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Pierre Asfar
Mervyn Singer
Peter Radermacher

Understanding the benefits and harms of oxygen therapy

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P. Asfar
Département de Réanimation Médicale et de Médecine Hyperbare, Centre Hospitalier Universitaire, 4 rue Larrey, Cedex 9, 49933 Angers, France

P. Asfar
Laboratoire de Biologie Neurovasculaire et Mitochondriale Intégrée, CNRS UMR 6214–INSERM U1083, Le Pôle de recherche et d'enseignement supérieur Université Nantes Angers Le Mans (PRES UNAM), Angers, France

M. Singer
Bloomsbury Institute of Intensive Care Medicine, University College London, Cruciform Building, Gower St, London WC1E 6BT, UK

P. Radermacher (✉)
Institut für Anästhesiologische Pathophysiologie und Verfahrensentwicklung, Universitätsklinikum, Helmholtzstrasse 8-1, 89081 Ulm, Germany
e-mail: peter.radermacher@uni-ulm.de
Tel.: +49-73150060214

Introduction

The Dr. Jekyll and Mr. Hyde character of oxygen (O_2) is well established [1], with O_2 the vital final electron acceptor within the respiratory chain, but also a strong oxidizer that leads to the formation of "reactive oxygen species" (ROS). Hyperoxia-related increases in ROS production are particularly pronounced during ischaemia/reperfusion (I/R) and hypoxia/reoxygenation [2]. This dichotomy also holds true for ATP synthesis and ROS formation. Approximately 2 % of mitochondrial O_2 consumption is directed towards ROS production, i.e., the more ATP produced, the more ROS generated [2]. ROS also share friend-and-foe characteristics, in that despite their toxic potential they are vital players in host defence systems and as signaling molecules [3].

Vincent and De Backer stated that circulatory shock "…represents an imbalance between O_2 supply and requirements…", thus "… administration of O_2 should be started immediately to increase O_2 delivery…" [4]. This is a cornerstone of "V" ("ventilate") within the "VIP" ("ventilate–infuse–pump") rule for resuscitation. Nevertheless, the administration of high-dose O_2 remains highly contentious [5, 6] (Fig. 1). Consequently, current guidelines recommend the lowest fraction of inspired O_2 (FiO_2) possible [7].

The window of opportunity

Oxyhaemoglobin saturation is near complete at the partial pressure of oxygen in the arteries (PO_2) of 90–100 mmHg. Despite a maximum fivefold increase in physically dissolved O_2 upon breathing 100 % O_2, total blood O_2 content will be only moderately raised. However, the lower the haemoglobin content, the more pronounced the effect, such that pure O_2 ventilation is particularly protective during critical haemodilution and/

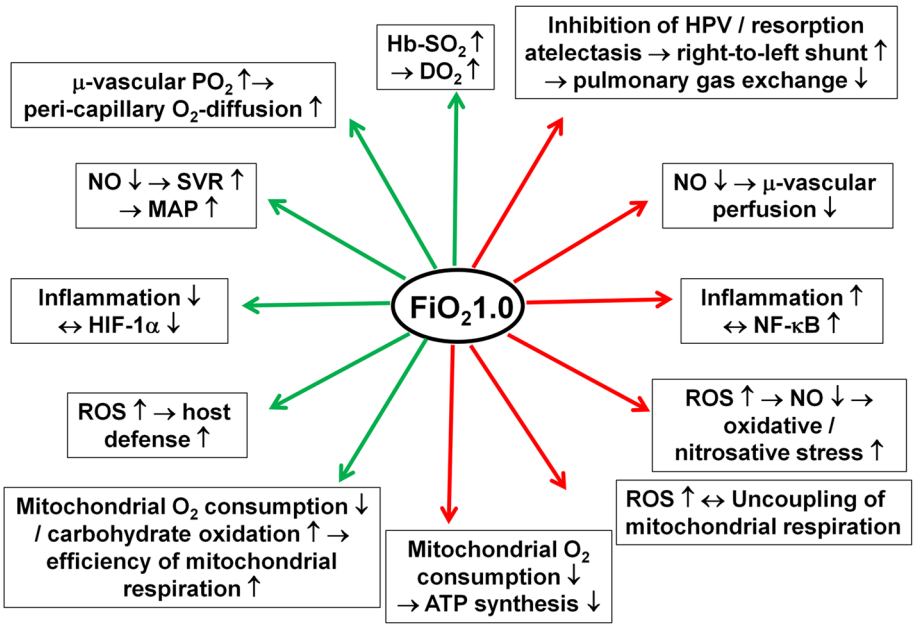

Fig. 1 Beneficial (*green arrows*) and deleterious (*red arrows*) effects of hyperoxia, i.e. breathing pure oxygen, during circulatory shock and/or in medical emergencies. FiO_2 Fraction of inspired oxygen, PO_2 oxygen partial pressure, μ micro, *Hb* haemoglobin, SO_2 oxygen saturation, DO_2 systemic oxygen transport, *HPV* hypoxic pulmonary vasoconstriction, *MAP* mean arterial pressure, *SVR* systemic vascular resistance, *NO* nitric oxide, *HIF-1α* hypoxia-inducible factor 1alpha, *NF-κB* nuclear transcription factor kappaB, *ROS* reactive oxygen species, *ATP* adenosine triphosphate

or blood loss [5]. Moreover, breathing pure O_2 increases the safety margin during airway management [5]. Preclinical data are equivocal [5], but the impact of breathing pure O_2 during haemorrhagic shock has not yet been investigated.

Pulmonary effects

Under normobaric conditions, "oxygen toxicity" refers to pulmonary inflammation. In animals, such toxicity requires long-term exposure and/or injurious ventilation, whereas lung-protective ventilation over shorter periods is not deleterious. In healthy volunteers, exposure to pure O_2 for 6–25 h provoked clinical and histological signs of tracheitis and/or alveolitis [5]. The only patient data originate from a study carried out in 1972 which focused on the effects of hyperoxic mechanical ventilation over periods ranging from 14 h to 30 days [8]. However, given the year of publication year, the intervention was unlikely to have been lung-protective.

Long-term pulmonary O_2 toxicity must be distinguished from adsorption atelectasis occurring within minutes, such as during the induction of anaesthesia [5]. This effect, due to N_2 wash-out in lung regions with low ventilation/perfusion-ratios, can be prevented by positive end-expiratory pressure.

Vascular effects

Hyperoxia decreases cardiac output by decreasing the heart rate and systemic vasoconstriction. Since vasoconstriction is particularly pronounced in cerebral and coronary circulations, the benefit–risk balance remains controversial. The studies conducted to date have mainly been performed under stable haemodynamic conditions; consequently, the impact during cardiorespiratory instability is uncertain. Hyperoxia-related increases in vasomotor tone may allow reducing vasopressor dose. Vasoconstriction also coincided with reduced systemic consumption, although the markers of energy balance remained unchanged [9]. Experimental data suggest that hyperoxia may redistribute cardiac output in favour of the hepatosplanchnic system [5] and may shift energy metabolism towards preferential carbohydrate utilization, thereby increasing mitochondrial respiratory efficiency—i.e. the ratio of ATP production to O_2 consumption.

Acute coronary syndrome

Supplemental O_2 breathing, a cornerstone of acute coronary syndrome (ACS) management, has recently been questioned [9] due to coronary vasoconstriction. European Resuscitation Council guidelines recommend an "O_2 saturation of …94–98 %, or 88–92 % if the patient is at risk of hypercapnic respiratory failure", while "supplementary O_2 should be given only to those patients with hypoxaemia, breathlessness or pulmonary congestion". Until recently, the evidence base relied on data from four clinical trials collected over four decades. The urgent need for data from a large clinical study [10] has been partly answered by the AVOID trial [Electronic Supplementary Material (ESM) Table 1] which reported that high-flow O_2 supplied via a face mask increased

myocardial injury, recurrent infarction, arrhythmias, and residual infarct size in non-hypoxaemic patients with myocardial infarction.

Cerebral effects (traumatic brain injury, stroke and cardiac arrest)

Theoretically, hyperoxia-induced vasoconstriction may be helpful in brain injury by decreasing intracranial pressure (ICP). ICP reduction has been shown in patients with traumatic brain injury (TBI) during *hyperbaric* oxygenation (HBO); combining HBO with subsequent normobaric hyperoxia improved long-term outcomes. Conversely, normobaric hyperoxia alone yielded equivocal results. Hyperoxia in TBI remains controversial because of conflicting outcome data [11, 12]. Despite compelling experimental evidence and encouraging pilot studies, hyperoxia is deleterious in patients with stroke and/or intracranial bleeding, i.e. those with ischaemic brain injury [13, 14].

The effects of hyperoxia on the cerebral circulation and its potential to aggravate I/R-injury have prompted investigations on the association between hyperoxia and outcome after cardiac arrest. To date, only data from retrospective analyses are available. The authors of a recent meta-analysis concluded that hyperoxaemia (PaO_2 >300 mmHg) "…correlated with increased in-hospital mortality…", however, this "…should be interpreted cautiously because of the significant heterogeneity…of studies analyzed" [15].

Peri-operative hyperoxia

Oxygen is recognized to have antibiotic properties. Peri-operative hyperoxia targeted to prevent surgical site infection (SSI) has been studied in >5,000 patients. Despite equivocal findings, the conclusion drawn by the authors of a recent meta-analysis is that hyperoxia (80 % inspired O_2) decreases the risk of SSI, both after elective and emergency surgery, without a major risk of post-operative atelectasis [16]. The molecular mechanisms remain as yet unclear, with both enhanced and reduced cytokine release having been implicated. However, despite these possible short-term benefits, hyperoxia was associated with higher long-term (>2 years) post-operative mortality in cancer patients.

What is the optimal PaO_2 for ICU survival?

To date, this question remains unanswered. Analysing retrospective data, de Jonge et al. demonstrated a U-shaped relationship between mortality and arterial PO_2, with a nadir at PaO_2 values of 15–20 kPa (110–150 mmHg) [17]. However, mortality sharply increased at <9 (67 mmHg) and >30 kPa (225 mmHg). In a more recent study, Eastwood et al. confirmed the harmful impact of hypoxaemia, but found that hyperoxaemia >40 kPa (300 mmHg) did not affect outcome [18].

Conclusion

Hyperoxia (i.e. pure O_2 ventilation) is a cornerstone of shock management that is based on experimental evidence indicating that correcting "oxygen debt" is crucial. However, "oxygen toxicity" limits the use of this strategy, especially in conditions of I/R and during long-term administration. A recent meta-analysis suggests that hyperoxia may be associated with increased mortality in patients after cardiac arrest, stroke and TBI [19]. Most existing data originate from heterogenous, observational studies with inconsistent results, and data from prospective randomized studies are scarce. Therefore, the results of ongoing large scale, randomized, controlled clinical trials are keenly anticipated (ESM Table 2). Until then, "conservative" O_2 therapy [7] should be the treatment of choice to avoid both hypoxaemia and excess hyperoxia.

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Conflicts of interest None.

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