Oxygenation of the Newborn: A Molecular Approach

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Abstract
In this review oxygenation and hyperoxic injury of newborn infants are described through molecular and genetic levels. Protection and repair mechanisms that may be important for a new understanding of oxidative stress in the newborn are discussed. The research summarized in this article represents a basis for the reduced oxygen supplementation and oxidative load of newborn babies, especially since the turn of the century. The mechanisms discussed may also contribute to an understanding of why hyperoxic resuscitation of the newborn may damage DNA and affect its repair, thus increasing the risk that it may be carcinogenic. Today, term babies should be resuscitated with air rather than 100% oxygen and very and extremely low birth weight infants in need of stabilization or resuscitation at birth should be administered initially 21–30% oxygen and the level should be titrated according to the response, preferably measured by pulse oximetry. In the postnatal period the oxygen saturation should be targeted low <95%; however, saturations between 85 and 89% seem to increase mortality. The optimal oxygen saturation target for these infants postnataally is still unknown.

Prologue
Early in the morning of April 27, 1986, O.D.S. left home in Oslo to catch a plane to Amsterdam to meet with some European colleagues to discuss the development of surfactant therapy. This meeting was later known as the First International Workshop on Surfactant Replacement Therapy. It was hosted by Janna Koppe with only 12–15 participants; today these annual meetings have grown to more than 300 participants from all over the world.

There was rain in the air on this morning in April 1986 and what O.D.S. did not know at that time was that radioactivity was on its way from the south-east. The night before, a Chernobyl nuclear reactor had exploded and winds were unfortunately blowing to Norway carrying radioactivity towards the country.

Bengt Robertson had invited everyone to the meeting in Amsterdam to discuss the use of a new natural surfactant, named Curosurf®, he developed with Tore Curstedt. April 27 and the following days carried death in the air from Chernobyl. At the same time in Amsterdam a project that turned out to be one of the most successful in the history of newborn medicine was discussed. Today Curosurf is the world’s leading pulmonary surfactant and has contributed to saving hundreds of thousands of lives all over the world. Death and life...
really crossed paths on those days at the end of April 26 years ago.

At that time, O.D.S. discussed the possible consequences of an abrupt increase in oxygenation following natural surfactant administration. At the end of the 1970s we understood that oxygen radicals produced in excess by the hypoxanthine-xanthine oxidase system during posthypoxic reoxygenation may contribute to reoxygenation injury, at that time a phenomenon known as the oxygen paradox [1]. On the blackboard at the Amsterdam meeting, O.D.S. drew a figure illustrating how hypoxanthine released from the tissues during reoxygenation may react with oxygen and generate oxygen radicals (fig. 1), suggesting that inspired oxygen concentration (FiO₂) should be turned down quickly when surfactant was given in order to reduce the oxidative stress and oxidative injury. The first surfactant protocols, however, kept FiO₂ high during the first 5 min, thus increasing the risk of oxidative damage immediately following surfactant replacement. In early studies we showed that hypoxanthine in the blood is released in parallel with surfactant administration, and its level was related to both mortality and development of intracranial hemorrhage [2]. Another early study showed that a high peak of arterial oxygen tension, especially in excess of 30 kPa during the first 30 min after surfactant was given, significantly increased the risk of intraventricular hemorrhage [3]. Consequently, in the later clinical protocols FiO₂ was reduced more quickly after Curosurf® administration.

Bengt Robertson had a unique ability to create an atmosphere where those of us who at that time were young were allowed to present and discuss our ideas openly. The first workshops were therefore essential not only for the development of surfactant therapy, but were also the cradle for important initiatives such as Henrik Verder and others’ development of the continuous positive airway pressure (CPAP) concept [4, 5] which led to the INSURE (intubation surfactant extubation) strategy now widely recognized all over the world [6]. The scientific basis for using primarily CPAP instead of mechanical ventilation even in extremely low gestational age infants originates from these workshops. Ideas about inflammation, minimal handling, CPAP, low oxygenation and other topics were first discussed in this forum. Several main concepts of present handling of immature babies therefore originate from these meetings and their influence cannot be overestimated when the history of neonatology of the last 25 years is written.

Introduction

Embyronic and fetal development occurs in a hypoxic environment indicating that redox processes are important in regulating embryogenesis. In the fetus, oxygen saturation of blood is about 50–60% [7]. What are the developmental consequences if the redox status is changed in immature infants treated with oxygen to achieve higher oxygen tensions than in fetal life? This was an important research question posed in the 1980s. This led us directly to basic problems related to oxidative stress in the newborn and especially in the preterm infant. Our understanding [1] that oxygen radicals are produced in excess during reoxygenation was based on two observations 5–10 years earlier: (1) hypoxanthine accumulates in the blood of newborns during hypoxia [8] and increases exponentially during the first minutes of resuscitation [9], and (2) xanthine, and consequently hypoxanthine, is a potential free radical generator [10].

It was known in the 1980s that oxygen is toxic to preterm infants. However, the new understanding that oxidative stress is related to other factors than oxygenation per se and the concept of an ‘oxygen radical disease of the newborn’ represented a breakthrough that paved the way for the present policy of a lower oxygenation of the most immature babies (see [11] for review). When pulse oximetry was introduced in the 1980s, the optimal SpO₂ of such babies was unknown and not usually discussed. It was by and large assumed that arterial oxygen satura-
ation should be close to 100% – a concept that probably contributed to many cases of severe retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD).

Supraphysiological concentrations of oxygen generate excessive amounts of reactive oxygen species (ROS), and not only through the xanthine-xanthine oxidase system. They are produced by membrane-bound nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [12] and by electron transport chain components in the mitochondria (reviewed in [13]). Even brief exposure to hyperoxia increases mitochondrial oxidation in fetal pulmonary artery smooth muscle cells [14]. ROS can damage macromolecules [15–17], with concomitant cell death and apoptosis in brain and lung tissue [18–20]. ROS can also alter gene expression by activation of transcription factors and signaling pathways to induce downstream targets (reviewed in [21]).

To ensure faithful duplication and inheritance of genetic material, eukaryotic cells have evolved a versatile response to DNA damage, collectively termed the DNA damage response. This carefully coordinates either the process of repair or the induction of cell death.

In the present article we discuss some effects of hyperoxia and oxidative stress in the newborn with particular focus on the integrity of DNA and expression of genes. We present some implications of hyperoxia on the cellular and tissue level and discuss the basic defense mechanisms against hyperoxia from oxidative stress. Based on these considerations, we finally discuss some important clinical implications for handling of oxygen therapy in newborn infants.

**Evolutionary Aspects**

The way for aerobic-based life was paved from the first biogenic processes involving photosynthesis, producing oxygen as a by-product that enabled diversification of metabolic pathways. Advantages, however, rarely occur without a ‘flipside’. With oxygen followed oxidation, and organisms were confronted with yet another frontier in the battle to preserve their integrity. The first photosynthetic bacteria, the Cyanobacteria, developed superoxide dismutase-like enzymes that were needed for survival in an increasingly hyperoxic atmosphere. The development of mitochondria that convert oxygen to water was another important step for protection from oxidative stress [22]. Although the primitive atmosphere was initially low in oxygen, it gradually increased. So it is easy to understand that the body developed its defense against low oxygen states through the evolutionary process.

But how can the defense against hyperoxia be explained? Monophyly of all known life from a universal common ancestor is a widely accepted hypothesis [23]. Our universal common ancestor probably inherited a rudimentary resistance to oxygen toxicity even before there was free oxygen in the air. This may have happened when life 4 billion years ago was forced through a ‘radiation bottleneck’, enforcing evolution of oxygen resistance and laying grounds for eukaryotic life in the present atmospheric oxygen [22] (see review in [24]). In addition, throughout evolution of life on earth, the atmospheric content of oxygen has varied [25]. Oxygen in the atmosphere has probably been higher than today, perhaps as high as 35%. Each rise in oxygen concentration was followed by an expansion of life. The existence of giant plants and insects 270–320 million years ago may have occurred in periods with high oxygen concentration. Since then minor fluctuations probably took place until the present level of 21% was reached [22]. Such fluctuations may have been another factor adapting life to higher oxygen levels than the present one, favoring the evolution of sophisticated defense mechanisms against hyperoxia.

**Why Is Oxygen Toxic?**

It has been known since 1891 that oxygen is paramagnetic. The spin of unpaired electrons makes it difficult for oxygen to form new chemical bonds due to spin restriction. Oxygen can only receive single electrons with antiparallel spin to complete electron pairings. By feeding oxygen with one electron at a time, for example from iron, the oxygen molecule is stabilized. This phenomenon explains the high affinity of iron to oxygen and the production of rust. However, during oxidative phosphorylation in the mitochondria, single electrons escape and join with 1–2% of the total oxygen consumed by cells to form superoxide radicals. By adding 2, 3 and subsequently 4 electrons, hydrogen peroxide, the hydroxyl radical, and finally water are formed, respectively.

In the 1950s, Gerschman et al. [26] at the Manhattan project understood that hyperoxic injury and radiation injury share a common mechanism through free radicals. This may explain how evolution through the ‘radiation bottleneck’ mentioned above simultaneously prepared life to resist hyperoxia.

Oxygen radicals or ROS have a number of actions and oxidize free fatty acids, proteins and DNA. They have im-

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important physiological properties as in defense against microbes [27]. They are also signaling substances, and redox processes probably are important for controlling growth and development. This was known in the 1980s and several of us realized ROS are important regulators of the circulation [28–31].

**Hyperoxic Injury**

Neonates require high levels of antioxidants and an intricate redox balance to ensure successful transition to the relatively hyperoxic extraterine environment [32]. Studies in newborn animals and in newborn babies clearly show that resuscitation with oxygen-supplemented air is directly toxic not only to the lungs but also to several organs such as the heart, liver and brain [33–36]. We found that resuscitation of newborn hypoxic piglets with oxygen increased the concentration of extracellular glyc erol from the striatum compared with air-resuscitated animals, indicating more injury with 100% oxygen [34]. Koch et al. [35] found that exposure to 100% oxygen after a hypoxic-ischemic brain injury in young mice increased secondary neural injury, interfered with myelination and impaired functional recovery. In our newborn hypoxia-}

reoxygenation piglet model, matrix metalloproteinases (MMP) 2 and 9 were measured to assess oxidative tissue damage and repair in lung, liver, heart and brain. Resuscitation with 100% oxygen gave significantly higher values compared with ambient air [34, 35, 37, 38]. Studies in newborn lambs also showed more injury to the brain when resuscitation was carried out with 100% oxygen compared with air [39].

We found it important to study whether there is a threshold beyond which supplemental oxygen becomes toxic or if there is a dose dependency for detrimental effects. Using different oxygen concentrations for newborn resuscitation in a newborn piglet model, we found a clear dose-dependent oxygen toxicity as shown in figure 2. In brain tissue, the most prominent changes occurred in neuronal populations in a dose-response manner. Caspase 3 also showed a dose-dependent increase and brain-derived neurotrophic factor a decrease in gene and protein expression, indicating more apoptosis and less neuroprotection if supplementary oxygen is used for resuscitation.

Felderhoff-Mueser and coworkers [41, 42] studied oxygen toxicity in the preterm brain and found neurodegenerative changes and caspase activation. Also around term a relatively short exposure to hyperoxia may cause

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**Fig. 2.** Oxygen vs. dose dependency: dose-dependent hyperoxic injury (adapted from Solberg et al. [37, 38, 40]). The graph visualizes how different parameters have a dose-dependent relative change according to the amount of oxygen used for resuscitation. The lines drawn show the increase/decrease, not the measured values. Damage to DNA is shown as the increase in 8oxodG/2dG, formed as a result of attack by hydroxyl radicals to DNA. 8-oxoG is highly mutagenic and must be removed prior to DNA replication. Hydroxyl radicals increase the O-tyrosine/phenylalanine ratio, a specific biomarker of oxidative damage to proteins. MMPs are important in ischemia-reperfusion injuries and can serve as biomarkers of tissue injury and repair. Caspase 3 plays an important role in the execution of apoptosis and both gene expression and activity are increased after hyperoxic resuscitation. Brain-derived neurotrophic factor (BDNF) indicates less neuroprotection if 40 or 100% oxygen is used for resuscitation.
harm. Exposure to 100% oxygen for 30 min without preceding hypoxia decreases the expression of vascular endothelial growth factor receptor 2 and transforming growth factor receptor-β3 in liver tissue, raising concern about impaired angiogenesis and tissue remodelling [35]. Caspase 3, brain-derived neurotrophic factor and MMP 9 are hypoxia-reoxygenation-responsive genes in the newborn brain [38].

In a human study, Vento et al. [43] found significantly higher values of plasma cardiac troponin T and N-acetyl-glucosaminidase in newborns resuscitated with 100% oxygen compared with ambient air, pointing at more oxidative tissue damage in the heart and kidneys.

Preservation of Genomic Integrity

A major challenge for all life has been to counteract the constant decay of macromolecules, in particular DNA. Damage to DNA can be a consequence of influence from both exogenous and endogenous sources [44]. DNA damage is sustained from various genotoxic chemicals, radiation, thermal disruption and viruses. Cellular metabolic processes, including those involving oxygen, are the source of more than 20,000 DNA lesions per human cell per day [45]. DNA damage may lead to mutations that provide the source of diversity and the substrate of natural selection. Although vital from an evolutionary point of view, genome modifications are often detrimental to organisms.

Several sophisticated mechanisms for DNA repair have evolved alongside the complexity of organisms and more than 130 DNA repair genes have been identified in humans [44, 46]. Impaired DNA repair is associated with severe consequences including embryonic lethality or impaired growth, cancers, rapid ageing and shortened life span, and a variety of human syndromes [44, 47, 48].

Oxidative DNA Damage Repair

The main catalyst for repair of small chemical alterations to DNA bases including oxidation, apurinic/pyrimidinic sites and single-strand breaks is the highly conserved base excision repair (BER) pathway [54]. BER is executed through four distinct reactions including recognition and removal of a damaged base from the DNA backbone, strand incision, gap filling, and nick sealing (fig. 3) [55, 56].

DNA glycosylases initiate BER by recognition of a vast number of base lesions. So far, 11 mammalian DNA glycosylases have been identified, nearly all possessing a broad and overlapping substrate range. The oxidized base-specific DNA glycosylases extend to the five enzymes: 8-oxoguanine DNA glycosylase (Ogg1), endonuclease III-like 1 (Nth1), endonuclease VIII-like 1 (Neill1), Neill2, and Neill3 [57, 58]. In addition, the MutY homolog (Myh) initiates BER by removal of mismatched adenine opposite 8-oxoG [59], thus providing Ogg1 with a second chance to excise the base lesion and prevent G:C to T:A mutations.

Ogg1-targeted mice accumulate 8-oxoG in hepatocytes and display elevated spontaneous mutation rates [60, 61]. The mutagenic and carcinogenic potential of ROS-derived base lesions is elegantly demonstrated in mouse models with targeted deletions in two DNA glycosylases: Neill2–/– Nth1–/– mice develop pulmonary and hepatocellular tumors [62], while Ogg1–/– Myh–/– mice accumulate G to T transversions and display a predisposition to tumors and lymphomas [63]. Neill2–/– mice are currently not described in the literature, while investigation of Neill3–/– mice has revealed no obvious disease phenotype [64] until recently, as discussed below. These models inherit great potential for understanding the relationship between oxidative DNA damage and the development of disease.

Unlike Neill1 and Neill2, displaying constitutive and widespread distribution in the mouse brain, expression of Neill3 is confined to regenerative subregions in the em-
Neil3 removes oxidative base lesions on single-stranded DNA, with preference for spiroiminodihydantoin and guanidinohydantoin, which are further oxidation products of 8-oxoG and potent sources of replication blocks in vivo [58, 67].

We have recently shown that the enhanced proliferation resulting from hypoxic-ischemic events in the newborn brain is greatly dependent on Neil3 (fig. 4) [68]. The pathogenesis of hypoxic-ischemic injury is complex, with increased oxidative stress being an early feature. Neil3 is the main contributor to repair of spiroiminodihydantoin and guanidinohydantoin lesions in neural stem/progenitor single-stranded DNA, but the presence of these lesions in vivo remains to be established [68].

Injury to the immature brain is a significant cause of severe and long-standing neurological disabilities, and identification of novel therapeutic targets in DNA repair processes to enhance the genesis of new neurons and reduce cognitive disability is a priority in our current research.

Hyperoxia and Gene Regulation

Increased oxygenation shuts down the master regulatory transcription factor, hypoxia inducible factor 1-α subunit, which controls several hundred genes involved in cellular growth and survival, angiogenesis, energy metabolism and vasomotor regulation [69]. Contrary to the hypoxia inducible factor 1-α subunit, other transcription factors such as activator protein-1, NF-κB, tumor protein p53 (p53), nuclear factor erythroid-related factor 2 (Nrf2), and signal transducers and activators of transcription are activated by hyperoxia [21, 70, 71]. At the cellular and molecular level the effect of hyperoxia is complex, reflecting several hyperoxia-responsive genes and proteins attending redundant and overlapping signaling pathways. The lungs, retina and brain of newborns are tissues particularly susceptible to oxygen-induced injury, and preterm infants are high-risk candidates for these injuries due to reduced antioxidant defense.

The Lungs and Brain

The lungs are directly exposed to high levels of oxygen. In experimental models excessive oxygen causes pulmonary toxicity characterized by well-defined stages that are typical for acute lung injury [72]. Genes and signaling pathways responsible for the changes seen in oxygen-induced lung injury, cell death, inflammation, modulation of cell growth and induction of stress responses have been found [71]. The mitogen-activated protein kinase (MAPK) signaling pathway seems to play an important role in hyperoxic cell death. MAPK subfamily members are extracellular signal-regulated kinase (ERK1/2), c-jun N-terminal (JNK1/2) and p38 kinase [73, 74]. ERK1/2 has a dual role in hyperoxia-mediated cell death as a protector [75] and as an inducer [76]. ERK1/2 upstream and downstream...
targets include Fas, p53, Bax proteins and Bcl-x [75, 77]. JNK1/2 is important in mediating ROS-induced cell death [78]. The NF-κB pathway activates genes that regulate inflammation, stress responses and apoptosis after exposure to hyperoxia [79]. Activator protein-1 regulates the expression of a range of stress-responsive genes, cytokines and growth factors, and seems to play an important role in IL-8 induction together with JNK [80]. Hyperoxia may additionally induce cell cycle arrest with p21 and DNA damage proteins (GADD) playing important roles [81].

Our group has focused on mechanisms related to hypoxia-reoxygenation and brief oxygen treatment in newborn animal models. Hypoxia followed by 100% oxygen during resuscitation induces upregulation of pro-MMP 2 and 9 in bronchoalveolar lavage fluid and IL-18 in pulmonary tissue indicating an inflammatory response [34].

We have performed a whole-genome study in newborn mice after hypoxia and reoxygenation with different FiO2 (0.21, 0.40, 0.60 and 1.00). In whole-brain homogenates, 458 transcripts out of 24,674 probe sets with a known gene symbol were differentially expressed and slightly dominated by upregulation. Sixty-six percent of these genes were changed after reoxygenation with 100% oxygen. Pathway analysis showed significantly decreased activity of oxidative phosphorylation after hyperoxic reoxygenation with FiO2 0.60 and 1.00.

**Oxygenation of Term and Preterm Newborn Infants**

**Resuscitation of Term Infants**

Clinical studies testing air versus 100% oxygen for resuscitating babies with birth weight >1,000 g showed that it is feasible to resuscitate with air. Meta-analyses subsequently showed that neonatal mortality is significantly reduced in term or late preterm babies resuscitated with air instead of pure oxygen [82, 83]. The reason for this is still not fully understood, but Vento et al. [84] have shown that resuscitation with 100% oxygen in contrast to air increases oxidative stress for weeks after birth. The most recent meta-analysis indicates that neonatal mortality is reduced 30% in this group of babies, corresponding to the potential saving of approximately 250,000 lives annually [82, 83].

It is amazing that even brief oxygen exposure at birth of a few minutes seems to trigger long-term effects. For term babies, the main consequence of this finding has been that resuscitation should not be carried out with 100% oxygen, but rather initiated with air [85].

**Resuscitation of Preterm Infants**

The optimal FiO2 for stabilizing and resuscitating preterm infants, especially those of extremely low birth weight, immediately after birth remains unknown. However, it is reasonable to believe that these babies are even more vulnerable to hypoxia than term babies. Studies that included this population of infants showed...
that 100% oxygen is not needed routinely for their stabilization. However, it also seems that air in several cases is insufficient [86]. A reasonable approach, until there is more evidence, is to start with 21–30% oxygen in the smallest babies and titrate FiO₂ according to the response. If a pulse oximeter is available, oxygen saturations should be monitored preductally and FiO₂ could be adjusted to maintain SpO₂ within the 10th to 50th percentile of normal SpO₂ values in the first 10 min of life [87].

**Hypoxemic Resuscitation**

Perhaps an even better result would be obtained by hypoxemic resuscitation. Piglet studies we performed in the 1990s [88] demonstrated that it is possible to resuscitate with 18% and perhaps even 15% oxygen. However, 12% oxygen seems to be insufficient to restore metabolic and neurological functions. Recently, a study in newborn mice indicated that an improved outcome is obtained by resuscitating with 18% oxygen [89]. Hypoxemic resuscitation should therefore be studied in more detail and perhaps also in clinical studies. However, reducing FiO₂ to <0.21 makes newborn resuscitation more complex.

**Effect of Hypothermia**

We have studied the effect of different oxygen concentrations combined with hypothermia. Hyperoxic resuscitation of term piglets and lambs induces inflammation in the brain [33, 39]. It is therefore likely that the effect of hypothermia is dependent on the initial FiO₂ during resuscitation. In human neuronal cells cultured in vivo, hypothermia protected the cells exposed to oxygen and glucose depletion. However, there was no additional effect of changing the oxygen concentration [90]. However, in newborn piglets and in a newborn rat model we found that the FiO₂ used for resuscitation influenced the effect of hypothermia [91, 92]. In the rat model we clearly found a reduced effect of hypothermia when resuscitation was carried out with 100% oxygen. In fact, no reduction in brain injury was found in animals resuscitated with 100% oxygen and then cooled compared with animals resuscitated with air and kept normothermic. Unfortunately, since most of the babies enrolled in the clinical hypothermia studies were resuscitated with 100% oxygen, the effect of hypothermia after resuscitation guidelines were changed from oxygen to air is not known and probably never will be. Any retrospective information available on this topic will be of less value than a prospective randomized study but this is not likely to be performed.

**Preterm Infants beyond the Delivery Room**

The understanding that evolved in the 1980s that oxidative stress in preterm infants is not only caused by hyperoxia but also by (1) low oxidative defense, (2) inflammation and (3) presence of free iron, facilitated the understanding that several morbidities and injuries of preterm infants are caused by oxidative stress in spite of normoxia [93]. Further, it was understood that the immature brain is especially vulnerable to oxidative stress due to its high content of omega-3 fatty acids and immature oligodendrocytes that are more susceptible to oxidative stress than mature ones. Activated microglia also contribute to the oxidative stress in immature and newborn brains (reviewed in [24]).

These are part of the rationale for several observational studies published after the turn of the century demonstrating that a lowered SpO₂ also reduces the risk of severe ROP and BPD/lung problems. It is of interest that in the 1950s preterm infants were treated in a hypoxemic environment with apparently good results [94]. Recently, a randomized study confirmed that a low oxygen saturation (85–89%) compared with a high (91–95%) reduces ROP [95]. In a recent systematic review, we showed that a low SpO₂ reduces severe ROP by more than 50% and BPD by 20–25% [96]. Unfortunately, it seems that mortality is also significantly increased if babies <29 weeks’ gestation are kept in SpO₂ between 85 and 89% compared with 91–95% [95, 97]. The optimal SpO₂ is therefore presently not known, but it should not be too low (85–89%) or too high (>94%) [98]. To make the issue even more complicated, there may be different optimal SpO₂ targets to prevent BPD and ROP. In addition, SpO₂ may need to be targeted according to postnatal age and gestational age. Many years of research are still needed before these issues can be clarified.

**Conclusion**

More than 30 years of research related to oxygenation of the newborn is summarized in this article. The effects of oxygen on tissue, cellular, molecular and gene level are discussed. Oxygen toxicity should be understood in relation to cellular and molecular repair mechanisms. Whole genome and gene studies and availability of transgenic animal models as well as whole transcriptomes may improve our understanding of hypoxia and hyperoxia in the newborn.

Studies performed over the last three decades have contributed to a lowered oxidative load in newborns both during resuscitation and in postnatal management. This
new understanding has significantly contributed to a lowered mortality following resuscitation and lower morbidity in very and extremely low birth weight infants. For term or late preterm infants in need of resuscitation after birth, it is best to start with air. For low and extremely low birth weight infants, the optimal FiO₂ is not known but it probably is best to start with 21–30% oxygen and titrate according to reported normal SpO₂ centiles in newborn babies in the first 10 min of life. In the postnatal period, low SpO₂ of very and extremely low birth weight infants of for instance 85–89% versus 91–95% reduces severe ROP by more than 50% and BPD by about 25%; however, such a low saturation may increase mortality. Therefore, presently we recommend that SpO₂ in such babies is targeted >89% and certainly should not exceed 94%.

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