Oxygen Therapy

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I. *Introduction*
   A. "The clinician must bear in mind that oxygen is a drug and must be used in accordance with well recognized pharmacologic principles; i.e., since it has certain toxic effects and is not completely harmless (as widely believed in clinical circles) it should be given only in the lowest dosage or concentration required by the particular patient." [Julius Comroe, 1945]
   B. Oxygen is the most commonly used therapy in neonatal intensive care units, and oxygen toxicity in newborns (cicatricial retinopathy or retrolental fibroplasia as it was known) was first described in 1951.
   C. The ultimate aim of oxygen therapy is to achieve adequate tissue oxygenation, but without creating oxygen toxicity and oxidative stress.

II. *Physiological considerations*
   A. The main factors relating to tissue oxygenation include:
      1. Effective breathing.
      2. Fractional inspired oxygen (FiO_2)
      3. Gas exchange mechanism within the lungs.
      4. Cardiac output (and the effects of shunts).
      5. Oxygen capacity of the blood: Maximum amount of oxygen that can bound to one gram of hemoglobin (1.34 ml × Hb level in grams).
      6. Oxygen Saturation: It is defined as percentage of Hb saturated with oxygen. Approximately 97% of oxygen transported to the tissue is carried by Hb and 3% is dissolved in plasma. It can be measured invasively from arterial blood (SaO_2) or noninvasively by pulse oximeter (SpO_2).
      7. Local tissue edema or ischemia.
      8. Altitude.

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B. Fetal oxygen transport and postnatal changes.
   1. Fetal hemoglobin (HbF) has higher oxygen affinity and lower P_{50} (oxygen tension at which 50% of hemoglobin is saturated at standard pH and temperature). This favors oxygen uptake from the placenta to the fetus as adequate transfer of oxygen is achieved at relatively low PO_2.
   2. High oxygen affinity of HbF, however, has disadvantage in oxygen delivery to the fetal tissue, but this is offset by the fact that the fetal oxygen-hemoglobin saturation curve is much steeper. Therefore, adequate dissociation of oxygen from hemoglobin can occur with a relatively small decrease in oxygen tension at the tissue level.
   3. The newborn infant needs more oxygen than the fetus (oxygen consumption of most animal species increases by 100% to 150% in the first few days of life); therefore, P_{50} which is adequate for tissue oxygenation in a fetus is not enough in a newborn.
   4. Changes in both oxygen affinity and oxygen carrying capacity occur postnatally, and in an infant born at term, P_{50} reaches adult levels by about 4 to 6 months of age.

C. Indices of oxygenation.
   1. *Alveolar-arterial oxygen pressure difference [P (A–a) O_2]:* The difference in partial pressure of oxygen between alveolar and arterial levels correlates well with ventilation/perfusion (V/Q) mismatch. In a newborn who is breathing room air, this value can be as high as 40 to 50 torr and may remain high (20–40 torr) for days. The increase in *P* (*A*–*a*) O_2 is generally caused by:
      (a) Reduced oxygen diffusion at alveolar-capillary level.
      (b) V/Q mismatch in the lungs (from either increase in physiologic dead space or intrapulmonary shunting).
      (c) Fixed right-to-left shunt (intracardiac shunting).
   2. *Oxygenation Index (OI):* OI is a commonly used index both clinically and in research because of its ease of calculation. It is a sensitive indicator for severity of pulmonary illness as mean airway pressure (Pāw) is taken into its calculation ($OI = Pāw \times FiO_2/PaO_2^* \times 100$) (*in mm Hg).
   3. *Arterial to alveolar oxygen tension ratio (a/A ratio).*
   4. There is no significant difference in the performance of these indices in predicting death and adverse respiratory outcome.

D. Relationship between PaO_2 and oxygen saturation (SaO_2/SpO_2).
   1. For values of 80% and below, there exists a linear relationship between oxygen saturation and PaO_2. However, beyond 80% of oxygen saturation, smaller changes in saturation result in higher changes in PaO_2 (Fig. 6.1).
   2. Several clinical studies have shown that fractional O_2 saturation above 92% can be associated with PaO_2 values of 80 mmHg (10.7 kPa) or even higher (Fig. 6.1).
   3. The correlation between PaO_2 and oxygen saturation is also influenced by several physiologic changes (quantity and quality of Hb, body temperature, acid-base status, PCO_2, and concentration of 2–3 DPG in red blood cells).

III. *Monitoring of Oxygen Therapy*

A. Noninvasive continuous monitoring.
   1. Pulse Oximetry (SpO_2): This is the most commonly used oxygen therapy monitoring system in neonates. It is based on the difference in absorption of infrared light by oxygenated and deoxygenated Hb. One of its major limitations is failure to detect hyperoxia and reduced reliability below 70–80% (Chap. 18).
   2. Transcutaneous PaO_2 ($tcPO_2$): The accuracy depends on skin thickness and perfusion status and sensor temperature. There is also a risk of local skin burns in very premature infants.

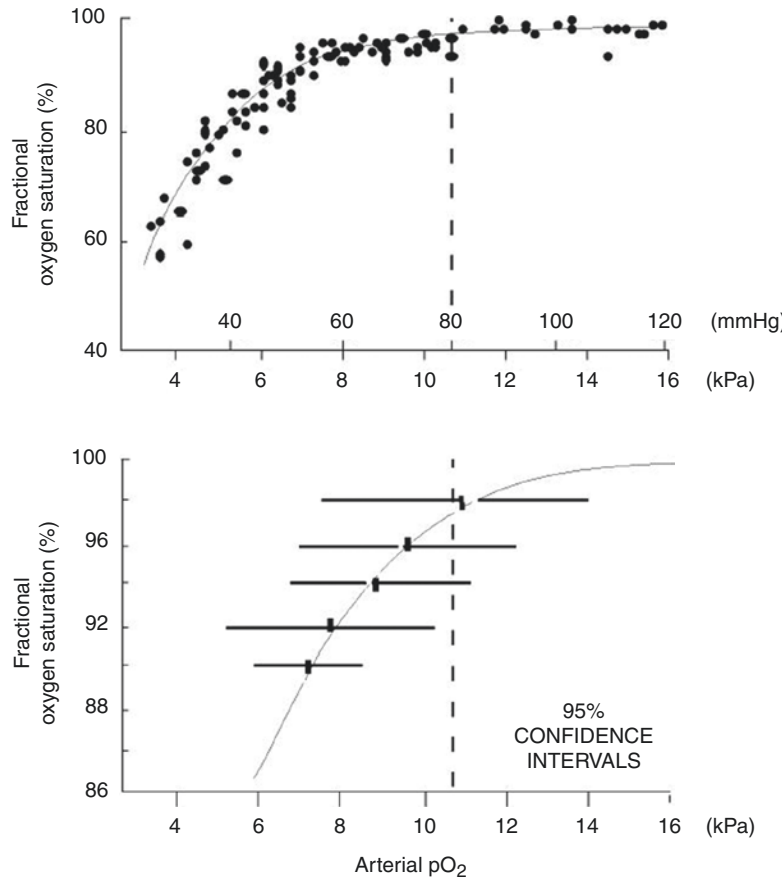

Fig. 6.1 The relation between fractional O_2 saturation measured with a pulse oximeter and arterial partial pressure (reproduced with permission from BMJ Books). The dashed line marks the TcO_2 above which there was an increased risk of ROP in the study reported by Flynn in 1992. The bars in figure show the range within which 95% of all measures of partial pressure varied when oximeter read 90%, 92%, 94%, 96%, and 98% in the study reported by Brockway and Hay in 1998

3. Near-Infrared Spectroscopy (NIRS): It involves continuous noninvasive monitoring of regional oxygen saturation at tissue level. This is reflective of perfusion and oxygenation of the underlying tissues.

B. Invasive monitoring.
   1. Arterial blood gas analysis.
      (a) Intermittent arterial PO_2 by sampling via an indwelling arterial line.
      (b) Continuous online arterial blood gas analysis (Paratrend®) by inserting a blood gas sensor (catheter) in an arterial line.
   2. Mixed central venous PO_2. This value, if taken from a catheter placed in the inferior vena cava, reflects the oxygen tension of the blood that has equilibrated with the tissues and therefore can be a useful indicator of tissue oxygen delivery.

IV. *Oxygen Toxicity* (Chap. 7)

A. Experimental and research work over more than a century have shown that oxygen can be toxic if not used judiciously. Oxygen toxicity can lead to oxidative stress and generation of reactive oxygen species. Preterm infants are far more vulnerable because of the immaturity of their antioxidant defense system.

B. Oxygen and Retinopathy of Prematurity (Chap. 84). One of the major tissues affected by harmful levels of oxygen is the retina. Fetal retina is initially avascular. New blood vessels start to develop from the center of the retina and progressively move to the periphery. Complete vascularization is nearly complete by 36 weeks of gestation. The vascularization process is hugely controlled by vascular endothelial growth factor (VGEF). Preterm infants are born with incomplete retinal vascularization. Treatment of these infants with oxygen lead to hyperoxia and vasoconstriction (suppression of VGEF) and at later stages vasoproliferation (increase in VGEF levels). These changes lead to aberrant vascularization, retinal fibrosis, retinal detachment, and blindness.

C. Oxygen and Bronchopulmonary Dysplasia (BPD) (Chaps. 78, 79, and 80). Oxygen toxicity is an important contributory factor in the pathogenesis of BPD. The reactive oxygen species can injure the pulmonary epithelium leading to interstitial edema, thickening, and fibrosis. Even if inspired oxygen concentrations are not high, oxidative stress can occur and contribute to tissue injury in the lung.

D. Oxygen and Brain. Reactive oxygen species can cause injury to the oligodendrocytes in white matter and result in periventricular leukomalacia (PVL). Oxidative stress is associated with impaired neurodevelopmental outcome in vulnerable infants even in the absence of intraventricular hemorrhage and PVL.

V. *Observational evidence of oxygen monitoring and clinical outcomes*

A. Pulse oximetry is the most commonly use oxygen monitoring technique in neonates. However, there is wide variation in SpO_2 monitoring policies among neonatal ICUs.

B. Several observational studies in the past have suggested that accepting lower arterial oxygen saturation (measured by pulse oximetry) in the neonatal period of preterm infants was associated with lower rates of severe ROP and other neonatal complications including BPD.

C. The STOP-ROP trial of preterm infants (median gestational age 25.4 weeks) with pre-threshold ROP looked at two different SpO_2 target ranges: 89–94% (conventional arm) versus 96–99% (supplemental oxygen arm). There was no difference in progression of ROP from pre-threshold to threshold ROP or the need for surgery. However, there were increased pulmonary complications including exacerbation of BPD in the supplemental oxygen arm.

D. The BOOST trial also showed that aiming to keep higher oxygen saturation in chronically oxygen-dependent babies, born before 30 weeks' gestation, was not associated with improvement in growth and development at 1 year but was associated with increase in duration of oxygen therapy and the utilization of healthcare resources.

VI. *Emerging evidence from the "Oxygen Saturation Targeting Trials"*

A. Five masked randomized controlled trials have been conducted to compare the clinical outcomes (primary outcome being death and/or severe disability) of targeting a "low" oxygen saturation range of 85–89% versus a "high" range of 91–95% in preterm infants of <28 weeks' gestation.

B. A meta-analysis of these trials showed that targeting the higher range (91–95%), compared to the lower range (85–89%), reduces the risk of mortality and necrotizing enterocolitis (NEC) but increases the risk of severe ROP.

C. A planned prospective individual participant data meta-analysis (NeOProM collaboration) showed that there was no significant difference in death or major disability at 18–24 months' corrected age between the lower (85–89%) and higher (91–95%) oxygen saturation range in extremely premature infants. However, targeting lower saturation range was associated with higher mortality and NEC but a lower risk of ROP and BPD (defined as oxygen requirement at 36 weeks' PMA).

D. In spite of the results from above studies, unanswered questions still remain. For instance, the saturation target ranges for more mature and term infants and at what age should transition to higher saturation range happen in extremely premature infants. The clinicians should be aware that the current oxygen trials may not give an answer to all the questions and controversies on "oxygen" – a powerful and the most commonly used "drug" in neonatal medicine.

Suggested Reading

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