death [6] and long-term risk of myocardial infarction [7].

Hyperoxia has a number of respiratory and cardiovascular effects. High FIO_2 can impede minute ventilation in the spontaneously breathing subject, worsen ventilation–perfusion matching by countering hypoxic pulmonary vasoconstriction and shift the oxygen dissociation curve to the left (Haldane effect), all three mechanisms further lowering arterial oxygenation. Systemic vasoconstriction increases by 8% in connection with a 10% reduced cardiac output, when the inspiratory oxygen fraction is adjusted from 0.30 to 1.00 as investigated under general anaesthesia [8]. A study of coronary blood flow during elective coronary angiography has even measured a 20% reduced coronary artery blood flow, when patients breathed 100% O_2 as compared to ambient air [9]. These findings are especially important to evaluate in future clinical trials, because many organ affections are silent, undetected and common in high-risk abdominal or emergency surgery such as covert stroke, myocardial injury and acute kidney injury. Cardiovascular events are the most common and severe adverse postoperative events with myocardial injury after non-cardiac surgery (MINS), affecting 8% of patients with minor to major risks with almost 10% 30-day mortality [10]. The numbers for extensive or emergency surgery are likely muck higher, and it is still not evaluated if the routine use of high oxygen concentrations comes with an indirect affection of these deleterious outcomes trough vasoconstriction or formation of direct oxygen toxicity (Table 1).

Hyperoxia will also promote atelectasis formation, by more rapid absorption of alveolar gas. This causes shunt of blood through non-ventilated lung, and the atelectasis may also promote an inflammatory reaction in the lung [11]. It might be noticed that the major cause of atelectasis during surgery is the pre-oxygenation during anaesthesia induction. Pre-oxygenation with 100%

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Table 1 Organ affections related to oxygen toxicity

Organ system	Condition	Comment
Central nervous system	Dizziness, headache, visual impairment, retinopathy, neuropathy and convulsions	Dose-dependent toxicity of high O_2 concentrations and prolonged exposure
Cardiovascular	Cardiac output	Decreased by 10%
	Coronary blood flow	Decreased by 20%
	Systemic vasoconstriction	Increased 8%
	Myocardial injury and –reinfarction	In STEMI: One RCT suggested association, but largest RCT with no association Surgery: post hoc study of a RCT suggested association between hyperoxia and long-term risk of myocardial infarction
Lungs	Oxygenation	Primary indication: prevents and corrects hypoxaemia
	Atelectasis	Full evidence, dose-dependent atelectasis, primarily at $FiO_2 > 0.80$
	Lung injury	Direct toxicity or second to inflammation and atelectasis
	Pneumonia	Not conclusive evidence
	Hypercapnic respiratory failure	Especially in patients with COPD, BMI $\geq$ 40 or chronic neuromuscular disease or restrictive lung disease
Gastrointestinal	Surgical site infection	No conclusive evidence in patients undergoing general or regional anaesthesia (RR 0.89, 95% CI 0.73–1.07)
	PONV	No conclusive benefit
	Cancer recurrence	One post hoc study with link to hyperoxia in patients with localised cancer
General	All-cause mortality at longest follow-up	Significantly increased in critically ill (RR 1.10, 95% CI 1.00–1.20) not conclusive in surgery (RR 0.96, 95% CI 0.65–1.42)
	Oxidative stress	Increased formation of reactive oxygen species

COPD chronic obstructive pulmonary disease, *FiO_2*, inspiratory oxygen fraction, *PONV* postoperative nausea and vomiting, *RR* relative risk, *STEMI* ST-segment elevation myocardial infarction

O_2 is a safety procedure to prevent desaturation in the event of a difficult intubation of the airway and to avoid the pre-oxygenation is hardly recommendable. However, using 80% O_2 during the pre-oxygenation instead of 100% reduces markedly not only atelectasis, but also apnea time [11]. It is possible by applying positive airway pressure to maintain FRC during and after induction of anaesthesia; so, 100% O_2 can be used without causing any atelectasis [11].

It is well known that higher concentrations of oxygen promote production of reactive oxygen species (ROS) with free radicals that can harm tissue. Although excess ROS production at moderate levels of PaO_2 during surgery and in ICU are less described, the lungs are exposed to the highest oxygen concentrations and are, therefore, the primary targets of oxygen toxicity. 70% oxygen injures isolated rat lungs due to the production of ROS within 1 h and lung injury can be detected in live mice breathing 100% O_2 within 24 h [12]. Breathing gas with high oxygen concentrations is used to produce an experimental model of acute respiratory distress syndrome, ARDS [13]. It has also been shown that stimulation of ROS by hyperoxia can transform normal cells to cancer cells [14]. In vivo studies have also documented increased migration of human breast cancer adenocarcinoma cells, when exposed to 65% as compared to 25% O_2 [15]. This, as well as findings of increased angiogenesis, provide a rationale to the hypothesis that hyperoxia may be involved in cancer recurrence, although the findings of shorter time to cancer recurrence among patients with localised cancer during hyperoxia exposure in the PROXI trial have not yet been replicated [2].

Increased mortality has been found with increasing arterial oxygen tension in intensive care patients. A randomised study on low versus high arterial oxygen tension (median PaO_2 87 vs. 102 mmHg) in mechanically ventilated patients with acute respiratory failure showed a much higher mortality in the high PaO_2 group (44 vs. 25%) [16]. Although this study was stopped early that decreased its power, the findings were similar in another observational cohort study in critically ill patients [17]. Thus, severe hyperoxia ($PaO_2 > 200$ mmHg) was accompanied by higher mortality (17%) than normoxia or mild hyperoxia ($PaO_2 < 200$ mmHg; 11%) [17]. In still another study, a higher number of ventilator-free days and decreased hospital mortality were seen in intensive care patients receiving conservative oxygen therapy, i.e., lower oxygen concentration [18]. Recent guidelines recommend strongly against oxygen therapy in non-hypoxemic patients with cardiac ischemia or stroke [19], whereas less evidence is present for neurointensive care although observational studies suggest that very high PaO_2 is

harmful in traumatic brain injury patients [20]. Guideline for acutely ill medical patients recommend stopping supplemental oxygen therapy when SpO_2 reaches 96% [19]. High-flow oxygen therapy can be ideal to reach such target in some hypoxic patients, but the delivered FIO_2 and resulting PaO_2 would presumable exert the same actions as in intubated patients. It should also be mentioned that most survivors of ARDS experience long-term neuropsychological morbidity, and moderate hypoxemia was proposed to be a risk factor (median and interquartile PaO_2 in those with symptoms 71 (67–80) mmHg vs those without 86 (70–98) mmHg; $p = 0.02$) in an observational study of 102 patients [21].

It is highly controversial that guidelines for prehospital care, emergency medicine, hospital wards, anaesthesia, and ICU are not aligned when patient with urgent surgical conditions likely will be exposed to all guidelines within few hours [8]. It is also interesting that only few perioperative studies have focused on oxygen therapy in emergency surgery with less than 1000 patients randomised so far [19].

So, in summary, there is nothing new regarding oxygen toxicity and we shall continue to limit excessive use of the gas. Ongoing studies will clarify the extent of how the well-known toxicity may translate into clinical complications. In the meantime, it could rather be that high oxygen concentrations and tensions, here called hyperoxia, may be more for the comfort of the emergency care provider, the anaesthetist and the intensivist than for the patient.

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Compliance with ethical standards

Conflicts of interest
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