HHS Public Access

Author manuscript

Can J Physiol Pharmacol. Author manuscript; available in PMC 2019 July 14.

Published in final edited form as:

Can J Physiol Pharmacol. 2019 March ; 97(3): 174–182. doi:10.1139/cjpp-2018-0376.

Hemoglobin oxygen saturation targets in the neonatal intensive care unit: Is there a light at the end of the tunnel?[1]

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Abstract

The optimal oxygenation target needed to prevent the extremes of hypoxia and oxygen toxicity in premature and sick newborns has been the subject of much research and debate. The advent of the pulse oximeter has allowed the continuous monitoring of oxyhemoglobin saturation and the delivery of oxygen with greater precision. Well-run, large clinical trials to determine the safest oxygen concentration have led to several revisions in guidelines for neonatal care. However, monitoring of oxyhemoglobin saturation has its limitations and does not provide a comprehensive assessment of tissue oxygenation. To identify optimal oxygen therapy, various other factors (partial pressure of arterial carbon dioxide, hemoglobin concentration, blood pH, and tissue metabolic demand) that influence perfusion and tissue oxygenation need to be considered.

Résumé:

L’oxygénation cible optimale nécessaire en vue de prévenir les situations extrêmes comme l’hypoxie et la toxicité à l’oxygène chez les nouveau-nés prématurés et malades a fait l’objet de beaucoup de recherches et de débats. L’avènement de l’oxymétrie de pouls a donné le moyen de surveiller la saturation en oxyhémoglobine en continu et d’administrer de l’oxygène avec une plus grande précision. De vastes essais cliniques bien réalisés en vue d’établir la concentration d’oxygène la plus sécuritaire ont mené à plusieurs révisions des lignes directrices pour les soins en néonatalogie. Cependant, la surveillance de la saturation en oxyhémoglobine en continu ses propres limites, et ne permet pas d’obtenir une évaluation intégrale de l’oxygénation tissulaire. En vue d’établir le traitement par l’oxygène optimal, il convient de prendre en compte divers autres facteurs qui influencent la perfusion et l’oxygénation tissulaire (pression partielle du sang artériel en dioxyde de carbone, concentration d’hémoglobine, pH sanguin et demande métabolique tissulaire). [Traduit par la Rédaction]

Keywords

oxygen saturation; newborn; oxygen target

[1]This Review is part of a Special Issue entitled “Connecting Maternal, Fetal, and Newborn Physiology”.

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Conflict of interest

The authors declare that there is no conflict of interest associated with this work.

Keywords

saturation en oxygène; nouveau-né; oxygénation cible

Introduction

Oxygen therapy is a life-sustaining intervention and remains the most commonly used drug in the care of sick newborns (Vento and Saugstad 2010). In the 1940s and 1950s, flooding the newly designed incubators with 100% oxygen contributed to the survival of some premature infants. The first clinical reports, dating back to the early 1950s, linked unrestricted use of oxygen with an increased risk of retrolental fibroplasia (now known as retinopathy of prematurity) (Campbell 1951) and prompted a change in neonatal care practice to restrict oxygen use. The resultant increase in mortality (Bolton and Cross 1974) was the first evidence of the central importance of adequate but not excessive oxygen delivery to the premature infant. New evidence from the same period suggested that oxygen can be toxic at the cellular level by generating free radicals (Gerschman et al. 1954). Over the ensuing decades, research has yielded an understanding that the immature antioxidant defense in newborns (particularly premature infants) predisposes this population to higher oxidative stress and cell damage (Vento et al. 2012; Torres-Cuevas et al. 2017). Even brief exposure to excessive oxygen used in the resuscitation of newborns in the delivery room may lead to an increased risk of childhood leukemia (Naumburg et al. 2002) as well as adverse physiological adaptation at birth (Comroe 1939; Hutchison 1987; Saugstad et al. 2008).

While the deleterious effects of administering high concentrations of oxygen to newborns in respiratory distress became apparent over half a century ago, determining the optimal fraction of inspired oxygen (FIO_2) that would prevent hypoxemia was challenging in the early decades of neonatology, as no reliable method to continuously measure oxygen concentrations in the blood was available. In the 1980s, pulse oximetry measurement of oxyhemoglobin saturation provided a reliable and easier means to continuously monitor oxygenation compared with transcutaneous oxygen tension measurements (Durand and Ramanathan 1986). Soon thereafter, it became the standard of care in neonatal intensive care units (NICU) (Van Meter et al. 2017).

Recognizing that a large number of neonates admitted to the NICU receive supplemental oxygen, there has been tremendous interest in determining the safest oxyhemoglobin saturation that would ensure adequate tissue oxygenation while preventing oxygen toxicity. With growing evidence that restricted use of oxygen decreases the incidence of retinopathy of prematurity and bronchopulmonary dysplasia, the American Academy of Pediatrics stated in 2007 that an oxyhemoglobin saturation between 85% and 95% provides a pragmatic range to guide oxygen therapy (American Academy of Pediatrics and the American College of Obstetricians and Gynecologists 2007). In 2010, the International Liaison Committee on Resuscitation (ILCOR) revised their recommendations to initiate resuscitation of term newborns in room air (Perlman et al. 2010), whereas the optimal FIO_2 in the resuscitation of preterm infants remains controversial (Rabi et al. 2015; Kapadia et al. 2017; Oei et al. 2017;

Lui et al. 2018). The safest saturation target for this subpopulation of NICU babies continues to generate considerable debate (Sola et al. 2014; Cummings et al. 2016). Through a collaborative effort by the Neonatal Oxygenation Prospective Meta-Analysis (NeOProM) study group (Askie et al. 2011), 5 randomized trials involving a total of ~5000 premature infants examined lower (85%–89%) and higher (91%–95%) saturation targets; unfortunately, the study yielded conflicting and controversial conclusions (Carlo et al. 2010; Schmidt et al. 2013, 2017; Stenson et al. 2013; Manja et al. 2015a; Tarnow-Mordi et al. 2016; Saugstad 2018). In addition, the optimal oxygen target in term neonates with hypoxic respiratory failure or newborns undergoing hypothermia therapy remains unknown and warrants further study. Table 1 summarizes the suggested oxygen therapy in newborns (Oei et al. 2018).

While the perfect oxygen saturation ranges for term and preterm infants remain uncertain, here we review data regarding the larger questions of the precision and accuracy of the current technology and the limitations of arterial oxygen saturation as a single marker of tissue oxygenation. Several common practices remain unjustified in the literature, including the tendency to more readily increase FIO_2 during hypoxic events while taking a more lax approach to decreasing FIO_2 when oxygen saturation is high; the continued use of the hyperoxia test in an era of readily available echocardiography; and preoxygenation (prior to intubation) in neonates to prevent oxygen debt (Sola 2008; Sola et al. 2014).

The fetus and basic concepts of oxygen physiology

Aerobic metabolism and maintenance of satisfactory cellular homeostasis are dependent on adequate oxygen delivery to and extraction by the tissues; only when this demand cannot be met does hypoxia ensue. Oxygen delivery, in turn, depends on oxygen content in the blood — influenced primarily by the concentration and percent saturation of hemoglobin — and cardiac output. Important considerations in the fetus include the higher affinity for oxygen in fetal hemoglobin (Hgb F), high Hgb concentrations in term fetuses, and higher cardiac output, factors that provide a substantial margin of safety for oxygenation (delivery is 3 times higher than demand). In addition, properties of Hgb F facilitate unbinding of oxygen in the tissues at lower partial pressures of arterial oxygen (PaO_2) (Maurer et al. 1970). Therefore, Hgb F has the ability to more efficiently bind oxygen as the fetal blood circulates through the placenta and to more readily relinquish it within the tissues (Fig. 1).

Several physiological adaptations of the placenta and developing fetus ensure that the fetus is exposed to a relatively hypoxemic environment. Through an elaborate system of shunts (ductus venosus, ductus arteriosus, foramen ovale) and distribution of blood flow, the fetal circulation diverts the richest concentration of oxygenated blood to the most essential organs (the brain and heart) while minimizing blood flow to the lungs. The coronary and cerebral artery oxygen saturations in the fetus range between ≈58% and 65% (PaO_2: 25–28 mm Hg) (Rudolph 1979, 2009; Prsa et al. 2014).

While PaO_2 has a minimal impact on the oxygen content of blood, the fraction of oxygen dissolved in blood plays an essential role in the physiology of ventilation and cardiovascular regulation (Giussani et al. 2016). The oxygen tension in blood can exert its effect directly through a complex cascade of endogenous mediators that act directly on the vascular smooth muscle cells and by triggering chemoreflexes through the activation of chemoreceptors

(Smith and Vane 1966; Ponte and Purves 1974; Giussani 2016). PaO_2 has opposing effects in the systemic and pulmonary vasculature. Hypoxia results in increased cerebral blood flow (through cerebral vasodilation) but decreased pulmonary blood flow (through pulmonary vasoconstriction), while hyperoxia leads to cerebral artery vasoconstriction (Wolff 1936; Rudolph and Yuan 1966). Normoxia results in pulmonary vasodilation, but hyperoxia does not cause additional pulmonary vasodilation (Lakshminrusimha et al. 2006).

The amount of blood pumped into the pulmonary circulation is dynamic and changes during fetal development. In a clinical trial, providing 60% oxygen by face mask to pregnant women at 20–26 weeks gestation did not alter fetal pulmonary blood flow, whereas an increase in pulmonary blood flow was appreciated at 31–36 weeks gestation (Rasanen et al. 1998). Early in gestation, the cross-sectional pulmonary vasculature is low, maintaining a high pulmonary vascular resistance (PVR), and the lungs receive only ~13% of the cardiac output at 20 weeks gestation, which increases to 25%–30% at 30 weeks gestation owing to the proliferation of pulmonary vessels with a resultant drop in PVR. Cardiac output to the lungs then drops to 16%–21% near term gestation in response to active hypoxic pulmonary vasoconstriction secondary to the pulmonary vessels developing greater sensitivity to oxygen (Kinsella et al. 1994; Rudolph 2009; Rasanen et al. 1996; Prsa et al. 2014). Therefore, the effect of oxygen varies depending on the gestational age of the infant.

Oxyhemoglobin saturation, oxygen tension, and oxyhemoglobin dissociation equilibrium

Several important discoveries — including the discovery of oxygen in 1772 and hemoglobin in 1840, the demonstration in the 1850s that hemoglobin exists in 2 states (oxygenated and deoxygenated), and the development of analytical spectroscopy and the capacity to detect pulsatile (arterial) blood flow — all contributed to the development of pulse oximeters in the early 1980s (Van Meter et al. 2017). Soon thereafter, owing to its safety profile, its noninvasive nature, and the ability to continuously monitor oxygenation, the use of pulse oximeters became widespread in NICUs across the United States (Vijayakumar et al. 1997).

The differential light absorption of oxyhemoglobin (red spectrum of visible light) and deoxyhemoglobin (infrared spectrum of light) and the distinction between pulsatile and nonpulsatile flow constitute the principles of pulse oximetry. The sensor, which in newborns is applied to an extremity, contains 2 light-emitting diodes (LEDs), infrared and red light, that transmit light through the extremity and are received by a phototransistor on the opposite side of the LEDs. Pulsatile blood flow results in fluctuations in blood volume, thus changing the distance the light travels. The pulsatile component of the red to infrared light modulation ratio is calculated, and a microprocessor with built-in algorithms converts this ratio to pulse oxygen saturation (SpO_2) based on a calibration curve (Chan et al. 2013; Tin and Lal 2015). Pulse oximeters are calibrated by data collected from healthy adults and correlated to arterial blood samples tested by co-oximetry (absorbance spectroscopy) that measures actual arterial oxyhemoglobin saturation (SaO_2). Hgb F has an absorption comparable to that of predominant adult Hgb A, and therefore SpO_2 measurement in newborns does not require a separate calibration (Harris et al. 1988; Rajadurai et al. 1992).

Hgb functions to carry blood to the tissues, and its configuration changes depending on whether it is in the deoxygenated (also known as tense) or oxygenated (relaxed) state. Once

oxygen binds the protein, an alteration in its configuration facilitates further oxygen binding. Conversely, as oxygen is released from Hgb, a change in configuration towards the tense state enables unloading of oxygen (Bell 1999). This ability of Hgb to alter its structure promotes the binding and unloading of oxygen. In addition, the affinity of oxygen to bind Hgb depends on the partial pressure of oxygen in the blood. At higher PO_2 (as in the pulmonary circulation), oxygen freely binds Hgb until it is fully saturated, whereas at the level of the tissues, oxygen is quickly released. This relationship can be better appreciated when plotting PaO_2 against SaO_2/SpO_2 (or CaO_2: arterial oxygen content), revealing the characteristic oxyhemoglobin dissociation curve (Fig. 1).

In a study to identify a better marker of oxygenation between oxyhemoglobin saturation (SaO_2) and oxygen tension (PaO_2) in hypoxemic patients, Ahmed et al. made strong arguments in favor of SaO_2 (Ahmed et al. 2017). Over 70 000 arterial blood gases collected from pediatric patients with cyanotic congenital heart disease were analyzed, and PaO_2 was plotted against SaO_2. Owing to the nonlinear relationship between PaO_2 and SaO_2, a narrow range of PaO_2 (30–35 mm Hg) in the hypoxemic range corresponds to a wide range of SaO_2 values (28%–85%). In summary, since (*i*) SaO_2 predominantly determines oxygen content and (*ii*) in hypoxemia the magnitude of SaO_2 changes is greater than that of PaO_2 changes, SaO_2 serves as the better marker of oxygenation. However, as Hgb becomes fully saturated, any further rise in PaO_2 does not alter SaO_2 (representing the plateau in the oxyhemoglobin dissociation curve). Therefore, patients who receive supplemental oxygen and have SpO_2 values in the high 90s may reach supraphysiological PaO_2 values (>100 mm Hg), putting them at risk of oxygen toxicity.

An important consideration, particularly in extremely premature infants, is the effect blood transfusions have on the PaO_2–SaO_2 relationship (Fig. 1). Hgb F, the predominant hemoglobin in newborns, has a high oxygen affinity and, as a result, a lower P50 (partial pressure of oxygen at which 50% of Hgb is saturated by oxygen) of ≈18–19 mm Hg, whereas adult Hgb A has a P50 of ≈26–27 mm Hg (Emond et al. 1993; Maurer et al. 1970). Following transfusion of packed red blood cells (≈27 mL/kg) in extremely premature infants, Hgb F dropped from a mean baseline of 92% to 43%, while the value of P50 increased from 18.5 to 21 mm Hg (Fig. 1) (De Halleux et al. 2002). Consequently, if SpO_2 were maintained at a constant value following adult blood transfusion, the newborn's post-transfusion PaO_2 would be higher. Therefore, in premature infants, SpO_2 values in the upper 90s following several adult blood transfusions pose an even greater risk for oxygen toxicity, as PaO_2 may approach values >100 mm Hg (Fig. 2) (Shiao 2005).

SpO_2 and SaO_2: pulse oximeter limitations and clinical implications

SpO_2 monitoring is ubiquitous in neonatal care. All healthy term and late preterm infants are screened for critical congenital heart disease with pulse oximetry (Ewer et al. 2013; Manja et al. 2015b). Most neonatal patients admitted to the NICU have their SpO_2 measured as soon as they are born. ILCOR recommends monitoring SpO_2 in the delivery room for infants in need of respiratory support. While the pulse oximeter has proven to be an indispensable technology in the care of premature and sick newborns, clinicians need to be cognizant of its limitations.

Pulse oximeters do not measure oxyhemoglobin saturations directly but generate an SpO_2 value using an algorithm generated from SaO_2 samples. One of the most widely used pulse oximeters, Masimo Radical 7, established the accuracy of its algorithm in neonates using 79 samples collected from 16 neonates over an SpO_2 range of 70%–100% (Lakshminrusimha et al. 2015a). The algorithm initially merged 2 curves (one derived from the higher saturation range and the other from the lower saturation range) that inadvertently generated higher SpO_2 values by 2% in the range of 87%–90%, where the 2 curves merged (Johnston et al. 2011). The algorithm has since been revised to include a single curve. This change in algorithm had an impact on results obtained from the BOOST-II trial in the UK and Australia (Tarnow-Mordi et al. 2016).

Pulse oximeters have been shown to have an accuracy of ~3%, which represents 1 standard deviation (SD) (Johnston et al. 2011; Milner and Mathews 2012). Therefore, a displayed SpO_2 of 90% may represent a true SaO_2 anywhere from 87% to 93% in 68% of cases, but may fall outside the range of 84%–96% in 5% of patients. Similarly, an SpO_2 of 95% may represent a true SaO_2 between 92% and 98% in 68% of cases, and results in hyperoxia (with SaO_2 at 99% and 100%) in 16% of cases (Fig. 2). Furthermore, in a study of preterm infants comparing postductal SpO_2 to umbilical artery SaO_2, SpO_2 between 85% and 89% was associated with an SaO_2 <85% in 39% of samples (Rosychuk et al. 2012). Also, in critically ill adults, changes in SpO_2 have been shown to overestimate changes in SaO_2, and this discrepancy worsened at lower Hgb concentrations (Perkins et al. 2003). As noted previously, SaO_2 is associated with a wide range of PaO_2 values depending on the oxyhemoglobin dissociation curve (Figs. 1 and 2). A shift to the left (as seen with Hgb F, hypothermia, and alkalosis) will result in lower PaO_2 for a given SaO_2 and can potentially influence vascular regulation (such as PVR). However, as dissolved oxygen contributes to a very small component of the oxygen content in arterial blood (CaO_2), this value is influenced mainly by Hgb content and SaO_2 (Fig. 2). Finally, to avoid erratic responses to aberrant signals, pulse oximeters do not display instantaneous readings, but rather use time-averaging to smooth out the signal. The default manufacturer time-averaging is set at 8 s, which may be adjusted to between 2 and 32 s. Longer averaging times reduce the detection of brief or severe desaturations (Ahmed et al. 2010; Vagedes et al. 2013), while short averaging times run the risk of worsening alarm fatigue (Johnson et al. 2017). However, for the purpose of SpO_2 monitoring in the delivery room, shorter averaging times may lead to quicker adjustments in FIO_2 in an attempt to prevent hyperoxemia.

While oxyhemoglobin saturation is currently the best marker to assess oxygenation, various other factors, including the partial pressure of arterial carbon dioxide ($PaCO_2$), Hgb concentration, blood pH, and tissue metabolic demand, play a crucial role in perfusion and tissue oxygenation (Fig. 3). Attempting to identify the optimal SpO_2 while not concurrently evaluating $PaCO_2$ and pH values, which are known to significantly alter cerebral and pulmonary blood flow (Rudolph and Yuan 1966; Yoon et al. 2012), may paint only part of the bigger picture. Continuous CO_2 monitoring by means of capnography and (or) transcutaneous monitors is a helpful surrogate for this information with less frequent blood gas monitoring. Near-infrared spectroscopy (NIRS) is a newer technology that differs from pulse oximetry in that near-infrared light is reflected from Hgb in tissues and capillaries and returns to the sensor to provide a continuous noninvasive estimate of tissue oxygenation,

thus serving as a surrogate marker for tissue oxygen consumption. The distance between the light source and the sensor determines the depth of the tissue interrogated. With careful selection of an appropriate probe, regional tissue saturation can be measured in organs such as the brain, kidney, liver, intestine, and skeletal muscle, while automated oxygen-controlling systems may help to maintain SpO_2 in a target range and thus assist in achieving an optimal FIO_2 (Claure and Bancalari 2013; Sood et al. 2015; Waitz et al. 2015); this advance is not designed to incorporate the additional factors noted previously.

In experimental studies in our laboratory, 15 term lambs with meconium aspiration syndrome Lakshminrusimha et al. 2015b; Rawat et al. 2016) were ventilated with different Hgb concentrations, and ventilator parameters were altered to adjust $PaCO_2$. A drop in Hgb concentration from 14–17 g/dL to 10–13 g/dL resulted in an increase in carotid blood flow. Further reduction in Hgb to 7–9.9 g/dL did not alter carotid flow. A rise in $PaCO_2$ significantly increased carotid blood flow at all levels of Hgb. Interestingly, Hgb did not alter pulmonary flow, albeit an increase in $PaCO_2$ from 38–48 mm Hg to 50–60 mm Hg decreased pulmonary flow only in the severely anemic lambs (Hgb of 7–9.9 g/dL). In the Hgb range of 10–17 g/dL, cerebral blood flow appears to be more sensitive to $PaCO_2$ than pulmonary blood flow (Fig. 3). Hence, mild hypercapnia may promote oxygen delivery to the brain without markedly increasing PVR and may be an effective strategy in the management of conditions such as congenital diaphragmatic hernia and persistent pulmonary hypertension of the newborn (in the absence of anemia) (Gupta et al. 2002; Puligandla et al. 2015).

Goals of oxygen therapy

The role of oxygen therapy in hypoxemia is to (*i*) provide sufficient oxygen to the tissues, thus avoiding anaerobic metabolism and lactic acidosis; (*ii*) prevent hypoxic pulmonary vasoconstriction, which would further exacerbate hypoxemia and lead to hypoxia; and (*iii*) promote brain and somatic growth. The ideal oxygen therapy would meet these goals while minimizing formation of oxygen free radicals (Fig. 4).

In determining the lower oxygenation limit, 2 main factors need to be considered: (*i*) the oxygen level when hypoxic PVR becomes significant and (*ii*) the critical point when oxygen delivery (DO_2) cannot sustain oxygen consumption (VO_2). The alveolar partial pressure of oxygen (PAO_2) has the greatest impact on pulmonary vascular reactivity (Moudgil et al. 2005). However, as PAO_2 is not directly measured in clinical settings, PaO_2 and SpO_2 cutoffs have been evaluated in newborn animal models, which have shown a significant rise in PVR below a PaO_2 of ≈45–50 mm Hg (Rudolph and Yuan 1966; Lakshminrusimha et al. 2009); in a lamb model of pulmonary hypertension induced by fetal ductus arteriosus ligation, maintaining SpO_2 between 90% and 97% resulted in low PVR (Lakshminrusimha et al. 2009). The oxygenation target to identify the critical point below which VO_2 decreases as DO_2 decreases is more difficult to ascertain given that Hgb concentration has a greater impact on arterial oxygen content (CaO_2) than oxyhemoglobin saturation, and because there are currently no reliable means to measure cardiac output continuously. Unpublished pooled data from newborn lamb experiments identified the CaO_2 at ≈12 mL O_2/mL when there is a notable reduction in the arteriovenous difference in oxygen. Once DO_2 falls below the

critical point, anaerobic metabolism and lactic acidosis ensue, consistent with tissue hypoxia. For example, a patient with a Hgb concentration of 10 g/dL who has an SpO_2 of 85% ($CaO_2 \approx 11.5$ mL O_2/mL) may fall below the critical point if cardiac output is low. An SpO_2 of 93% under the same conditions would yield a CaO_2 of ≈12.5 mL O_2/mL, whereas an increase in Hgb to 13 g/dL (following a blood transfusion) would increase the CaO_2 to ≈16 mL O_2/mL. One needs to be mindful, however, that as Hgb drops, a compensatory increase in cardiac output can maintain oxygen delivery and thus prevent reaching of the critical point. An ongoing study funded by the NICHD (through the neonatal research network) and the NHLBI, the Transfusion of Prematures (TOP) trial (https://clinicaltrials.gov NCT01702805), aims to evaluate whether a liberal Hgb threshold (13 g/dL during the first week of postnatal life on respiratory support) or a restrictive strategy (Hgb of 11 g/dL) for blood transfusion improves neurological outcomes in preterm infants.

An interesting observation in the SUPPORT trial was that the increased mortality among infants randomized to the lower target SpO_2 did not occur until after the first 2 postnatal weeks (Carlo et al. 2010). Vento et al. have speculated that the postnatal decrease in Hgb (especially in NICUs where there is low Hgb transfusion threshold) may result in low CaO_2 values in preterm infants managed with low target SpO_2 values (Fig. 5) (Vento 2014). Promoting placental transfusion at birth, minimizing iatrogenic blood loss, and using strategies to maintain higher Hgb levels should increase CaO_2.

The upper limit of oxygenation should represent the level of oxygenation that results in toxicity, which in return leads to adverse effects (retinopathy of prematurity, bronchopulmonary dysplasia, and poor neurodevelopment). Experimental studies have shown that targeting PaO_2 >80 mm Hg does not result in additional pulmonary vasodilation (Rudolph 1979; Lakshminrusimha et al. 2006, 2009). Furthermore, PaO_2 >100 mm Hg following excessive use of oxygen in the resuscitation of babies with hypoxic–ischemic encephalopathy has been shown to be associated with poor neurodevelopmental outcomes (Kapadia et al. 2013).

SpO_2 target limits

The final results from the NeOProM collaboration were recently reported (Askie et al. 2018). In this analysis, there was no significant difference between the lower SpO_2 (85%–89%) and higher SpO_2 (91%–95%) target range on the primary composite outcome of death or major disability at a corrected age of 18–24 months. However, patients who were randomized to the lower SpO_2 target range were shown to have a higher risk of death and necrotizing enterocolitis, but a lower risk of retinopathy of prematurity (Askie et al. 2018). The results from this study suggest that an SpO_2 target range of 91%–95% may be safer than a range of 85%–89% in extremely preterm infants (<28 weeks gestation) based primarily on an observed increase in the risk of death associated with the lower range (Bizzarro 2018).

Current evidence suggests that the safest SpO_2 range in term infants with hypoxic respiratory failure and persistent hypertension of the newborn is 90%–95% (Vali and Lakshminrusimha 2017). A multi-center randomized study comparing SpO_2 ≥94% to ≥90% in infants suffering from bronchiolitis has demonstrated that infants who were maintained at an SpO_2 closer to 90% had less need for oxygen supplementation (56% versus 73%), a

lower duration of oxygen use (5.7 h versus 27.6 h), and were discharged from the hospital sooner (40.9 h vs. 50.9 h) (Cunningham et al. 2015). Finally, in a large adult trial, patients who were expected to be admitted for >72 h in the intensive care unit were randomized to receive oxygen therapy to maintain PaO_2 between 70 and 100 mm Hg (SpO_2 between 94% and 98%; conservative group) or to allow PaO_2 values up to 150 mm Hg (Spo_2 values between 97% and 100%; conventional control group) (Girardis et al. 2016). Patients who were maintained at the lower oxygen range had lower risk of mortality, shock, liver failure, and bacteremia. Although children are not small adults and neonates (especially preterm) are not small children, from a physiological standpoint there may be some similarities in oxygen saturation targets across age groups while individuals receive supplemental oxygen (Fig. 6).

Conclusion

The human body has an extraordinary ability to maintain homeostasis. When this equilibrium is disturbed, restoring balance by means of medical therapies may lead to unexpected adverse effects. In premature and sick newborns, many of whom suffer from respiratory distress, one of the biggest challenges is balancing the optimal oxygen supplementation to ensure adequate tissue metabolism while avoiding hypoxia and oxygen toxicity. The advent of the pulse oximeter to provide continuous, reliable, noninvasive, and safe measurements of SpO_2 has radically influenced oxygen therapy in neonates. While the optimal oxyhemoglobin saturation target to preserve the well-being of these patients needs further elucidation, future studies should include other variables (pH, $PaCO_2$, Hgb concentration) that influence perfusion and tissue oxygenation.

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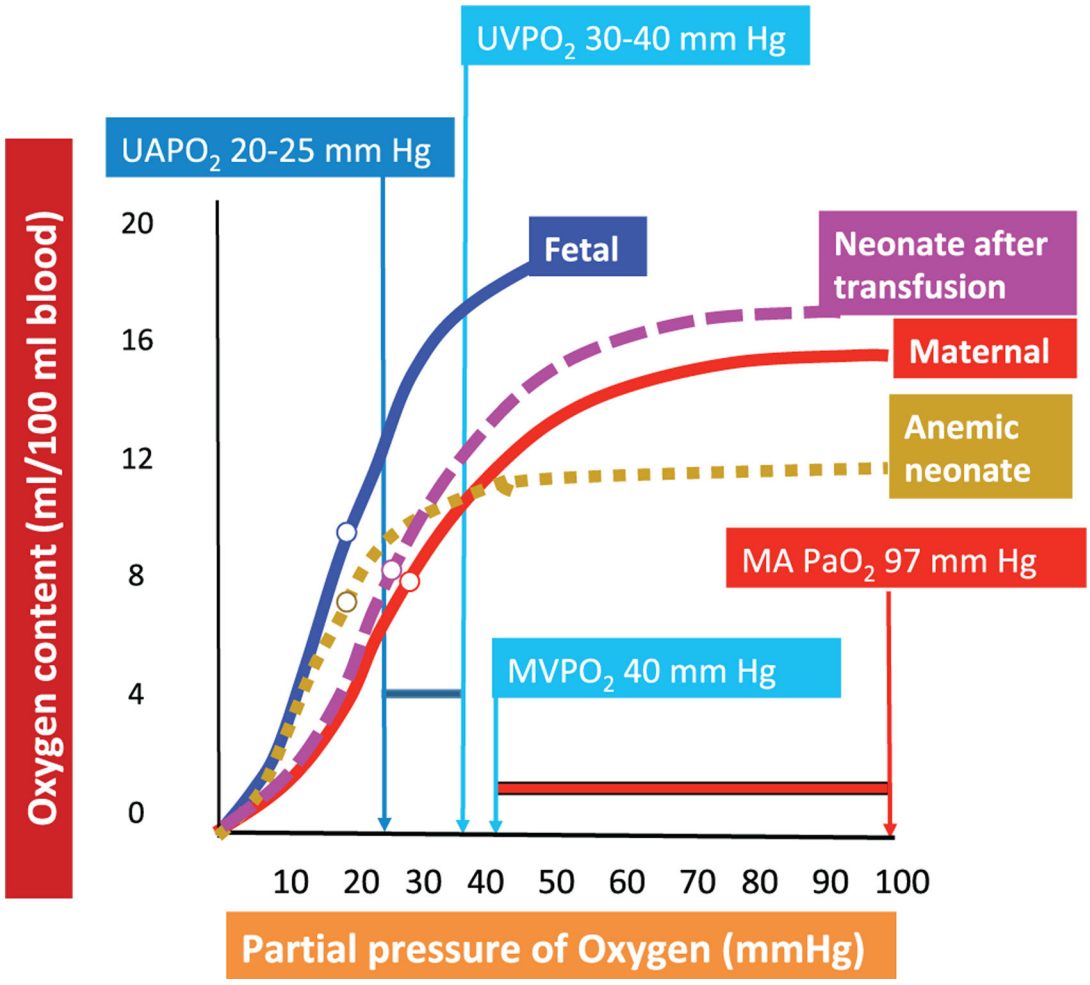

Fig. 1.

Oxyhemoglobin dissociation curve (CaO_2 versus PaO_2). The higher oxygen affinity of fetal hemoglobin (blue curve) shifts the oxygen dissociation curve to the left, which results in a greater release in oxygen at a lower partial pressure of oxygen (PO_2) compared with adult hemoglobin (red curve). Only a small change in PO_2 (≈10 mm Hg) from the higher oxygenated fetal venous blood (30–40 mm Hg) to the arterial blood (20–30 mm Hg) results in a release of ≈25% of oxygen to the tissues. In the pregnant woman, however, a similar release in oxygen from adult hemoglobin requires a drop from the arterial PO_2 (97 mm Hg) to the venous PO_2 (40 mm Hg) of 57 mm Hg. In a neonate, anemia (hyphenated orange curve) is associated with lower CaO_2 without any change in P50 (partial pressure of oxygen resulting in 50% oxygen saturation or 50% peak CaO_2). P50 is shown as an open circle along the oxygen–hemoglobin dissociation curve. Transfusion with packed red cells from an adult source (with hemoglobin (Hgb) A) results in increased CaO_2 and also an increase in P50 towards adult values. $MAPO_2$, maternal arterial PO_2; $MVPO_2$, maternal venous PO_2; $UAPO_2$, umbilical artery PO_2; $UVPO_2$, umbilical vein PO_2. Data from Rudolph (2009). Note that the oxyhemoglobin dissociation curve is often presented with SaO_2 on the *y*-axis; we opted to present these data with CaO_2 on the *y*-axis to more clearly demonstrate the impact of blood transfusion.

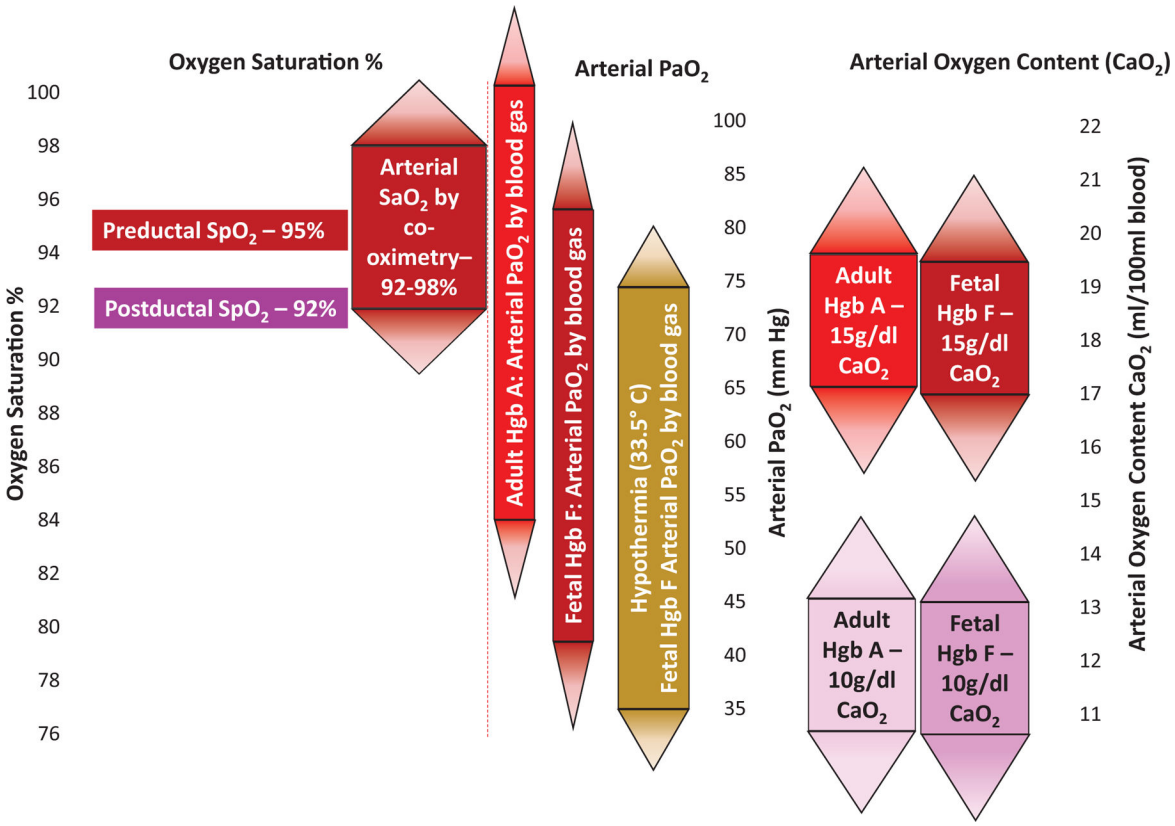

Fig. 2.

Relationship between oxyhemoglobin saturation, arterial partial pressure of oxygen (PaO_2), and arterial oxygen content (CaO_2). Oxyhemoglobin saturation measured by pulse oximeter (SpO_2) has an accuracy of 3% when compared with the true arterial oxyhemoglobin saturation (SaO_2) by co-oximetry (1 standard deviation (SD) = 3%; rectangular area represents 1 SD, and thus 68% of values; triangular areas represent 2 SD, so 95% of values). An SpO_2 value of 95% can therefore represent an SaO_2 between 92% and 98%. This represents a wide range in PaO_2, and since adult hemoglobin (Hgb A) has a lower affinity for oxygen, for any given SaO_2, the PaO_2 is higher in blood containing Hgb A. Note the impact of hemoglobin on oxygen content (CaO_2).

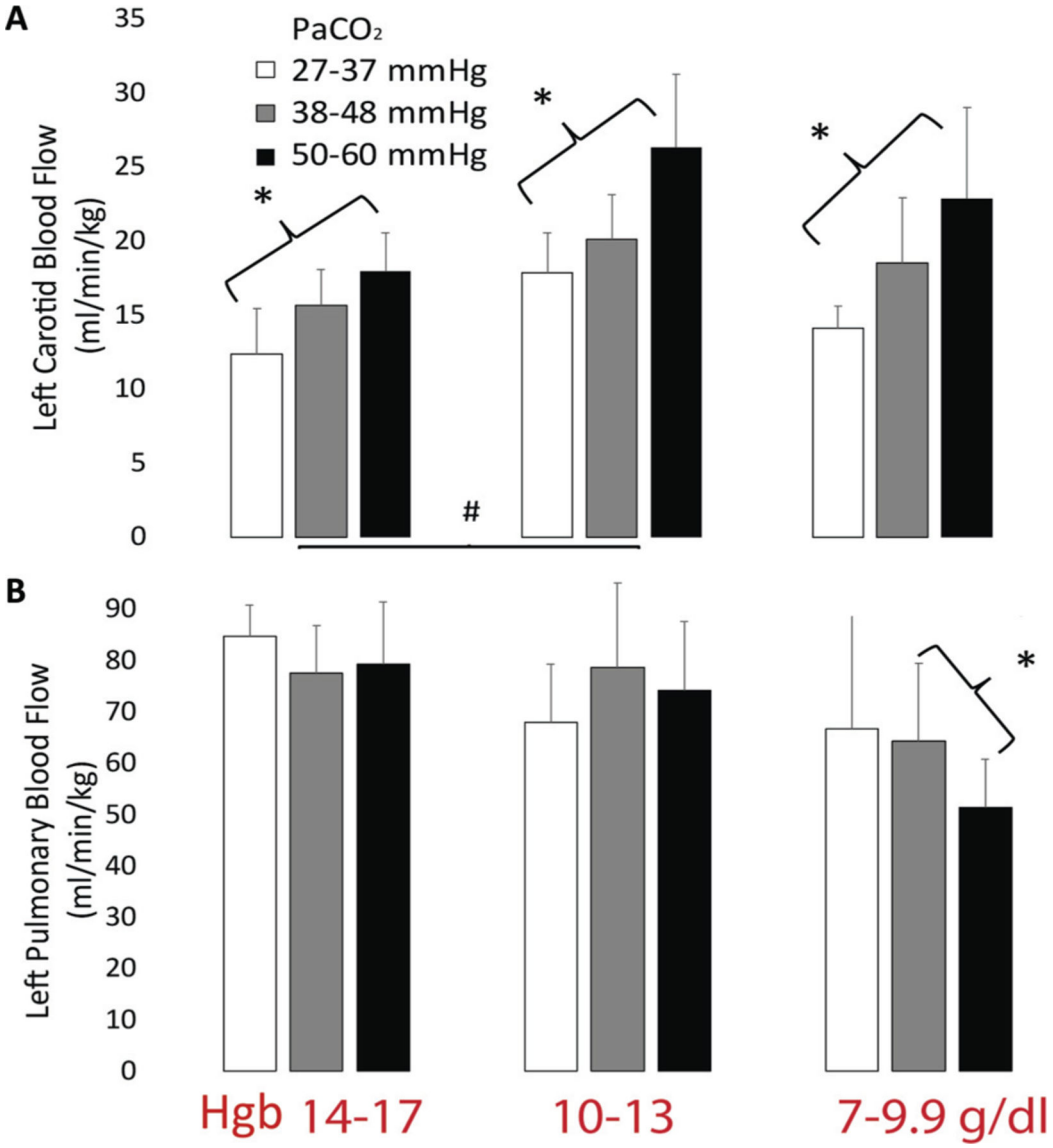

Fig. 3.

Effect of hemoglobin (Hgb) and arterial partial pressure of carbon dioxide ($PaCO_2$) on pulmonary and left carotid blood flow. Pooled data from 15 lambs sorted by Hgb and $PaCO_2$ showing changes in carotid (A) and pulmonary (B) blood flow. Carotid blood flow is more sensitive than pulmonary blood flow to changes in $PaCO_2$. *, $P < 0.05$ by analysis of variance (ANOVA) post hoc test with change in $PaCO_2$; #, $P < 0.05$ between Hgb groups.

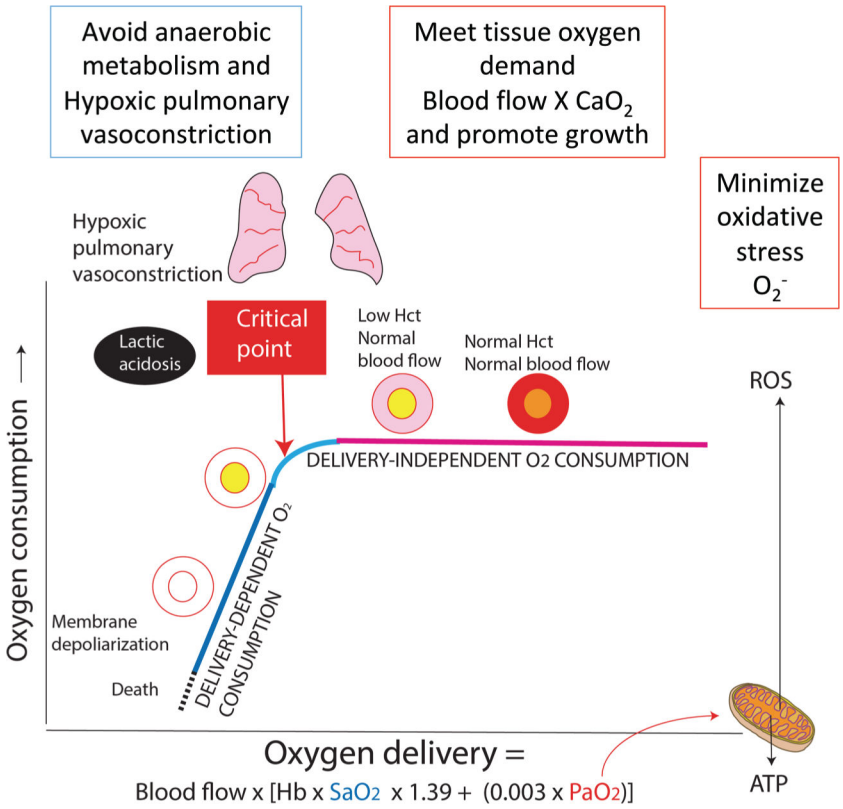

Fig. 4.

Relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2). DO_2 is a product of blood flow and arterial oxygen content (CaO_2). The driving force for oxygen from alveoli to mitochondria is the partial pressure of oxygen (PO_2). Increased mitochondrial PO_2 can lead to formation of reactive oxygen species (ROS). When DO_2 decreases below a critical point, VO_2 becomes dependent on delivery. Hypoxemia leads to hypoxic pulmonary vasoconstriction, anaerobic metabolism, and lactic acidosis. Persistent hypoxemia can result in cell death.

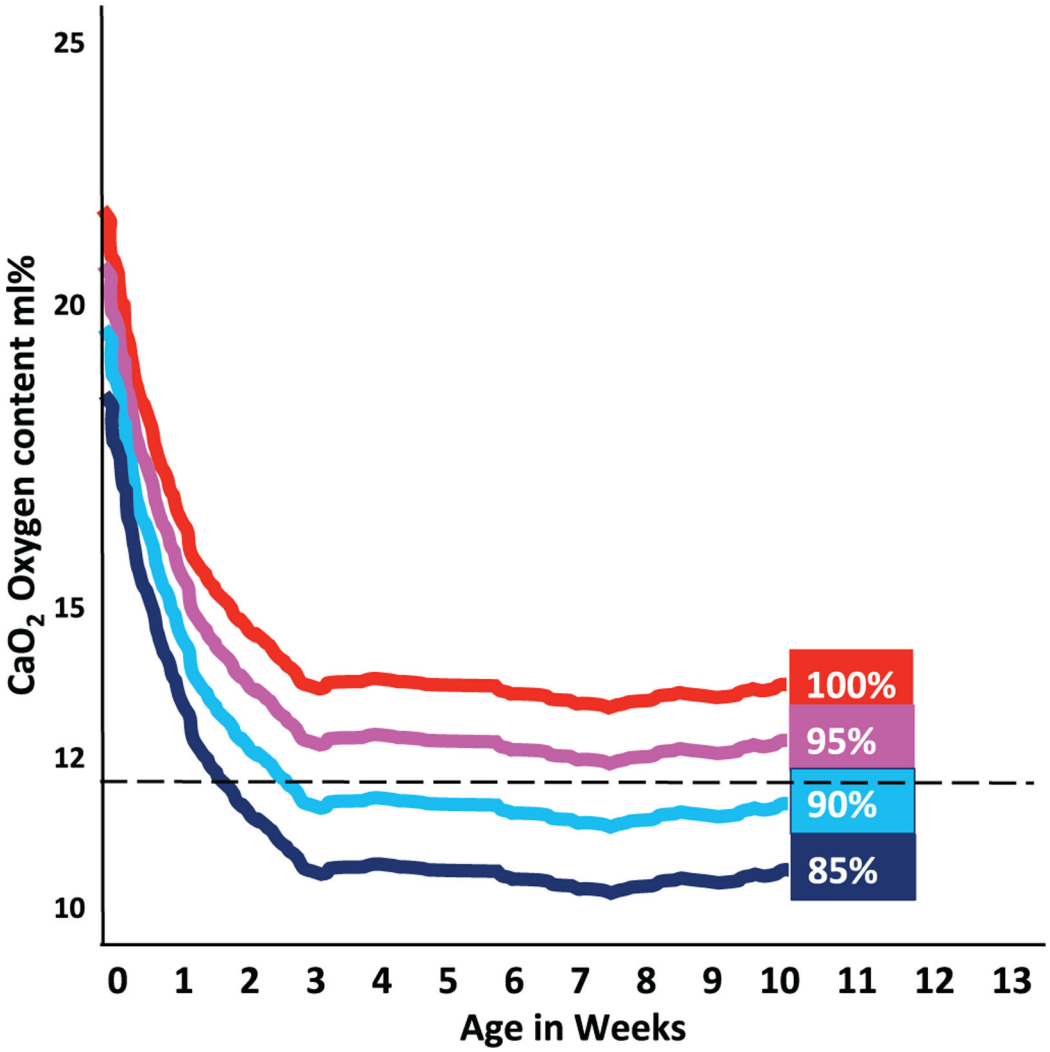

Fig. 5.

Plausible explanation for late mortality in oxygen saturation trials in preterm infants. The increased mortality observed in extremely preterm infants randomized to the 85%–89% SpO_2 arm of the Neonatal Oxygenation Prospective Meta-Analysis (NeOProM) trials occurs after the first 2 weeks of postnatal life. Vento et al. (2012) have speculated that a gradual postnatal decrease in hemoglobin (especially if threshold for transfusion is low in the neonatal intensive care unit and hemoglobin gradually decreases with time) results in decreased CaO_2, which may lead to an oxygen delivery below the critical point (dashed line), as shown in Fig. 4. Suboptimal oxygen delivery can potentially result in necrotizing enterocolitis and mortality, as has been observed in the low saturation target group of the NeOProM trials.

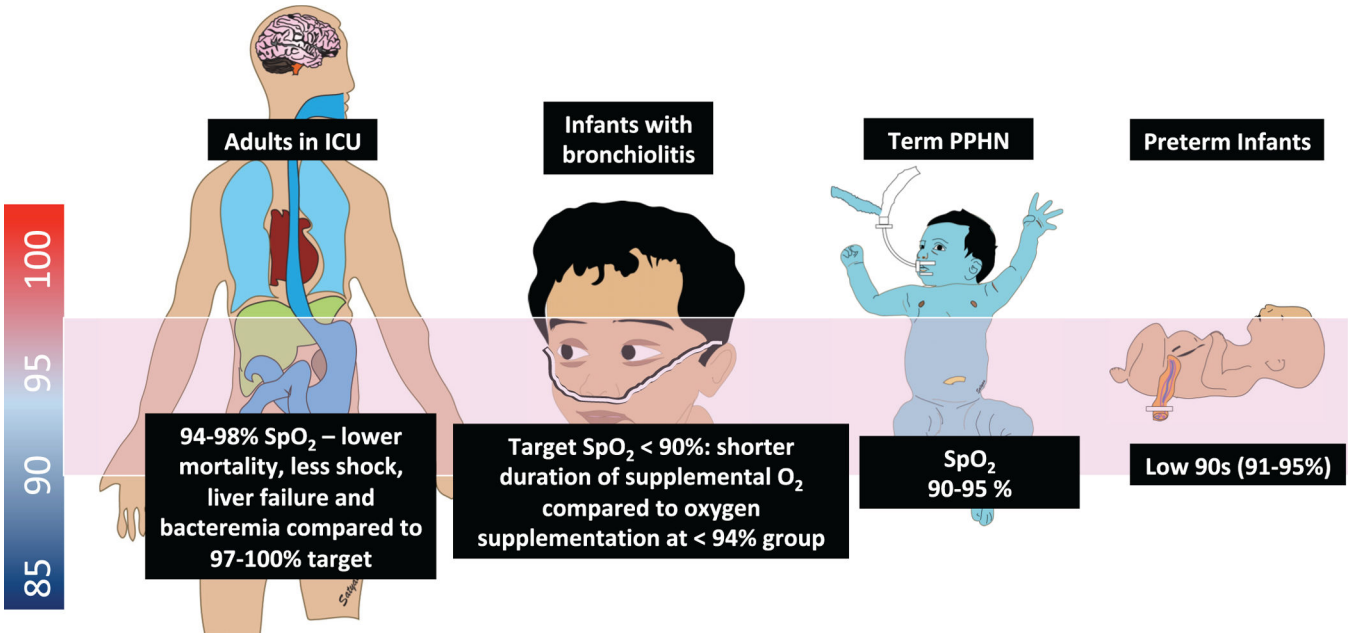

Fig. 6.

Optimal oxyhemoglobin saturation across age groups. Current evidence suggests that maintaining an SpO_2 target range ~90%–95% has the most favorable outcomes in extremely premature infants, term newborns suffering from pulmonary hypertension, older infants admitted with bronchiolitis, as well as critically ill adults (94%–98%) admitted to the intensive care unit (ICU). PPHN, pulmonary hypertension of the newborn.

Table 1.

Suggested oxygen therapy in the delivery room and during neonatal intensive care unit (NICU) stay.

Gestational age	Delivery room: initial FIO_2	NICU stay: SpO_2 target
<28 weeks	0.3 *	91%–95%
28–31 weeks	0.21–0.3 *	
≥32 weeks	0.21 *	

Note: FIO_2, fraction of inspired oxygen; SpO_2, oxyhemoglobin saturation as measured by pulse oximeter (Oei et al.2018).

* Titrate FIO_2 to Neonatal Resuscitation Program (NRP) target SpO_2.