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 more than 60 years ago.
   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. Tissue oxygenation depends on:
      1. Fractional inspired oxygen (FiO_2)
      2. Gas exchange mechanism within the lungs
      3. Cardiac output (and the effects of shunts)
      4. Oxygen-carrying capacity of the blood. Approximately 97 % of oxygen transported to the tissue is carried by hemoglobin and 3 % is dissolved in plasma.
      5. Altitude
      6. Local tissue edema or ischemia
   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

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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 100–150 % 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 4–6 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 40–50 Torr, and may remain high (20–40 Torr) for days. The increase in $P(A-a)O_2$ is generally caused by:
   a. Block of 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)*: This is most frequently used clinically as well as in clinical research studies because of its ease of calculation, and is felt to be a more sensitive indicator for severity of pulmonary illness as mean airway pressure (Pāw) is taken into its calculation

   $$OI = P\bar{a}w \times FiO_2/PaO_2 \times 100$$

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. PaO_2 and O_2 saturation

1. 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)
2. Although PaO_2 and O_2 saturation are directly related to each other, this correlation is influenced by several physiologic changes (quantity and quality of Hb, temperature, acid-base status, PCO_2, and concentration of 2–3 DPG).

III. Monitoring Oxygen Therapy

A. Continuous, Non-invasive monitoring

1. Pulse oxygen saturation (Pulse oximetry, SpO_2): This is the most user friendly method and therefore most widely used for monitoring oxygen therapy, but it has limitations, mainly the failure to detect hyperoxia (Chap. 19).
2. Transcutaneous PO_2 ($TcPO_2$): This is the preferred method by some clinicians, particularly for monitoring in the early life of newborn infants. The accuracy depends on skin thickness and perfusion status and sensor temperature. There is a risk of local skin burns in very premature infants.

B. Continuous, Invasive monitoring (via indwelling arterial catheters)

1. Arterial PO_2
2. Blood gas analysis

C. Intermittent Monitoring

1. Arterial PO_2 (via umbilical or peripheral arterial catheters)
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.

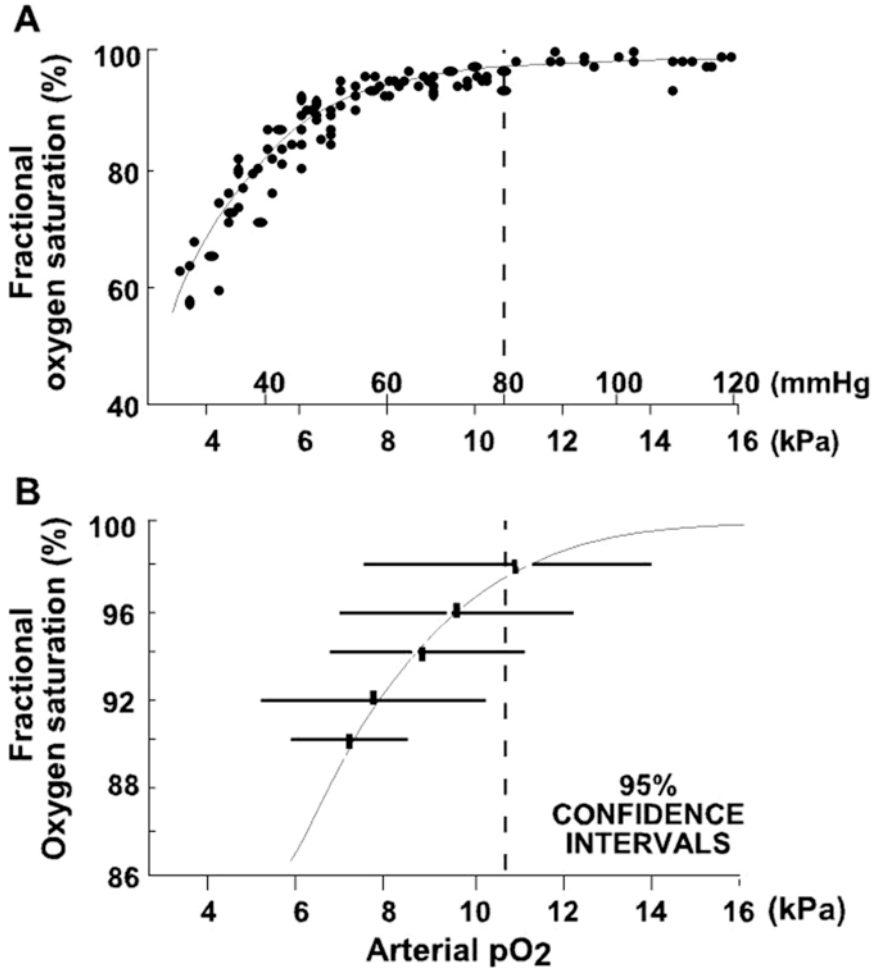

Fig. 6.1 The relation between fractional O_2 saturation measured with a pulse oximeter and arterial partial pressure (reproduced with permission from BMJ Books). The *dashed line* marks the TcO_2 above which there was an increased risk of ROP in the study reported by Flynn in 1992. The *bars* in figure (**b**) 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

IV. Oxygen Toxicity (Chap. 7)
   A. Experimental and research work over more than a century has shown that oxygen can be toxic, and it is now much clearer that preterm infants are more vulnerable to harmful effects of free oxygen radicals and oxidative stress (defined as an imbalance between pro-oxidant and antioxidant forces).
   B. Oxygen and retinopathy of prematurity (ROP, Chap. 83): The retina is completely avascular in early fetal life. New vessels grow outward from the center around the optic nerve, controlled by vascular endothelial growth factor (VEGF), released from normally hypoxic retinal tissue, and this process is completed in utero by about 36 weeks of gestation. Treatment with supplemental oxygen in premature infants, who have incompletely vascularized retinas, may cause hyperoxia and vasoconstriction. This in turn leads to local hypoxia, abnormally high secretion of VEGF, and excessive proliferation of new vessels and fibrous tissue that invades the

vitreous. Contraction of fibrous tissue may result in retinal detachment and visual loss. Although retinal detachment can be prevented by ablative surgery (cryo or laser therapy), the risk of significant visual impairment remains high among infants who develop "threshold ROP."

C. Oxygen and bronchopulmonary dysplasia (BPD, Chaps. 77–79): Direct oxygen toxicity from high concentrations of inspired oxygen is an important cause of BPD. Even if inspired oxygen concentrations are not high, oxidative stress can occur and contribute to tissue injury.

D. Oxygen and brain injury (Chap. 84): Oxidative stress and damage to pre-myelinating oligodendrocytes in cerebral white matter has been proposed as a mechanism of periventricular leukomalacia, increasing the risk of cerebral palsy and cognitive deficit in preterm infants.

V. Clinical Evidence for Monitoring Oxygen Therapy

A. There is no clear evidence to date to suggest what the optimal SpO_2 or PaO_2 values are in premature infants (who receive supplemental oxygen therapy) in order to avoid potential oxygen toxicity while providing adequate oxygen delivery to tissues.

B. Pulse oximetry is more widely used (and is often used solely) as continuous, noninvasive monitoring for oxygen therapy, yet there remains a wide variation in SpO_2 monitoring policies among neonatologists.

C. 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.

D. The STOP-ROP Trial, showed that keeping saturation above 95 % in very premature infants (mean gestational age 25.4 weeks) when they were found to have developed pre-threshold ROP (mean postmenstrual age 35 weeks) slightly reduced the risk of the disease progressing to severe ROP needing retinal surgery, but the benefit was only seen in those without "plus disease." However, this study also suggested that aiming to keep higher oxygen saturation was associated with significantly increased adverse pulmonary outcomes, without any benefit in growth or the eventual retinal outcome as assessed 3 months after the expected date of delivery.

E. The BOOST trial also showed that aiming to keep high 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 health care resources.

VI. Emerging Evidence from the "Oxygen Saturation Targeting Trials"

A. Five masked randomized controlled trials (with a planned prospective meta-analysis) have been conducted recently to compare the clinical outcomes (primary outcome being death and 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. Meta-analysis of the masked oxygen saturation targeting trials showed that targeting the higher range (91–95 %), compared to the lower range (85–89 %) reduces the risk of mortality and necrotizing enterocolitis but increases the risk of severe ROP.

C. More information will be available when the all the trials report the primary outcome of death and severe disability and the prospective meta-analysis is completed. However, clinicians should be aware that the current oxygen trials may not resolve the questions and controversies on "oxygen"—a powerful and the most commonly used "drug" in neonatal medicine.

Suggested Reading

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