6 Oxygen: Origin, Physiology, Pathophysiology, and Use in the Critically Ill

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6.1 Introduction

Oxygen is crucial for the critically ill. These patients have a high risk of hypoxemic harm, which can lead to compensatory hyperoxemia by superfluous oxygen administration. Hyperoxia can cause direct toxic effects on the lungs, whereas hyperoxemia can exert vasoconstrictive effects on the circulation, and lead to cellular and organ injury by increased production of reactive oxygen species (ROS). In the last 5 years, an increasing number of large randomized, controlled trials (RCTs) have been performed to determine optimal oxygenation targets, but the discussion is ongoing. In this chapter, we will elaborate on the physiological and pathophysiological background of oxygen, and subsequently discuss the current status of clinical evidence.

6.2 Origin of Oxygen in the Earth's Atmosphere

Over a period of approximately 4.5 billion years, the oxygen fraction (FO_2) of the atmosphere of the earth changed from 0 to 0.21. A complex interaction between biological evolution and geology led to the present FO_2 and the diversity of life forms on earth [1, 2]. Based on the distance to the sun and the position in the solar

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system, the earth is within the 'habitable zone'. Oxygen is an extremely reactive element produced by photosynthesis in cyanobacteria or plants' chloroplasts. Contemporary plants still use symbiosis with cyanobacteria for photosynthesis. Before the appearance of cyanobacteria, anaerobic microbes used sulfate instead of oxygen for their energetic needs. Approximately 2.45 billion years ago, cyanobacteria took over from anaerobes, producing the extremely reactive element oxygen in the period known as the Great Oxidation Event. After another billion years, during which there were very few new developments (the boring billion), the O_2 concentration became high enough for the development and further evolution of animal life. During the history of the earth's atmosphere, a maximum FO_2 of approximately 0.30 has been reached, now stabilizing at 0.21. Its high electronegativity and abundance made oxygen uniquely suitable as the final electron acceptor in a series of transfers from high-energy to low-energy molecular states: the electron transport chain. In this way, the increasing oxygen levels were a prerequisite for the development of many new organisms, including human beings. However, the same levels were toxic for others. Oxygen's propensity to acquire electrons meant that organisms had to develop antioxidant defenses to prevent inadvertent molecular oxidation and dysfunction. As Paracelsus stated "the dose makes the poison".

6.3 Measurements and Estimations of Oxygenation

To estimate the oxygenation status of critically ill patients, several different methods and parameters can be used: oxygen saturation of the blood (SO_2) by pulse oximetry (SpO_2) or by arterial blood gas analysis (SaO_2), oxygen pressure (PO_2) by arterial blood gas analysis, oxygen extraction by adding central or mixed venous blood gas analysis ($ScvO_2$ or SvO_2), lactate concentration and oxygen delivery (DO_2). A pulse oximeter measures SpO_2 with use of two near infrared wavelengths combined with the circulatory pulsations. The two wavelengths are differently absorbed by oxygenated (O_2-Hb) versus de-oxygenated (H-Hb) hemoglobin. Carbon monoxide bonded to hemoglobin (CO-Hb) is not differentiated from O_2-Hb by the two wavelength pulse oximeter and will thus cause a falsely high SpO_2 reading. The main advantages of SpO_2 measurement are that it can be measured easily, continuously, and non-invasively. Disadvantages are the relative unreliable results in patients with dark skin color [3] and the impossibility to detect hyperoxemia. The method using near infrared wavelengths can also be used directly on blood and with up to four different wavelengths instead of the two used in pulse oximetry, enabling determination of concentrations of methemoglobin and CO-Hb [4]. PO_2 can be measured in blood samples with a polarographic electrode that has an electrical resistance varying with PO_2, and tissue PO_2 can be measured by small polarographic electrodes on the skin or on organs. The major limitation of this application is the restricted depth of the measurements. The advantage of PO_2 measurements in arterial blood (PaO_2) is its accuracy. In addition, pressure is the driving force of O_2 diffusion, making pressure a more relevant parameter than saturation, which is not directly related to O_2 diffusion. Disadvantages are the discontinuous and invasive

nature of this method. There are equations to calculate PO_2 from SO_2, and *vice versa*, for oxygen levels within normal ranges [5, 6]. However, these equations do not completely take into account the effects of temperature, 2,3-diphosphoglycerate, pH and PCO_2 (the Bohr effect) on the lateral position (right or left shift) of the oxyhemoglobin dissociation curve and are thus only of limited clinical value. Furthermore, in the high oxygen range with high arterial O_2 saturations (SaO_2 > 97%) large changes of PO_2 are related to extremely small changes of SO_2 that cannot be accurately measured. Thus in the SpO_2 range > 97% hyperoxemia can go undetected unless PO_2 is simultaneously measured. Adequate oxygenation can be estimated by calculating oxygen extraction between arterial and venous blood or by measuring lactate production [7]. Extraction of oxygen and production of lactate depends on severity of hypoxemia, but also on the conservation of tissue perfusion and adequate supply of glucose or other metabolic substrates. Calculating oxygen extraction of the whole body can be done by simultaneous sampling of arterial and central or preferably mixed venous blood. $ScvO_2$ can be sampled relative easily and is a well-documented parameter for assessing the circulation of patients in shock. The problem of SvO_2 measurement is the requirement of a pulmonary artery catheter. Lactate is a simple measurement, but its level can be affected by many other variables [8]. Tissue DO_2 can be calculated using Hb, SaO_2, and PaO_2 [(1.34 x Hb x SpO_2 x 0.01) + (0.023 x PaO_2)] and cardiac output and is about 1000 ml of O_2 per minute under normal conditions. DO_2 is related to oxygen extraction and to oxygen uptake (VO_2), but dependent on many circulatory and metabolic variables.

6.4 Definition of Hypoxemia, Normoxemia, and Hyperoxemia

Administration of extra oxygen can lead to hyperoxia, which is generally defined as any FO_2 >0.21. Supranormal FO_2 in normal physiological conditions will lead to hyperoxemia or higher than normal PaO_2. The normal range of PaO_2 is 10–13.3 kPa. Thus any PaO_2 >13.3 kPa can be considered as hyperoxemia and any PaO_2 value <10 kPa as hypoxemia. Many different definitions and cut-off values for hypoxemia, normoxemia, and (mild, moderate, or severe) hyperoxemia are used in the O_2-literature, which makes comparison of study results very difficult. Due to the shape of the oxyhemoglobin dissociation curve and the weak correlation, especially at the high extreme of the SO_2 range, between PaO_2 and SO_2, the measurement of SO_2 is an unreliable method to distinguish mild, moderate, and severe hyperoxemia.

6.5 Physiology of Oxygen in Humans

The transport and the levels of oxygen (expressed as PO_2) from the inspired gas (air and/or O_2) to the mitochondria are described in the oxygen cascade (Fig. 6.1). Oxygen transport along the cascade is facilitated by ventilation and circulation on the one hand

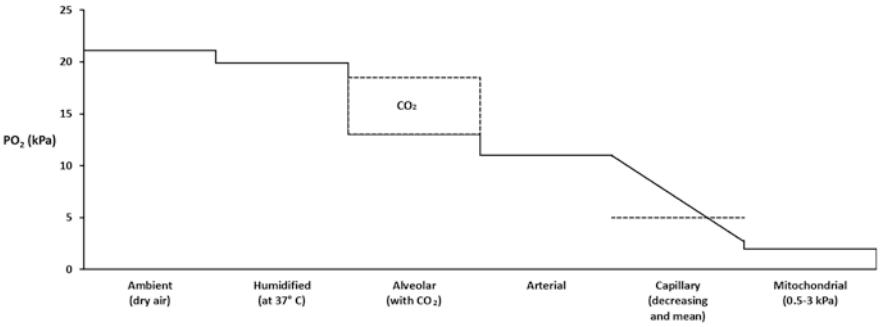

Fig. 6.1 The oxygen cascade: steps from dry ambient air to the mitochondria

and by diffusion on the other. The PO_2 of dry atmospheric air is 21.1 kPa. In the airways, the air is saturated with H_2O at 37 ° C and the inspiratory PO_2 (PIO_2) drops from 21.1 kPa to 19.9 kPa. The next decrease is caused by the exhalation of carbon dioxide (CO_2) in the alveoli. The alveolar carbon dioxide pressure ($PACO_2$) is determined by the alveolar ventilation. Using a simplified alveolar air equation and the respiratory exchange ratio (RQ), the alveolar PAO_2 can be calculated to be approximately 13 kPa under normal conditions and when breathing air. Hypoventilation when breathing air may cause a significant decrease in PAO_2; hyperventilation on the contrary causes only a relatively small increase of PAO_2. This can also be explained by using the alveolar air equation and the PIO_2 (19.9 kPa) in H_2O saturated air in the airways. The highest PAO_2 will be (19.9-$PACO_2$) kPa when breathing air.

Before the circulation takes over the oxygen transport, diffusion of oxygen from the alveoli to the arterial blood is necessary. In normal subjects the alveolar/arterial PO_2 gradient ($\Delta PA\text{-}aO_2$) is limited to less than 2 kPa and is mainly caused by resistance to diffusion. Venous admixture, decreased ventilation/perfusion ratios within the lung, and decreased PAO_2 are the most common causes of an increased $\Delta PA\text{-}aO_2$. The normal arterial O_2 pressure (PaO_2) is therefore slightly higher than 11 kPa. This is the pressure available for diffusion and is directly related to the small amount of oxygen dissolved in blood (0.0232 ml O_2 per 100 ml blood per kPa PO_2).

Most oxygen carried by the blood is bound to hemoglobin (maximum 1.39 ml oxygen per gram of hemoglobin at an SO_2 of 100%). There is a direct equilibrium between dissolved oxygen in blood and oxygen bound to hemoglobin, determined by the oxyhemoglobin dissociation curve and its lateral position. The next stop in the oxygen cascade is the capillary. Over its length in the tissues, more and more O_2 is extracted from the blood by diffusion along a pressure gradient to the tissues. The mean value of PO_2 in capillary blood is slightly >5 kPa. Further steps in the cascade are from capillary to tissue and within the cell. Finally, oxygen reaches the mitochondria. Physiological mitochondrial PO_2 is estimated to be between 3 and 0.5 kPa. In the cells and the mitochondria, O_2 is used by enzymes (oxidases), such as the cytochrome c oxidase system and cytochrome P450. In the mitochondria, O_2 is utilized for aerobic metabolism by oxidation of mainly carbohydrates (glucose). The first step of this process is anaerobic glycolysis taking place in the cells and

converting glucose into pyruvate while producing only two ATP per glucose molecule. In anaerobic conditions, the next step will be the conversion of pyruvate to lactate. Lactate levels in metabolic acidosis can be used to estimate the severity of disease and to a lesser extent of hypoxia [8, 9]. In aerobic circumstances, pyruvate will enter the tricarboxylic acid (TCA) cycle in the mitochondria allowing oxidative phosphorylation, thus producing as much as 36 ATP for each glucose molecule. Further products of this metabolic pathway are CO_2, NADH, $FADH_2$ and H_2O.

6.6 Pathophysiology of Oxygen in Humans: Hypoxemia and Effects of Lack of O_2

When critically ill patients become hypoxemic, aerobic glycolysis will be hampered, causing energy depletion, cellular dysfunction, and progressive metabolic lactic acidosis. Longer lasting (chronic) hypoxemia activates intracellular hypoxia-inducible factor, which can activate gene transcription leading to pathophysiological effects opposing hypoxia. These effects include: increased production of hemoglobin through erythropoietin, an increase in vascular growth factors improving tissue perfusion, and sympathetic activation.

6.7 Pathophysiology of Oxygen in Humans: Hyperoxia, Hyperoxemia, and O_2 Toxicity

At a normal atmospheric pressure of 101 kPa, changing FO_2 from 0.21 to 1.0 has negligible effects on SaO_2 and thus on O_2 content ($C\text{-}O_2$) of the blood. However, PaO_2 will largely increase with an increase in FO_2. Hyperoxia therefore will increase the risks of O_2 toxicity without significantly increasing tissue DO_2. Increasing FO_2 is used in clinical medicine to improve oxygenation in cases of hypoventilation, venous admixture or pulmonary pathology with a diffusion disorder. In anemic patients, the factor limiting $C\text{-}O_2$ is hemoglobin and administration of red blood cells (RBCs) is far more efficient than an increase in FO_2; in patients in shock, tissue DO_2 can best be improved by optimizing the circulation. The increase in FO_2 results in hyperoxia, which has a direct effect on the airways and lungs [10]. Signs and symptoms of toxicity are tracheobronchial inflammation, retrosternal pain, cough, resorption atelectasis, and finally hyperoxic acute lung injury (HALI) at the alveolar level. Alveolar damage is related to nitric oxide (NO) production increased by inflammation.

Hyperoxemia leads to higher than normal levels of O_2 in the cells and mitochondria. At these high levels, mitochondrial O_2 can be transformed to ROS, which have unpaired electrons in the outer shell. *In vitro* experiments showed a strong, exponential correlation between increasing oxygen levels and ROS production in porcine lung mitochondria [11] and capillary endothelial cells from rat lungs [12]. In a reperfusion/re-oxygenation model of cultured hepatocytes, increasing oxygen from 0 to 2% led to a sharp increase in ROS production, whereas further increase in the oxygen content up to 95% induced a steady rise in the formation of ROS [13].

ROS are highly reactive and harmful because they react with intracellular molecules damaging proteins and DNA [14–16]. Thus, unopposed ROS react with fatty acids of lipid membranes causing damage to these membranes and lipid peroxidase reactions leading to further cell damage. The effects of ROS may be increased by systemic inflammation, frequently present in critically ill patients. ROS are physiologically inactivated by superoxide dismutase and catalase, enzymes which support the conversion of ROS into H_2O and normal O_2. ROS can also be inactivated by for example vitamin C, vitamin E, and glutathione in the cells. Antioxidant drugs are pharmacological options to influence ROS formation and deformation. Hyperoxemia not only increases serum ROS but also inflammatory cytokines and is linked to progressive inflammation and organ dysfunction. Oxidative stress in hyperoxemia lowers NO levels and causes vasoconstriction in the microcirculation. Depending on circulatory pathology (the type of shock), vasoconstriction may have different effects on the circulation.

6.8 Effects of Normoxia, Hypoxia and Hyperoxia in Critically Ill Patients

Based on the effects of hypoxemia and hyperoxemia described above, large numbers of observational and interventional studies have been performed over the last decade in critically ill patients. In 2008, a retrospective observational landmark study described the oxygenation targets in 36,307 ICU patients in 50 ICUs in the Netherlands and the relationships between used FiO_2 or achieved PaO_2 and clinical outcome [17]. A U-shaped relationship between PaO_2 and mortality (corrected for several variables) was found, with the lowest mortality in the PaO_2 range from 8.9 to 10.6 kPa. Recently [18], a higher nadir for the relationship between PaO_2 and hospital mortality (13.2 kPa) and ICU mortality (13.5 kPa) was reported in ARDS patients. Since 2008, several RCTs have studied the effects of lower versus higher FiO_2, PaO_2, SaO_2 and/or SpO_2 in critically ill patients [19–25]. These RCTs differed in patient selection, target oxygenation in the low and high oxygen groups, and in primary and secondary endpoints. Table 6.1 gives an overview of the characteristics of the RCTs and of two ongoing RCTs.

The first study [19] was a small feasibility study with 103 participants. There were significant differences between PaO_2, SaO_2, and SpO_2 in the experimental and control groups. The authors concluded that conservative oxygenation targets were feasible even though there were significantly more hypoxemic ($SpO_2 < 88\%$) and hyperoxemic ($SpO_2 > 98\%$) saturations found in the conservative versus the liberal oxygenation groups, respectively. The secondary endpoints (new organ dysfunction, mortality in the ICU and at 90 days) were not significantly different in the two groups in this small study.

The Oxygen-ICU study [20] planned to include 660 patients randomized to normoxic PaO_2 and SpO_2 targets versus 'standard practice' of allowing hyperoxic PaO_2 and SpO_2 values. The study was stopped prematurely after inclusion of 480 patients of whom 434 were analyzed. The primary endpoint (ICU mortality) was

Table 6.1 RCTs comparing conventional (high) and conservative (low) oxygenation targets in critically ill patients ventilated in the intensive care unit (ICU)

Study	Year of publication	Type of patients	Number of participants Conservative/ Conventional	Oxygenation targets		Endpoints		
				Conservative (low) O_2	Conventional (high) O_2	Primary	Secondary	Primary endpoint conclusion
Panwar [19]	2016	Mechanically ventilated in ICU	52/51	SpO_2 88–92%	$SpO_2 \geq 96\%$	Feasibility	New organ dysfunction Mortality	Feasible No difference
Oxygen-ICU Girardis [20]	2016	ICU ≥ 72 h	216/218 (prematurely stopped)	SpO_2 94–88% or PaO_2 70–100 mmHg	$PaO_2 \leq 150$ mmHg SpO_2 97–100% ($FiO_2 \geq 0.4$)	ICU mortality	New organ failure New infection	Primary and many secondary end points: Conservative favorable
HYPERS2S Asfar [21]	2017	Septic shock with mechanical ventilation	223/219 (prematurely stopped)	SpO_2 88–95%	FiO_2 1.0 (24 h)	Mortality 28 d	SAEs	No difference more SAEs in hyperoxia
ICU-ROX Mackle [22]	2020	Mechanically ventilated in ICU	501/499	SpO_2 90–97%	No limit FiO_2 or SpO_2	Ventilator-free days 28 d	Mortality 180 d	No difference
$LOCO_2$ Barrot [23]	2020	ARDS	99/102 (prematurely stopped)	PaO_2 55–70 mmHg SpO_2 88–92%	PaO_2 90–105 mmHg $SpO_2 \geq 96\%$	Mortality 28 d	Mesenteric ischemia	No difference More mesenteric ischemia in conservative group
ICU-ROX post-hoc Young [27]	2020	Sepsis	130/120	SpO_2 90–97%	No limit FiO_2 or SpO_2	Mortality 90 d	ICU/hospital length of stay Ventilator-free days	No difference

(continued)

Table 6.1 (continued)

Study	Year of publication	Type of patients	Number of participants Conservative/ Conventional	Oxygenation targets		Endpoints		
				Conservative (low) O_2	Conventional (high) O_2	Primary	Secondary	Primary endpoint conclusion
HOT-ICU Schjørring [24]	2021	ICU and hypoxia	1441/1447	PaO_2 60 mmHg	PaO_2 90 mmHg	Mortality 90 d	Shock, myocardial ischemia, ischemic stroke, intestinal ischemia	No difference
Gelissen [25]	2021	SIRS in ICU	205/195	PaO_2 8–12 kPa	$FiO_2 \leq 0.6$ PaO_2 14–18 kPa	$SOFA_{RANK}$	Mortality	No difference
Study	*Inclusion period*		*Total planned*					
UK-ROX [33]	2020–2023	Invasive ventilation in ICU	16,500	SpO_2 88-92%	No limit	Mortality 90 d costs/ QALY	Mortality (ICU, hospital, 1 year) Stay (ICU, hospital) Economic	
Mega-ROX [32]	2020–2025	Invasive ventilation in ICU	40,000	$SpO_2 < 94\%$ and FiO_2 0.21 with SpO_2 target 90%	$FiO_2 > 0.3$	Mortality in hospital	Duration of survival, length of stay (ICU, hospital)	

SpO_2 oxygen saturation by pulse oximetry, *FiO_2* inspired oxygen fraction, *QALY* quality-adjusted life year, *$SOFA_{RANK}$* ranked sequential organ failure assessment, *SIRS* systemic inflammatory response syndrome, *ARDS* acute respiratory distress syndrome, *SAE* serious adverse event

significantly lower in the conservative group (12% vs. 20%). Among the secondary endpoints, new shock, new liver failure, and bloodstream infections occurred less frequently in the conservative group. The authors considered their conclusions to be preliminary due to the smaller than planned size of the analyzed groups.

The HYPERS2S study [21] combined a study of oxygenation targets (hyperoxia at FiO_2 of 1.00 compared to SO_2 of 88 to 95%) with a study of isotonic versus hypertonic saline infusion in a two-by-two factorial, multicenter RCT in mechanically ventilated patients with septic shock. The primary endpoint of 28-day mortality was not significantly different in the two oxygenation groups. However, the trial was stopped prematurely due to a high number of serious adverse events (SAEs) in the hyperoxia group. Atelectasis occurred significantly more frequent with an FiO_2 of 1.00 and there was a potentially important but statistically not significant difference in the incidence of ICU-acquired weakness. The authors concluded that in patients with septic shock an FiO_2 of 1.00 might increase the risk of mortality, although at the moment of discontinuation, mortality was not significantly higher in the hyperoxic group.

The ICU-ROX trial [22] included 1000 patients with at least 1 day of mechanical ventilation. Hypoxemia was prevented by setting the lower limit of SpO_2 to 90%. In the conservative group, the upper limit of SpO_2 was 97% and the FiO_2 was lowered to a minimal value of 0.21 as long as SpO_2 was >90%. In the usual (conventional) oxygen group, there were no limits to FiO_2 or SpO_2. The primary endpoint (ventilator-free days at day 28) was not different between the usual and experimental oxygenation groups. Mortality up to 180 days after inclusion was also not different.

In the $LOCO_2$ trial [23], patients with acute respiratory distress syndrome (ARDS) were exposed to either conservative oxygenation targets (PaO_2 55–80 mmHg and SpO_2 88–92%) or liberal oxygenation targets (PaO_2 90 to 105 mmHg and SpO_2 ≥96%) for 7 days. Mechanical ventilation strategies were identical in both groups. The primary endpoint of mortality at 28 days was not significantly different between the groups. However, the trial was stopped prematurely because five cases of mesenteric ischemia occurred in the conservative oxygenation group versus none in the liberal oxygenation group and because the mortality at 90 days was higher (44 vs. 30%) in the conservative oxygenation group.

The HOT-ICU [24] is the largest RCT of lower-oxygenation versus higher-oxygenation in critically ill patients up to now, in which 2888 patients admitted to the ICU for hypoxemic respiratory failure were randomized for target PaO_2 of either 60 mmHg or 90 mmHg. The primary outcome of mortality after 90 days was not significantly different, at 42.9% and 42.2% in the lower-oxygenation and the higher oxygenation groups, respectively. Secondary endpoints were similar in the two groups.

Recently we published results from an RCT in 400 patients with at least two positive systemic inflammatory response syndrome (SIRS) criteria [25]. Target oxygenation was chosen within the range of clinical practice for both the control and the experimental groups. The control group (high-normal) was targeted for a PaO_2 of 14 to 18 kPa and the risk of hyperoxic pulmonary damage was limited

by restricting the FiO_2 to a maximum of 0.60 in this group as much as clinically possible. The experimental group (low-normal) had a target PaO_2 of 8 to 12 kPa. A novel substitute endpoint for organ failure (ranked sequential organ failure assessment [$SOFA_{RANK}$]) was developed based on a previous study [26]. $SOFA_{RANK}$ is a ranked outcome of SOFA scores over the first 14 days after randomization and excluding the respiratory component of the SOFA score since that is being influenced by the targeted oxygenation. Organ failure ranking in the two groups was not significantly different ($p = 0.06$), but tended to favor the high-normal oxygenation target (i.e., the confidence interval was not consistent with clinically important harm from high-normal oxygen target). Mild hypoxemia occurred more often in the low-normal oxygenation group, but severe hypoxemia (PaO_2 <5 kPa) was similar in both the oxygenation groups. Other secondary endpoints (duration of mechanical ventilation and mortality) were similar in the two groups.

In a *post hoc* subgroup analysis of ventilated patients with sepsis from the ICU-ROX study [27], no differences were found between conservative and usual oxygen therapy for the primary endpoint (mortality at day 90) or for any of the secondary endpoints. Point estimates of treatment effects favored usual (conventional) oxygen therapy, in line with our recent results [25].

Since 2014, a number of systematic reviews and meta-analyses [28–31] including the above mentioned RCTs and other studies in critically ill patients have been published.

In 2014, a meta-analysis was published [28] including 17 observational studies and 1 prospective before-after study. Only four of the included studies specifically addressed critical care patients. Due to the heterogeneity of these four studies, data could not be pooled. Mortality was increased in the hyperoxic groups in the pooled studies of post-cardiac arrest, stroke, and traumatic brain injury patients.

In the IOTA systematic review and meta-analysis [29], 27 RCTs with 16,037 acutely ill patients from several subgroups were included. In-hospital, 30 day, and longest follow-up mortality were significantly increased in the overall liberal oxygen versus the overall conservative oxygenation groups.

In 2021, a meta-analysis including seven RCTs with 5265 patients was published [30]. Longest follow-up mortality was identical in the conservative and conventional oxygenation groups overall. However, in a subgroup analysis of three studies that only included patients with mild to moderate hypoxemia (PaO_2/FiO_2 >100 mmHg), mortality was significantly lower when using conservative oxygen therapy.

Also in 2021, a network meta-analysis of eight RCTs in mechanically ventilated critically ill patients was performed [31]. Surface under the cumulative ranking (SUCRA) scores and survival curves suggested superiority of the moderate (90–150 mmHg) PaO_2 target in the trinary and quadruple classification and also the conservative (70–90 mmHg) PaO_2 in the quadruple classification when compared to liberal (>150 mmHg) and far-conservative targets (55–70 mmHg).

6.9 Future Studies

Two large ongoing RCTs comparing conservative versus conventional oxygenation targets in ICU patients have been registered and are currently recruiting [32, 33]. The Mega-ROX trial [32] aims to include 40,000 adults admitted to the ICU for invasive mechanical ventilation or starting invasive mechanical ventilation after admission. For the control group (liberal oxygen or usual care) the only condition is FiO_2 ≥0.30. In the treatment group (conservative oxygen therapy), FiO_2 will be decreased to 0.21 if possible, but limited to a minimum acceptable SpO_2 of 90% and aiming for a maximum SpO_2 of 94 or 95%. The primary endpoint is in-hospital mortality up to 90 days after randomization. Using a response-adaptive randomization procedure, more subjects will be assigned to the group with the lowest mortality during the ongoing period of recruitment, stratified by subgroup. Power calculations were made based on data from the IOTA systematic review and meta-analysis [29] and from the ICU-ROX trial [22]. Heterogeneity of treatment effect in diagnostic subgroups (hypoxic ischemic encephalopathy, acute brain injury, and sepsis) of critically ill patients will be explored.

The UK-ROX trial [33] aims to include 16,500 adult patients admitted to the critical care unit for mechanical ventilation or receiving mechanical ventilation after being admitted for another reason. For the control group (usual oxygen therapy), there are no conditions other than usual care as per local practice. For the intervention group (conservative oxygen therapy), SpO_2 values of 88 to 92% are the target. The primary endpoints are mortality at day 90 and economic outcome (incremental costs, quality-adjusted life year (QALY) and net monetary benefit at 90 days). Economic outcome has not been studied previously in this setting.

6.10 Conclusion

In heterogeneous critically ill patients, the potentially deleterious effects of hyperoxemia found in preclinical research and large observational studies have not been confirmed in well-sized RCTs. In view of the current body of literature, it seems reasonable and prudent to avoid far-conservative and far-liberal oxygenation values. It is presently unknown whether there are specific subgroups or conditions within the critically ill population that might benefit from oxygenation targets outside the normoxemia range. As far as oxygen is concerned half a millennium after the Paracelsus statement "the dose makes the poison", it is still not completely clear at what dose the transition from useful drug to dangerous poison takes place.

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