Submitted October 2017; Accepted January 2018

CORRESPONDENCE

# Pro/con debate
# Conservative oxygenation in the intensive care unit: Pro

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Keywords - **oxygen therapy, conservative oxygenation, hyperoxia, mechanical ventilation, intensive care unit, pro-con**

Owing to its indispensable nature, oxygen may be the most appealing element in life, but it is also a vital element in medical practice and among the most universally used agents for the treatment of critically ill patients. In order to ensure sufficient oxygenation, oxygen therapy during mechanical ventilation, anaesthesia and resuscitation usually exceeds physiological levels. It is highly effective in increasing the oxygen content of arterial blood when tissues are at risk of a critical deficiency in oxygen concentrations.

However, physiological concepts, preclinical data and recent clinical studies suggest that excessive oxygenation can have significant deleterious properties in various sequelae of disease and may lead to a paradoxical decrease in oxygen delivery to prone regional areas.[1-3] Because an excess of oxygen is difficult to monitor on a continuous basis and oxygen is generally administered in a liberal manner, arterial hyperoxia is frequently encountered in the intensive care unit.[4-6] Hyperoxia can be defined as a state in which supraphysiological levels of oxygen are inspired and/or reach the arterial circulation. A formal definition for arterial hyperoxia does not exist, but a partial pressure of arterial oxygen ($PaO_2$) higher than 120 mmHg (>16 kPa) has previously been characterised as mild hyperoxia and $PaO_2$ >200 mmHg (26.7 kPa) as severe hyperoxia.

Several studies indicate that targeting conservative oxygenation or at least normoxia after initiation of mechanical ventilation is safe, may prevent complications and improve patient-centred outcomes.[7-9] Conservative oxygen therapy may contribute to acclimatisation and cellular adaptation to the lower ranges of normoxia, which may result in improved efficiency of adenosine triphosphate production and protection of mitochondria. From a physiological point of view this makes perfect sense as the human body has evolutionarily been adapted to successfully maintain aerobic metabolism with a fraction of inspired oxygen ($FiO_2$) of 21% in ambient air at sea level. It provides the ideal environment for the eukaryotic cell that is perfectly capable of efficient oxygen consumption at partial pressures of arterial oxygen of 75-100 mmHg (10-13.3 kPa) and corresponding mitochondrial oxygen concentrations of approximately 11 mmHg (1.5 kPa). One can argue that oxygen delivery and tissue oxygen tension not only depend on the arterial oxygen tension but also on perfusion and oxygen consumption. These two factors are frequently impacted by critical illness and may vary in different tissues, and at different temperatures and pH. However, higher oxygen concentrations have been shown to increase the peripheral vascular resistance and decrease cardiac output.[10,11] As a result oxygen delivery in the organs at risk may actually be impaired through peripheral vasoconstriction and bradycardia. Hyperoxia-induced haemodynamic changes impose a further risk during cardiovascular instability. Likewise, increased mortality and morbidity have been observed with hyperoxia during events such as ischaemic heart disease,[12,13] cardiac arrest,[14,15] stroke,[16,17] traumatic brain injury[18-21] and mechanical ventilation.[22,23] The relationship between arterial hyperoxia and hospital mortality is quite consistent over several subgroups, but associations with delayed cerebral ischaemia, poor cerebral performance and disability have also been shown in patients after cardiac arrest, traumatic brain injury and stroke.[23,24] Also, a decline in ventilation-free days (28 days after admission) have been observed in patients where the average $PaO_2$ over the ICU admission time was larger than 200 mmHg.[24]

Another pathway through which conservative oxygenation may be favourable in comparison with hyperoxygenation is by establishing a healthy balance between oxidants and antioxidants. Oxygen free radicals, which are commonly referred to as reactive oxygen species (ROS), are versatile molecules with an important role in cell signalling and homeostasis. ROS are formed during aerobic metabolism but physiological levels may be exceeded during environmental stress or when supplemental oxygen is administered. Critical illness may be viewed as an important environmental stressor and a typical setting for inadequate levels of ROS. When antioxidant systems are insufficient, supplemental oxygen can cause accumulation of

oxygen radicals and may initiate or perpetuate oxygen toxicity. As a result of ROS and damage associated molecular pattern (DAMP) molecules, DNA and cell damage may manifest as apoptosis and necrosis leading to tissue injury and local organ-specific complications. DNA damage has been suggested to underlie the worse outcomes of patients exposed to high $FiO_2$ levels during oncological surgery.[25,26] Pathways of cell damage and oxidative stress contribute to a pro-inflammatory state in which tissue injury is exaggerated and the innate immune system may be impaired.[27]

Interestingly, it has long been suggested that hyperoxia may have antibacterial properties and can reduce surgical site infections (SSI) or infectious complications, but in recent meta-analyses this effect appeared to be marginal or even absent.[28,29] A lively debate has only recently been launched in reaction to a recommendation by the World Health Organisation (WHO) stating that '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 hrs'.

The rationale for such measures is to improve oxidative killing of bacteria by neutrophils. However, not only was there insufficient evidence from methodologically limited studies with heterogeneous outcomes, but other effects of hyperoxic ventilation were completely ignored in this international recommendation. The concept of a beneficial effect of hyperoxia on infections emerged when an experimental study showed that SSI may occur less frequently when subcutaneous tissue oxygen tensions stay above 60-80 mmHg, which happens when $PaO_2$ levels are higher than 300 mmHg.[30] It is exactly at those levels where the risk of in-hospital death has been shown to rise sharply in critically ill patients,[24] especially when the exposure to such supraphysiological levels is prolonged. Also, a more complete Cochrane review of the literature in 2015 concluded that evidence does not support the routine use of $FiO_2$ higher than 60% during anaesthesia and surgery, as the risk of adverse events, including mortality, may be increased by a fraction of inspired oxygen of 60% or higher.[31]

Furthermore, neurological symptoms following hyperoxic ventilation can be transient or severe but are usually less pertinent and difficult to diagnose in sedated critically ill patients. Pulmonary complications are more frequently encountered as absorption atelectasis, inflammation and pulmonary oedema can have major influence on oxygenation and ventilation.

In conclusion, the side effects of supraphysiological oxygenation can be roughly subdivided in cell damage, inflammation, pulmonary complications, neurological symptoms and vascular effects. These major features are responsible for the large majority of the unfavourable effects associated with the (prolonged) exposure to hyperoxia. Therefore, a more conservative approach by targeting relative normoxia at physiological levels and avoiding exposure to sub-physiological as well as supraphysiological oxygenation should be considered the most rational choice in most cases. In selected patients, targeting the lower ranges of normoxia (55-80 mmHg) may also be safely pursued, but this remains to be confirmed in future clinical trials.

## Disclosures

The author declares no conflict of interest. No funding or financial support was received.

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