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LASTING LEGACY IN INTENSIVE CARE MEDICINE

Oxygen targets

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A truly historical perspective on oxygen targets begins billions of years ago. In Earth's early history, there was essentially no oxygen in the atmosphere. Evolution of cyanobacteria resulted in oxygen production through photosynthesis. However, initially, as Earth's iron rusted, oxygen did not appreciably accumulate in the atmosphere. Around 2 billion years ago oxygen in the atmosphere rose to between 2 and 4%, where it remained for over a billion years. It was in this low oxygen environment that the precursors to our mitochondria evolved. Around 850 million years ago, oxygen levels in the atmosphere rose substantially before levelling out at ≈21% where they have remained for 100 of millions years. The accumulation of atmospheric oxygen and the evolution of multicellular life on Earth are inextricably linked. Humans evolved in an atmosphere of 21% oxygen but, within our cells, our mitochondria are typically exposed to much lower oxygen levels more akin to those present in Earth's atmosphere a billion years ago.

Oxygen is an intrinsically highly reactive chemical that oxidises lipids and damages DNA. Antioxidants protect our cells from oxygen-induced damage; however, when their capacity is overwhelmed, we are exposed to oxidative stress. As well as cellular effects, hyperoxaemia has readily demonstrable physiological effects. It reduces heart rate and cardiac output and increases systemic vascular resistance [1]. It also decreases coronary and cerebral blood flow [2, 3]. It has long been recognised that oxygen can cause harm [4]. Neurotoxicity and pulmonary toxicity from hyperbaric and supranormal oxygen were first described in 1878 and in 1899, respectively [4].

In the critically ill, supplemental oxygen is often required to prevent hypoxaemia; oxygen is, unequivocally, a potentially life-saving therapy. However, choosing the right amount of oxygen to give involves balancing opposing risks. A more liberal approach to provision of oxygen risks inadvertent hyperoxaemia while a conservative approach risks inadvertent hypoxaemia. The sigmoid shape of the oxygen-dissociation curve means targeting low arterial oxygen levels on pulse oximetry (SpO_2), even with close monitoring, may risk brief periods of rapid and marked desaturation (for example, if a patient develops a sputum plug). On the other hand, because an SpO_2 of 100% may occur with either normal or high arterial oxygen tension (PaO_2), hyperoxaemia may not readily detectable by a pulse oximeter. With this in mind, it is reasonable to avoid an SpO_2 of 100% to minimize the risk of inadvertent hyperoxaemia. Moreover, because clinically important discrepancies between SpO_2 and arterial oxygen saturation (SaO_2) can occur, caution is required when targeting oxygen therapy using SpO_2 recordings. Usually, a major change in a critically ill patient's oxygen requirements or SpO_2 recordings should prompt arterial blood gas sampling.

A number of observational studies suggest both low and high PaO_2 are associated with increased mortality in critically ill patients [5, 6]. However, it is not possible to draw causal inferences about particular oxygen regimens from such studies and it is likely that residual confounding exists even in the most sophisticated adjusted analyses. For example, poor peripheral perfusion leading to unreliable SpO_2 recordings might lead to more liberal provision of oxygen and resultant high PaO_2 in patients with more severe illness and such poor perfusion is not recorded in databases used for observational studies.

The first high profile randomised controlled trial (RCT) evaluating oxygen regimens in the intensive care unit (ICU) was the Oxygen-ICU trial [7], a single centre Italian trial conducted in heterogeneous ICU population ($N=480$). A statistically significant difference in mortality between groups was reported with 20.2 and 11.6% of patients allocated to conventional and conservative oxygen therapy respectively dying in the ICU. Notably, this study

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was stopped early after a non-pre planned interim analysis. The reported absolute mortality reduction with conservative oxygen therapy of 8.6 percentage points implies that more than a third of all ICU deaths could be avoided by implementing a conservative approach to oxygen therapy. This effect was not replicated in the multicentre ICU randomized trial comparing two approaches to oxygen therapy (ICU-ROX) [8] ($N=1000$). The primary outcome in ICU-ROX was ventilator-free days, which were not significantly affected by conservative oxygen therapy. In the ICU-ROX trial, 32.2 and 29.7% of conservative and usual oxygen therapy patients respectively died in hospital. Published simultaneously with the ICU-ROX trial, a French multicentre RCT LOCO2 ($N=205$) comparing conservative and liberal oxygen regimens in patients with acute respiratory distress syndrome (ARDS) raised the possibility that conservative oxygen therapy might increase the risk of mesenteric ischaemia [9]. The study was stopped early and there was no statistically significant difference in the primary outcome, 28-day mortality, which occurred in 34.3 and 26.5% in the conservative and liberal groups, respectively. Subsequently, the international multicentre (Handling Oxygenation Targets in the ICU) HOT-ICU trial [10] ($N=2928$), which focused on a broad group of patients with hypoxic respiratory failure with a PaO_2/FiO_2 ratio at baseline below 120 mmHg and very similar to the baseline value in the LOCO2 trial, provided reassuring data that conservative oxygen therapy was not significantly associated with mesenteric ischaemia, and also showed that 90 day mortality rates were not significantly different by treatment group. Most recently, a Dutch RCT ($N=400$) conducted in ICU patients fulfilling the systemic inflammatory response syndrome criteria, found no significant difference between high-normal and low-normal oxygenation targets for non-respiratory organ dysfunction over the first 14 days, or in 90 day mortality [11].

While the very large effect of conservative oxygen therapy in the ICU on mortality suggested by the Oxygen-ICU trial appear to have effectively been excluded by more recent multicentre RCTs, it is notable that, given that oxygen is used very widely in patients who are critically ill patients, clinically important mortality effects attributable to oxygen targets either overall, or in particular patient subgroups, have not been excluded. Data from the ICU-ROX and HOT-ICU trials highlighted the potential for important heterogeneity of treatment effect. Post-hoc analyses from the ICU-ROX trial suggested that lower oxygen targets may be preferable for patients with hypoxic ischaemic encephalopathy [12] while higher oxygen targets might be preferable for patients with other brain pathologies and sepsis [13]. A post-hoc analysis of the HOT-ICU trial raised the possibility that higher oxygen targets might be preferable for patients with shock [14].

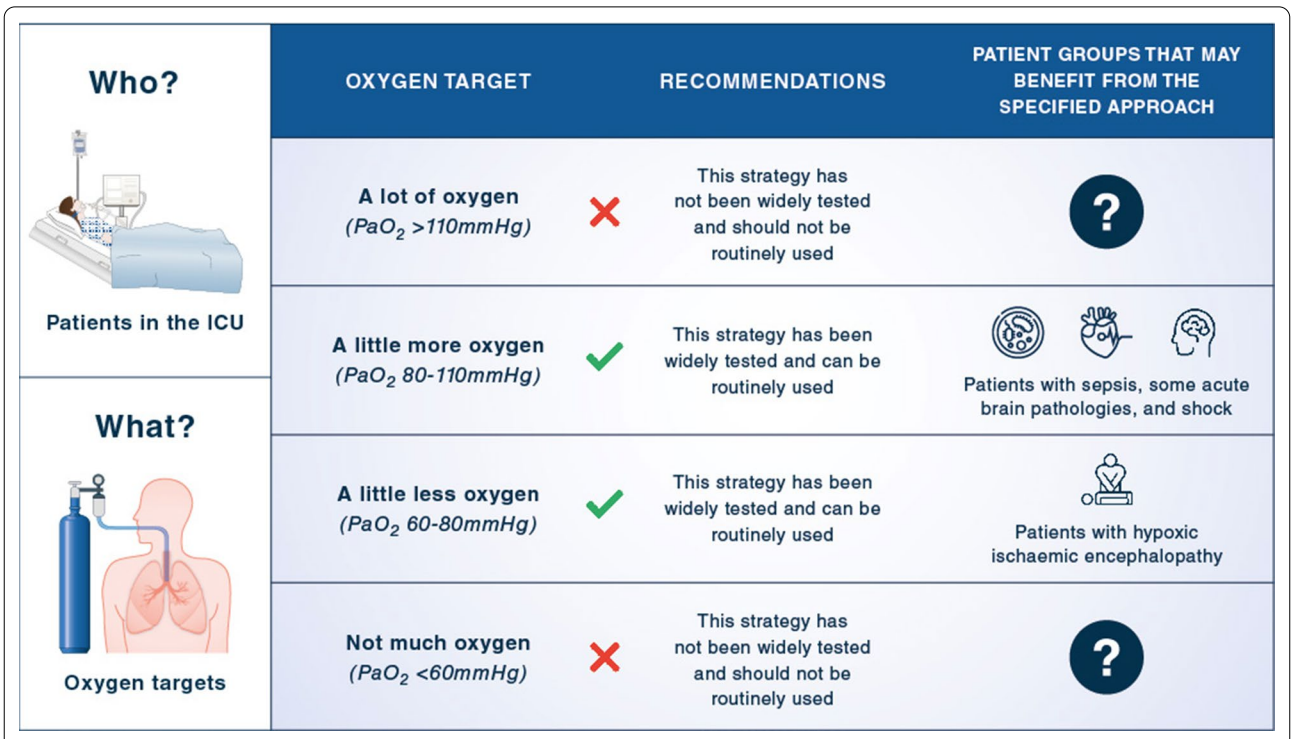

Fig. 1 Reasonable oxygen therapy targets for adults in the ICU

Although published RCTs comparing oxygen therapies in critically ill patients specified different oxygen therapy regimens in their methods, the exposures to oxygen which actually occurred in their respective higher and lower target groups were broadly similar. Nevertheless, because these studies included distinct patient populations, they may not be directly comparable to each other. Certainly, outstanding questions about the approach to oxygen targets for ICU patients both overall, and for particular subgroups remain. Many of these will be addressed by the Blood Pressure and OXygenation Targets After Out-of-Hospital Cardiac Arrest (BOX) trial (NCT03141099), the conservatIve versus CONventional oxygenation targets in Intensive Care patients" trial (ICONIC) (NTR7376), the Strategy to Avoid Excessive Oxygen for Critically Ill Trauma Patients (SAVE-O_2) (NCT04534959), Restrictive vs. Liberal Oxygen in Trauma (TRAUMOX2) (NCT05146700), the United Kingdom Randomised Oxygen (UK-ROX) trial (ISRCTN13384956), and the Mega Randomised Oxygen (Mega-ROX) trial (ACTRN12620000391976). For clinicians who want to know what to do now (Fig. 1) [15], the approaches to conservative and liberal oxygen therapy evaluated in recent RCTs can reasonably be implemented for most patients. For patient groups where one strategy or the other *may* be potentially preferable, clinicians may choose to implement that strategy while acknowledging that uncertainty remains. If a higher oxygenation target is used for a specific patient, it is important to measure PaO_2 to prevent unintentional exposure pronounced hyperoxaemia. Approaches to oxygen therapy that fall outside of the range tested in recent trials should be regarded as experimental and should not be used routinely.

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Declarations

Conflicts of interest
The authors have no conflicts of interest to declare.

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