16 Oxygen Therapy

Maximo Vento

Introduction

Aerobic Metabolism

Highly energized electrons liberated in the mitochondrial tri-carboxylic cycle are transported to the electron transport chain, and finally captured by oxygen. In this process known as oxidative phosphorylation, ADP is transformed into ATP and ground molecular di-oxygen is reduced by four electrons, and combining with protons intruded through the ATP synthase pump forms water. Remarkably, aerobic metabolism (i.e., with the concourse of oxygen) is 20 times more efficient than anaerobic metabolism thus providing sufficient energy for cell growth, development, and reproduction (e.g., 1 molecule of glucose forms 34 molecules of ATP through the aerobic pathway and 4 through the anaerobic). Of note is that specific cells such as neurons are unable to accumulate energy and are only able to survive for few minutes under hypoxic conditions rendering oxygen indispensable for central nervous system survival.

Each oxygen molecule has two unpaired electrons in its outer shell that prevent it from forming new chemical bonds. Partial reduction of oxygen with just one electron at a time will lead to the formation of reactive oxygen species (ROS) such as anion superoxide (O_2^-), hydroxyl radical (OH●), and hydrogen peroxide (H_2O_2). Some of these chemicals will be highly reactive species known as free radicals. Free radicals are atomic or molecular species capable of independent existence that contain one or more unpaired electrons in their molecular orbits. They are able, therefore, to oxidize cellular membranes, structural proteins, enzymes, and nucleic acids.

Oxygen Free Radicals

In the presence of nitric oxide, these oxygen free radicals will react forming reactive nitrogen species (RNS) such as peroxynitrite (ONOO–) (*Fig 16.1*). ROS and RNS are potent oxidizing and reducing agents with an extremely short half-life that will damage any nearby cellular structure.

Antioxidant Defenses

Biologic systems using aerobic metabolism have been able to survive the deleterious effects of free radicals because a large number of enzymatic and non-enzymatic antioxidants has evolved. The antioxidant enzymes are represented by the family of superoxide dismutases (SOD) formed by Cu-Zn SOD or soluble SOD1 located in the cytosol, Mn-SOD or SOD2 located in the mitochondria, and extracellular or SOD3. In addition, catalase, glutathione peroxidases, and glucose 6-phosphate dehydrogenase altogether constitute the most relevant enzymatic defense against free radicals. The major non-enzymatic intracellular antioxidant is glutathione (GSH), a ubiquitous tri-peptide formed by γ-glutamine, L-cysteine, and glycine. GSH is able to reduce free radicals by establishing a di-sulfur bond with another GSH molecule forming oxidized glutathione (GS=SG) and thus providing one electron. Oxidized glutathione is reduced again to its reduced form (GSH) by the action of glutathione reductase (GSH-reductase) with the electrons provided by NADPH. Other relevant non-enzymatic antioxidants are proteins that bind transition metals such as transferrin and ceruloplasmin, or molecules that quench free radicals such as uric acid and bilirubin.

Oxidative Stress

This concept refers to the imbalance between the formation of free radicals and the capability of the biologic system to neutralize them. In order to evaluate oxidative stress different biomarkers have been used. They may directly reflect a pro-or-antioxidant status such as GSH/GSSG quotients, one of the most reliable and employed oxidative stress markers. Other biomarkers may reflect direct damage to the cell structures. Hence, for lipid peroxidation, malondialdehyde or *n*-aldehydes (e.g., 4-hydroxy-nonenal) have been widely employed. Nucleic acid damage is generally reflected by guanosine base oxidation products such as 8-oxo-dyhydro-guanosine. Isoprostanes and isofurans have evolved as one of the most reliable markers of oxidative stress and reflect

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_16,

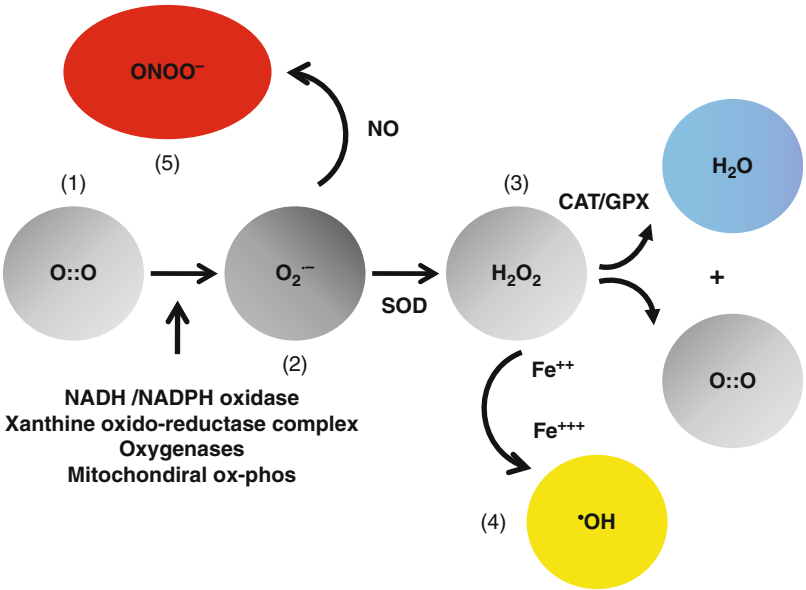

Figure 16.1

Oxygen (1) is partially reduced by the action of a series of enzymatic complexes to anion superoxide (2). Anion superoxide is dismutated by superoxide dismutases (*SOD*) to hydrogen peroxide (3), which in turn is transformed into water and oxygen by the action of catalases (*CAT*) and glutathione peroxidase (*GPX*). In the presence of transition metals (e.g., iron, copper), hydrogen peroxide can be transformed into hydroxyl radical (4). Moreover, in the presence of nitric oxide (*NO*), anion superoxide can also be transformed into peroxynitrite (5)

non-cyclo-oxygenase peroxidation of polyunsaturated fatty acids (PUFA) and intriguingly have important vaso-active properties. Oxidation of proteins can be measured by the action of free radicals on specific amino acids such as phenylalanine. As a consequence of the attack by hydroxyl radicals, phenylalanine is converted into orto-tyrosine (o-tyr). Other markers of protein oxidation are known as carbonyl compounds (C=O), which have been closely correlated when found in the lung alveolar lavage fluid with development of chronic lung disease.

In addition to causing oxidative damage to cell structures, ROS and RNS are capable of triggering inflammatory response in the cells triggering the transformation of I-κB into NF-κB, a transcription factor for multiple inflammation related genes. ROS and RNS are also capable of activating the tumor necrosis factor alpha (TNFα) essential in the inflammatory response as well as in the activation of apoptosis.

Fetal to Neonatal Transition

Fetal life develops in an environment that is relatively hypoxemic as compared to the extra uterine; hence, arterial partial pressure of oxygen (P_aO_2) in utero is of 25–35 mmHg. Immediately after birth, with the initiation of spontaneous respiration and alveolar-capillary gas exchange P_aO_2 rises to 50–70 mmHg in the first 5–10 min of life. This abrupt change causes a physiologic oxidative stress necessary to trigger the expression of a number of significant genes necessary for postnatal adaptation. The first studies of fetal pulse oximetry (SpO_2) during labor revealed that normal values were approximately 58 ± 10%. Studies performed in term newborn infants have shown that SpO_2 does not reach stable values ≥85% until 5 min after birth have elapsed, and some normal newborn infants need even more time especially if they are born by cesarean section. In addition, preterm infants especially extremely low birth weight infants will not reach an SpO_2 of ≥85% at least after 10–15 min after birth.

Arterial Oxygen Saturation Nomogram

In a large prospective observational study a total of 468 newly born infants covering gestational ages from 25 through 42 weeks of gestation and who did not need

resuscitation maneuvers in the delivery room were recruited (Fig. 16.2). SpO_2 using advanced technology with maximum sensitivity was measured in the right wrist thus representing pre-ductal oxygen saturation during the first 10 min after birth. Two graphs have been developed from the data set for babies between 32 and 36, and between 37 and 42 weeks gestation, respectively. It took a median of 7.9 (interquartile range (IQR): 5.0–10.0) min to reach $SpO_2 > 90\%$, and preterm infants needed significantly more time to reach this saturation.

Oxygen Administration in the Delivery Room

In experimental and clinical studies, it has been shown that the use of room air (21% oxygen) offers substantial advantages over the use of 100% oxygen as had been traditionally recommended in the resuscitation of depressed newborn infants. Meta-analysis of the published evidence has concluded that the use of room air significantly reduces mortality in term neonates. Moreover, air-resuscitation also shortens the time needed to initiate spontaneous respiration, improves Apgar score, and

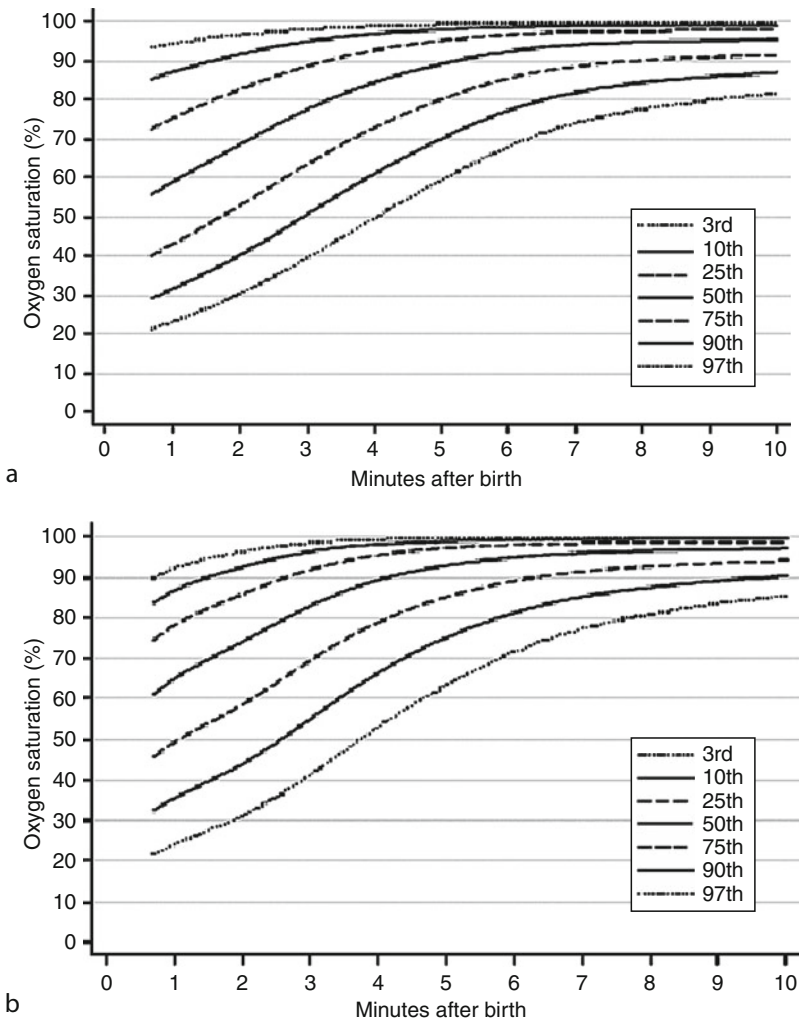

Figure 16.2

Panel a: Third, 10th, 25th, 50th, 75th, 90th, and 97th SpO_2 percentiles for preterm infants at 32–36 weeks of gestation with no medical intervention after birth. Panel b: Third, 10th, 25th, 50th, 75th, 90th, and 97th SpO_2 percentiles for infants at <32 weeks of gestation with no medical intervention at birth (From Dawson JA et al (2010) Pediatrics 125:e1340–e1347. With permission)

reduces oxidative stress and oxidative damage to vital organs such as myocardium and kidneys. As a consequence, 2010 international guidelines recommend the use of air as the initial gas admixture for the depressed neonate. Moreover, both pulse oximetry monitoring of SpO_2 and titration of the inspiratory fraction of oxygen (FIO_2) to avoid hyper-or-hypoxic damage are also encouraged.

Preterm babies do not frequently suffer from birth asphyxia; however, they experience difficulties in adapting to extra uterine due to lung and thoracic cage immaturity. Hence, a significant proportion of preterm infants will need proactive interventions in the delivery room. Positive pressure ventilation is the cornerstone of preterm resuscitation. Initial ventilation is performed in spontaneous breathing neonates with continuous positive pressure ventilation (CPAP) applying 4–8 cmH_2O. Available studies have shown that it is feasible to start resuscitation even in the most preterm infants using an initial FIO_2 of 21–30%. Regardless of whether high or low oxygen concentration was used initially, on average, the infants were on similar FiO_2 of 30–40% within 5–10 min of life with no difference in SPO_2, heart rate, Apgar scores, or acid–base status. While more studies are needed, many clinicians now opt to initiate resuscitation with 30% oxygen in preterm infants in whom normal lung function cannot be assumed. Immediately after birth, pulse oximeter probe should be adjusted to the right wrist. Reliable pre-ductal readings will be obtained in 60–90 s. Once readings are available FIO_2 should be titrated against SpO_2 readings in the pulse oximeter adjusting the air/oxygen blender to keep SpO_2 within saturation nomogram (*Fig. 16.2*). Changes should be performed every 30–60 s allowing infant's response in the form of increase/decrease in SpO_2. Abrupt changes in heart rate or saturation may be a consequence of mask leakage or incorrect endotracheal tube position. End tidal CO_2 detectors are useful in these circumstances. Once the baby is stable and maintains an adequate heart rate and SpO_2, he/she can be transferred to the NICU. Using lower oxygen load in the resuscitation process it has been shown that oxidative stress biomarkers are significantly reduced and there is less need for oxygen supplementation, and less tendency toward developing chronic lung disease.

Oxygen During Neonatal Care in Premature Infants

The conundrum regarding the establishment of upper and lower limits of oxygen saturation especially in extremely low birth weight (ELBW) infants is still open (*Fig. 16.3*). ELBW infants are very sensitive to both hyperoxia, which may lead especially to lung and retinal damage, and to hypoxia, which may cause white matter injury. Studies that have compared different limits for SpO_2 have concluded that neonatal units maintaining ELBW infants within low saturation limits (85–92%) have significantly lower incidence (~50%) of retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) than those units allowing SpO_2 within higher limits (>95%). This has been confirmed in the SUPPORT trial, the only randomized study published to date. Although some concerns have been raised in relation to a small

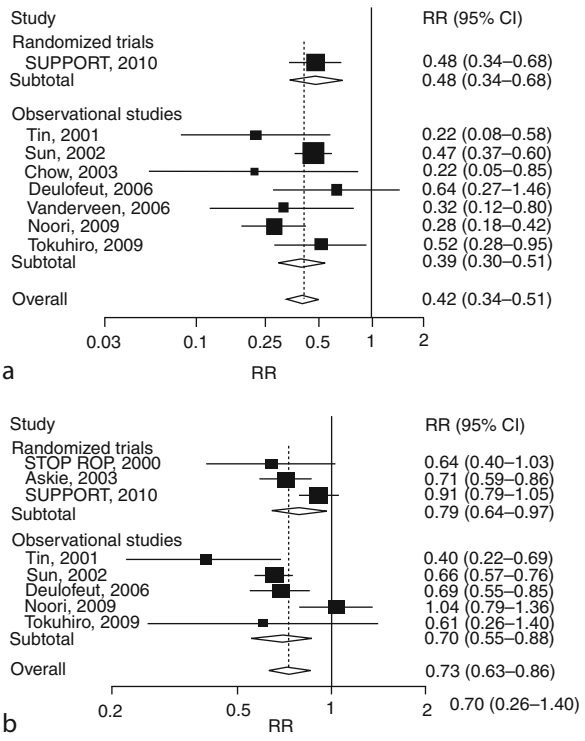

Figure 16.3

Panel a: Relative Risk (*RR*) and 95% Confidence Interval (*CI*) for randomized studies and observational studies as well as overall estimate in eight studies examining the effect on ROP of high versus low SpO_2 in preterm infants. A RR < 1 favors low SpO_2. Panel b: RR and 95% CI for randomized studies and observational studies as well as overall in eight studies examining the effect on BPD and/or lung problems of high versus low SpO_2 in preterm infants. An RR < 1 favors low SpO_2 (From Saugstad OD et al (2011) Neonatology 100:1–8. With permission)

increase in mortality in the low saturation group, there is no conclusive evidence and 85% as lower saturation limit seems to be safe. Several other clinical trials are underway with close monitoring of the mortality rate by their data safety monitoring boards. Until these studies are published, definitive recommendations are difficult. However, majority of NICUs in the USA and Europe appear to have adopted the range of 85–92% in preterm infants, and anecdotal evidence supports the decreased incidence of ROP.

Of note, studies have suggested the establishment of two different periods with different oxygen saturation targets. Preterm infants below 32 weeks postmenstrual age would benefit from lower SpO_2 limits (e.g., 85–95%). In a phase of rapid vascular growth and extreme tissue sensitivity to oxygen due to an immature antioxidant defense system, the use of higher oxygen limits would lead to oxidative stress and inflammation in the lung, intestine, or brain leading to BPD, necrotizing enterocolitis (NEC), or intra-periventricular hemorrhage (IPVH). However, older neonates (>32 weeks postmenstrual age) with a more mature antioxidant system and a tendency toward hyper-proliferation of the vascular bed of the retina due to a relative hypoxia of the retinal tissue might benefit from higher SpO_2 ranges (98–99%). This latter approach is intended for infants with pre-threshold ROP, but its benefit has not been conclusively established. Further, the potential benefit on the retina must be weighed against the apparent adverse effects on the lungs as suggested by the STOP ROP study. Perhaps, in addition to pulse oximeter monitoring levels of growth factors such as insulin-like growth factor (IGF), vascular endothelial growth factors (VEGF) and others should be closely monitored aiming to advert the initiation of ROP 2 phase that would prompt the use of higher oxygen saturation limits to avoid retinal vessel overgrowth.

Oxygen Therapy in the Term Infant

Term infants with meconium aspiration syndrome, pneumonia, or other conditions may have pulmonary hypertension and often also require respiratory support. Traditionally, clinicians were less concerned about hyperoxia in view of their more mature antioxidant defenses and often used high FiO_2 in infants with or at risk for pulmonary hypertension (PPHN). More recently, it has become clear that hyperoxia and exposure to high FiO_2 is not only unnecessary in terms of treating PPHN, but actually increases pulmonary vasoreactivity to hypoxia and decreases response to inhaled nitric oxide. Many infants with meconium aspiration and/or PPHN have a history of perinatal asphyxia and are uniquely vulnerable to oxygen radical injury to the brain. Additionally, prolonged exposure to high FiO_2 will cause lung injury even in term infants. Therefore, the current recommendations are to target normoxia (PaO_2 60–80 s) and avoid PaO_2 over 90 mmHg. The upper limit of SPO_2 should be set no higher than 99%, because when SPO_2 is >99%, the PaO_2 may well be over 100 mmHg.

References

Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM (2003) Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 349:959–967

Chen ML, Guo L, Smith LE, Dammann CE, Dammann O (2010) High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. Pediatrics 125:e1483–e1492

Dawson JA, Morley CJ (2010) Monitoring oxygen saturation and heart rate in the early neonatal period. Semin Fetal Neonatal Med 15:203–207

Dawson JA, Kamlin COF, Vento M et al (2010) Defining the reference range for oxygen saturation for infants after birth. Pediatrics 125: e1340–e1347

Escrig R, Arruza L, Izquierdo I et al (2008) Achievement of targeted saturation values in extremely low gestational age neonates resuscitated with low or high oxygen concentrations: a prospective, randomized trial. Pediatrics 121:875–881

Farrow KN, Groh BS, Schumacker PT, Lakshminrusimha S, Czech L, Gugino SF, Russell JA, Steinhorn RH (2008) Hyperoxia increases phosphodiesterase 5 expression and activity in ovine fetal pulmonary artery smooth muscle cells. Circ Res 102(2):226–233

Finer N, Leone T (2009) Oxygen saturation monitoring for the preterm infant: the evidence basis for current practice. Pediatr Res 65:375–380

Lakshminrusimha S, Swartz DD, Gugino SF, Ma CX, Wynn KA, Ryan RM, Russell JA, Steinhorn RH (2009) Oxygen concentration and pulmonary hemodynamics in newborn lambs with pulmonary hypertension. Pediatr Res 66:539–544

Maltepe E, Saugstad OD (2009) Oxygen in health and disease. Pediatr Res 65:261–268

Perlman JM, Wyllie J, Kattwinkel J et al (2010) Part 11: Neonatal resuscitation: 2010 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation 122:S516–S538

Rabi Y (2010) Oxygen in the delivery room. Neoreviews 11:e130–e138

Saugstad OD (2005) Oxidative stress in the newborn – a 30-year perspective. Biol Neonate 88:228–236

Saugstad OD (2007) Optimal oxygenation at birth and in the neonatal period. Neonatology 91:319–322

Saugstad OD (2010) Resuscitation of newborn infants: from oxygen to air. Lancet 376:1970–1971

Saugstad OD, Aune D (2011) In search of the optimal saturation for extremely low birth weight infants: a systematic review and meta-analysis. Neonatology 100:1–8

Saugstad OD, Ramji S, Soll RF, Vento M (2008) Resuscitation of newborn infants with 21% or 100% oxygen: An updated systematic meta-analysis. Neonatology 94:176–182

Sola A (2006) Avoiding hyperoxia in infants < or = 1, 250 g is associated with improved short- and long-term outcomes. J Perinatol 26: 700–705

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR et al (2010) Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 362:1959–1969

Tin W, Milligan DW, Pennefather P, Hey E (2001) Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 84:F106–F110

Vento M (2010) Titrating oxygen needs in the very preterm in the delivery room. J Neonatal Perinat Med 3:161–169

Vento M, Sastre J, Asensi MA, Viña J (2005) Room-air resuscitation causes less damage to heart and kidney than 100% oxygen. Am J Respir Crit Care Med 172:1393–1398

Vento M, Aguar M, Leone TA et al (2009a) Using intensive care technology in the delivery room: a new concept for the resuscitation of extremely preterm neonates. Pediatrics 122:1113–1116

Vento M, Moro M, Escrig R et al (2009b) Preterm resuscitation with low oxygen causes less oxidative stress, inflammation and chronic lung disease. Pediatrics 124:439–449

Vento M, Cheung PY, Aguar M (2009c) The first golden minutes of the extremely low gestational age neonate: a gentle approach. Neonatology 95:286–298

Vento M, Aguar M, Escobar J et al (2009d) Antenatal steroids and antioxidant enzyme activity in preterm infants: influence of gender and timing. Antioxid Redox Signal 11:2945–2955

Wang CL, Anderson C, Leone TA, Rich W, Govindaswami B, Finer NN (2008) Resuscitation of preterm neonates by using room air or 100% oxygen. Pediatrics 121:1083–1089