Oxygen Toxicity

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I. Oxygen toxicity in the newborn period
   A. Historical aspects
      1. Oxygen was discovered independently by Scheele and Priestly in 1772 and 1774, respectively. However, in 1604 the Polish alchemist Michael Sendivogius had described oxygen as vital air.
      2. Lavoisier coined the term oxygen in 1775. Only 5 years later oxygen was used to treat newborns. In 1928, Flagg published in the *Journal of the American Medical Association* (JAMA) a method to resuscitate newborns with oxygen and CO_2.
      3. Priestly understood that oxygen might be toxic, and during the nineteenth century, more and more information was collected showing its toxic effects.
      4. In the 1950s, oxygen was associated with the development of retrolental fibroplasia (today called retinopathy of prematurity, ROP), and at the end of the 1960s oxygen toxicity was associated with the development of bronchopulmonary dysplasia (BPD).
      5. Some years later, it was hypothesized oxygen might be toxic during resuscitation and in 2010 international guidelines were changed to recommend starting resuscitation of term or late preterm infants with air instead of oxygen. Still the optimal FiO_2 for extremely low birth weight (ELBW) infants is not defined.
   B. Evolutionary aspects
      1. Life developed in an oxygen-free and reducing atmosphere.
      2. The so-called last universal common ancestor was a cell probably resistant to oxygen toxicity, and it is hypothesized that this was secondary to the fact that primitive organisms were

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forced through a "radiation bottleneck," making life resistant to both radiation injury and oxygen toxicity.
3. This prepared eukaryocytes for a life in a high oxygen atmosphere.

C. Basic mechanisms
1. In 1891, the Scottish chemist Sir James Dewar discovered that oxygen is paramagnetic. This is caused by spin of unpaired electrons in the outer electron orbit, and this makes it difficult for oxygen to form new chemical bonds.
2. In order to complete electron pairing, oxygen can only receive single electrons with antiparallel spin. Accepting electrons stabilizes the oxygen molecule.
3. During oxidative phosphorylation in the mitochondria, single electrons escape and join with 1–2% of the total oxygen consumed by the cells to form superoxide radicals. By adding another 1, 2, or 3 electrons, hydrogen peroxide, hydroxyl radicals, and finally water are formed.
4. Oxygen-free radicals or reactive oxygen species (ROS) have the capability to oxidize unsaturated free fatty acids, proteins, and DNA. They are also important as signaling substances and therefore regulate physiologic processes such as circulatory aspects as well as growth and development. Therefore, it is important for the organism to tightly control the redox status and oxidative stress; even short deviations in oxidative stress indicators may trigger long-term effects.
5. The premature baby has less capacity to bind free iron, and thus these babies are more susceptible to damage through the Fenton reaction, which produces hydroxyl radicals.

D. Defense mechanisms
1. The body has a number of intracellular and extracellular antioxidants. In fetal life, activities of the intracellular anti-oxyenzymes superoxide dismutases, catalases, and glutathione peroxidases are low and increase toward term.
2. Extracellular defense is not so low in the premature and the first days after birth; for instance, vitamin C is high. Other important antioxidants in this period of life are bilirubin and uric acid.
3. DNA is protected against oxygen toxicity. Base cutting repair is the most important cellular mechanism for repairing oxidative DNA injury. This repair is initiated by DNA glycosylases, which recognize and repair DNA base injuries. A number of glycosylases have been described as Neil 3, Mutyh, OGG1, and others.

E. Control mechanisms
1. HIF-1α is an important transcription factor, which is activated in hypoxia and closed down by normoxia or hyperoxia. HIF-1α transcribes a series of genes, such as vascular endothelial growth factor (VEGF) and erythropoietin, which increases oxygen utilization and reduces oxygen consumption/demand.
2. A number of other transcription factors are involved in hyperoxia.
   (a) NF-erythroid 2-related factor (Nrf2) is activated by hyperoxia and activates antioxidant response element (ARE) and regulates detoxifying and antioxidant enzymes and increases expression of antioxidant enzymes. It is cytoprotective in type II cells of the lung and ameliorates O_2-induced lung injury in mice.
   (b) AP-1 controls genes regulating apoptosis, inflammation, and oxidative stress.
   (c) NF-κB activates genes regulating apoptosis, inflammation, and oxidative stress. It is activated by endotoxins and oxidative stress via toll-like receptors in the cell membrane.
   (d) P53 regulates expression of target genes related to cell cycle arrest, cell death, and DNA repair.
   (e) CCAAT/enhancer binding protein (CEBP) regulates cell proliferation and tissue development and is increased in the lung of rats exposed to hyperoxia.

(f) STATs are polypeptides participating in signaling pathways and may be protective to hyperoxia by induction of heme-oxygenase which is a cytoprotective enzyme highly inducible following exposure to hyperoxia.

II. Potential risks of hyperoxia and oxygen toxicity

A. Brain

1. The neonatal brain is susceptible to oxidative stress because of its high content of unsaturated free fatty acids, which are easily exposed to peroxidation, the presence of free iron, low antioxidant enzymes, and vulnerable oligodendrocytes. A simultaneous exposure to inflammation will increase the oxidative stress even more.
2. Pre- and immature oligodendrocytes are especially vulnerable to hyperoxia and oxidative stress.
3. This vulnerability is probably time-dependent. The vulnerability of the rodent brain to hyperoxia seems to be confined to a short window postpartum, especially the first week of life. Whether such a vulnerable window exists in humans is not clear.
4. Microglia, which peak in white matter in the third trimester, when activated, generate free radicals and secrete cytokines.

B. Retina

1. The transition from intra- to extrauterine life increases oxygen tension and decreases VEGF not only in the retina but also in other tissues.
2. Angiogenesis in the retina of the immature baby is halted. However, after a few weeks, typically after 32 weeks' postconceptional age, the retina becomes hypoxic because of its increase in size without angiogenesis and consequently VEGF increases. This may lead to an uncontrolled vessel growth and development into stage II ROP (Chap. 84).
3. In order for VEGF to be active, insulin-like growth factor must reach a threshold level. Thus, the pathogenesis of ROP is complex, dependent on both hyperoxia and a number of other non-hyperoxic factors related to growth.
4. Several studies (NeoPROM), including one meta-analysis, strongly indicate that severe ROP can be significantly reduced by keeping the arterial oxygen saturation low and avoiding fluctuations.

C. Lungs

1. Oxidative stress generally induces apoptosis in a relatively short period of time (hours).
2. Hyperoxia predominantly induces non-apoptotic cell death over a long period of time (days).
3. Hyperoxia-induced lung injury is also characterized by necrosis and swelling of capillary endothelial cells. Later, the epithelial cells are affected.
4. Hyperoxia-induced lung injury is also characterized by inflammation, destruction of the alveolar-capillary barrier, impaired gas exchange, and pulmonary edema.
5. Hyperoxia and ROS lead to increased release of chemo-attractants and other proinflammatory cytokines promoting leukocyte recruitment to the lung. These activated leukocytes produce ROS; thus a vicious circle is established.
6. Hyperoxia activates caspase 3 and 9 as well as proinflammatory cytokines as IL-1, IL-6, IL-8, TGFβ, TNFα, and VEGF.
7. Hyperoxia reduces protein synthesis. This seems to be mediated via mTOR pathways. Hyperoxia inhibits translation of mRNA.
8. Hyperoxia has the potential to alter genomic activity via changes in DNA methylation and induce epigenetic changes in the lung with possible long-term consequences.
9. A recent meta-analysis of the NeoPROM studies indicates that BPD can be reduced by 20–25% by keeping arterial oxygen low.

III. Clinical implications
  A. Oxygen in the delivery room
    1. Term and late preterm infants. Recent international guidelines recommend starting resuscitation with air instead of supplemental oxygen. This is based on animal studies and 10 clinical human studies, including more than 2000 babies resuscitated with either 21% or 100% oxygen. It seems that the use of 100% oxygen increases time to first breath by approximately 30 seconds, reduces the Apgar scores, and heart rate at 90 sec of life. More importantly is that resuscitation with air reduces relative risk of neonatal mortality approximately 30%. It is therefore recommended to start ventilation with air, and if possible have a blender, so oxygen could be given in case the baby does not respond adequately. A proper ventilation strategy to open the lungs is essential before oxygen is supplemented.
    2. In babies with non-healthy lungs (for instance, after meconium aspiration), oxygen supplementation may be needed, and no clinical data exist regarding optimal FiO_2 for such babies. 100% oxygen use impairs subsequent vasodilation with iNO, and high O_2 in combination with iNO may result in formation of peroxynitrite, so avoiding hyperoxemia may be as important as avoiding hypoxemia in the management of PPHN. In the rare event of the need of chest compressions (<1/1000 term or late preterm babies), the optimal initial FiO_2 is not known.
    3. If a pulse oximeter is available, arterial oxygen saturations (SpO_2) should be aimed to reach 80% within the first 5 minutes of life.
    4. ELBW infants. Fewer data are available regarding how to oxygenate these babies in the delivery room. There are, however, data from smaller studies indicating that one should avoid starting with FiO_2 90–100%. Until more data are collected, advice, based on the limited data available, is to start ventilation with 21% or 30% oxygen and adjust FiO_2 to reach SpO_2 of 80% within 5 minutes of life.
    5. Hyperoxia and hypoxia are both involved in the development of neonatal diseases through contributing to increased mitochondrial ROS generation.
  B. Oxygen beyond the delivery room
    1. Term and late preterm babies should be weaned as quickly as possible, and this is often not difficult since their lungs are mostly mature.
    2. The optimal SpO_2 target of ELBW infants is not known. It is clear that especially severe ROP and also BPD (if defined as oxygen dependence at 36 weeks' PMA) are reduced by keeping the SpO_2 lower (85–89%) and avoiding fluctuations. On the other hand, recent data indicate that a low saturation target between 85% and 89% increases mortality and NEC compared with a higher target of 91–95%. Tight alarm limits are recommended in order to prevent fluctuations and hyperoxic peaks.

IV. Prevention of hyperoxia and hyperoxic injury
  A. The best prevention of oxidative stress injury of the newborn is to avoid hyperoxia and inflammation, especially the combination of these.
  B. Beta-carotene and vitamin A in one study were lower in preterm babies developing BPD. Postnatal vitamin A supplementation in the US multicenter trial reduced BPD (RR 0.89, 95% confidence interval 0.80–0.99, number needed to treat = 14–15).
  C. Antioxidant enzymes, such as superoxide dismutase, as well as antioxidants such as vitamin E, have so far not been convincingly successful in preventing hyperoxic injury in newborn infants.
  D. Early routine use of inhaled nitric oxide (iNO) in preterm infants with respiratory disease does not improve survival without BPD, and iNO has been linked to increased cancer risk.

E. A number of different antioxidants, such as allopurinol and erythropoietin, have been tested with some positive effects. Nutrients, such as omega-3 fatty acids, especially docosahexanoic acid, may have antioxidant properties in the newborn.
F. In the future, new and more powerful antioxidants may be developed giving clinical effects when administrated both pre- and postnatally.

V. How to reduce hyperoxia/oxygen toxicity in the newborn
A. Early aeration of the lungs. Titrate O_2 and keep SpO_2 within the target ranges.
B. Late cord clamping/intact cord resuscitation contributes to earlier aeration, SaO_2 increase, and lower FiO_2.
C. Colostrum and breast milk (BM). The BM antioxidants are adapted to gestational age providing higher levels to infants with lower degree of maturation.
D. Lung ultrasound (LUS) <3 hrs. in newborns with RDS contribute to early identification of babies in need of surfactant treatment earlier than clinical signs alone and thereby reduced oxygen load.
E. Measure arterial PaO_2 in addition to SpO_2 in premature newborns to achieve the most appropriate FiO_2 for the specific child. NIRS is being investigated to measure tissue oxygenation index, TOI (in the brain, myocardium, and intestine).
F. Attenuation of oxidative damage after HI by targeting the deactivated mitochondrial complex I, which changes its conformation from active form (A) into the catalytically dormant deactive form (D). Reoxygenation may rapidly convert the D-form into the A-form and thereby increase ROS generation. Pharmacologically controlled gradual reactivation of complex I could therefore attenuate oxidative damage.

Suggested Reading

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