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Oxygen metabolism and oxygenation of the newborn

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ABSTRACT

The premature infant is to some extent protected from hypoxia, however defense against hyperoxia is poorly developed. The optimal assessment of oxygenation is to measure oxygen delivery and extraction. At the bedside PaO_2 and SpO_2 are approximations of oxygenation at the tissue level. After birth asphyxia it is crucial to know whether or not to give oxygen supplementation, when, how much, and for how long. Oxygen saturation targets in the delivery room have been studied, but the optimal targets might still be unknown because factors like gender and delayed cord clamping influence saturation levels. However, $SpO_2 > 80\%$ at 5 min of age is associated with favorable long term outcome in preterm babies.

Immature infants most often need oxygen supplementation beyond the delivery room. Predefined saturation levels, and narrow alarm limits together with the total oxygen exposure may impact on development of oxygen related diseases like ROP and BPD. Hyperoxia is a strong trigger for genetic and epigenetic changes, contributing to the development of these conditions and perhaps lifelong changes.

1. Introduction

The oxygen delivery and supply to tissues and cells are in normal circumstances sufficient and generous. During evolution eukaryotic cells and organisms have developed a defense strategy if hypoxia occurs. Physiological and biochemical defense mechanisms quickly react to prevent hypoxia through change in circulation, ventilation and metabolism. HIF-1α for instance activates 2500 genes or more to prevent hypoxia if oxygen level decreases [1–4]. However, evolution has not been as generous regarding protection against hyperoxia, perhaps because hyperoxia mostly is an iatrogenic condition. Still eukaryotic cells and organisms have developed defenses against oxidative stress. 3 billion years ago blue-green bacteria developed anti-oxyenzymes probably to be protected from radiation from the space. When oxygen in the atmosphere started to increase, especially during the great oxygen event 2.2–2.4 billion years ago, life was therefore to some extent prepared to live in an oxygen enriched and toxic atmosphere [5,6].

The embryo and fetus develop in a low oxygen milieu and is therefore not prepared to live in an atmosphere with 21% oxygen or more. HIF1-α is important for embryonic and fetal development and is developed early in life in contrast to especially intracellular anti-oxyenzymes which mature closer to term [7–10]. In addition, non-enzymatic antioxidants such as glutathione are synthesized late in gestation only, when the limiting enzymes (e.g.: gamma-cystathionase) of the trans-sulfuration pathway are expressed [11]. The preterm baby is therefore to some extent protected from hypoxia but poorly protected from hyperoxia.

These facts represent some of the challenges for the clinician when newborn, and especially preterm infants, need oxygen therapy, to decide the optimal oxygenation.

2. Oxygen assessment

The definition of the optimal oxygenation of a newborn is tightly related to how oxygenation is assessed. There is a discrepancy between the ideal and the practical way to monitor the optimal oxygenation [12,13].

2.1. Oxygen delivery extraction and consumption

Oxygen delivery is the product of cardiac output and the oxygen carrying capacity of the blood. The oxygen carrying capacity is influenced by the PaO_2 and hemoglobin level [14]. Cardiac output is dependent on heart rate and stroke volume. Therefore, there are several potential factors which can be manipulated in the clinical setting to affect oxygen delivery [12,13]. In normal conditions oxygen delivery is

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generous, approximately 3 times higher than demand. Fetal hemoglobin has a high affinity to O_2. This facilitates unbinding of oxygen in the tissues at lower PaO_2. As oxygen delivery decreases oxygen extraction will increase and eventually the metabolism is switched from aerobic to anaerobic, resulting in the production of lactic acid and a metabolic acidosis. So far there are no routine methods to measure oxygen delivery at the newborn's bedside.

Oxygen extraction is the proportion of oxygen unloaded from hemoglobin into the tissue and represents an ideal way to assess optimal oxygenation. Oxygen extraction is a measure of total endogenous and exogenous influences on the oxygen delivery and indicates the oxygen delivery and consumption of an organ. However, in routine clinical practice an assessment of the oxygen extraction is not available [13]. Balegar et al. measured cerebral fractional tissue oxygen extraction in preterm infants ≤30 weeks GA, and found significantly higher extraction in infants with early poor outcome, however without any change in extraction the first 72 h after birth [1].

Oxygen consumption is difficult to measure in the clinical situation and little is known about the normal levels [13] The use of Near Infrared Spectroscopy (NIRS) at different anatomical locations can be applied to analyse oxygen extraction. For instance abdominal NIRS has been employed to analyse mesenteric perfusion and indirectly measure hemodynamic significant ductus arteriosus [15].

By measuring *oxygen delivery* and *oxygen consumption* we gain information on the optimal oxygenation of the newborn. PaO_2 and SaO_2 are both approximations of the oxygenation status. PaO_2 is the measurement of the partial pressure of oxygen in arterial blood, whereas the SaO_2 is the percentage of hemoglobin bound with oxygen. SaO_2 varies with the PaO_2 in a nonlinear relationship and is affected by temperature, pH, 2,3 diphosphoglycerate, hemoglobin, and $PaCO_2$ [12,13,16]. Because oxygen saturation measured by pulse oximetry (SpO_2) is a noninvasive method, this has the last 3-4 decades been the predominant method to assess oxygenation of the newborns. Regional tissue saturation by Near Infrared Spectroscopy (NIRS) is another noninvasive method which is gaining popularity. There is accumulating information based on NIRS studies especially in the fetal to neonatal transition and postnatal adaptation, and also on longterm safety and impact [17–19].

Hypoxia occurs when the oxygen delivery is insufficient to meet the demands of the peripheral tissues – either due to impaired oxygenation of the blood or severely increased oxygen consumption. Hyperoxia is the opposite, with delivery grossly exceeding the demands of the peripheral tissues. Normoxia thus indicates that oxygen delivery and demand are balanced which is what we aim to achieve both in the delivery room and beyond.

In this paper we are presenting SpO_2 values when we describe oxygenation of the newborns.

3. Oxygenation in the delivery room

Studies from the beginning of the 1990's demonstrated the feasibility of resuscitating newborn babies with air [20,21]. At the turn of the century data accumulated showing the toxic effects of resuscitating with pure oxygen which had been the rule [22–25]. Initially only term and late preterm infants were studied. Meta-analyses including more than 2000 infants clearly showed a typical reduction in mortality of about 30% favoring air instead of oxygen [26–30]. It also became clear the use of 100% oxygen for newborn resuscitation triggered inflammation in a number of organs as the brain, heart and kidney [31–33], increased the risk of pulmonary hypertension [34,35], and was even associated with childhood cancer, especially leukemia [36,37]. In 1998 WHO, and in 2010 ILCOR, therefore changed guidelines recommending to start with air if term or late preterm infants need resuscitation in the delivery room [38,39].

In 2008 the first resuscitation studies only comprising preterm newborn infants resuscitated either with air/30% or 100/90% oxygen were published showing good outcome using air/30% oxygen [40–43]. The so-called Torpido trial where newborn babies < 32 weeks' gestation in need of ventilation in the delivery room, showed no difference in survival between those resuscitated with air compared to pure oxygen [44]. However, when a *post hoc* analysis was carried out on these data for immature infants < 28 weeks' gestation an almost four-fold increased relative risk of mortality was found for those resuscitated initially with air versus 100% O_2. So far, these results are based on few data, and more studies are pressing.

4. Development of SpO_2 the first minutes after birth

Dawson and coworkers published in 2010 data on the normal development of oxygen saturation in term infants and this is used as a guide for the development of the saturation for all newborn infants, term and preterm [45]. Trials on the development of oxygen saturation in healthy term infants with delayed versus immediate cord clamping show a slightly different rise in SpO_2, with significantly faster increase in SpO_2 when delayed cord clamping over the first few minutes of life, and a median SpO2 of approximately 90% at 5 min [46,47]. Further, oxygen saturation develops differently in girls versus boys and with or without CPAP [48]. These factors are worth taking into consideration when assessing saturation targets at birth, and warrants further studies on delayed cord clamping and saturation targets, especially in the preterm population.

By analyzing the Torpido data in more detail it became clear that outcome was better in those infants who reached a SpO_2 of 80% within the first 5 min of life. They had higher survival, less severe intraventricular hemorrhage and even better cognitive outcome at follow-up [49,50]. Those who did not reach a saturation of 80% within 5 min could for various reasons be sicker than those who reached this target. Still, as long as it cannot be ruled out that a slow increase in SpO_2 may contribute to higher mortality and morbidity, the aim should be to reach a saturation of 80% within 5 min [51,52].

This raises a clinical challenge. The first stable pulse oximetry signal is obtained close to 2 min of age. At 2–3 min there is no difference in SpO_2 in those who reaches a saturation of 80% at the age of 5 min and those who fail this target [53]. This means the clinician in order to reach SpO_2 of 80% within 5 minutes of age has only a couple of minutes and perhaps less, to decide how and when to regulate FiO_2 when ventilating such infants.

5. Oxygenation beyond the delivery room

The recent decades the question how to oxygenate premature infants beyond the delivery room has been investigated and discussed. This literature has recently been extensively summarized [54–59] Suffice here to repeat that the NEOPROM (SUPPORT, COT, BOOST 2 from Australia, New Zealand, and UK) studies enrolled 4911 newborn infants < 28 weeks' gestation randomized within the first 24 h of life to a high (91–95%) or low (85–89%) SpO_2 target. There was no difference in primary outcomes of these studies which were mortality or neurodevelopmental impairment. However, mortality (18%) and NEC (25%) were significantly decreased in the high target group, while ROP (24%) and BPD defined non-physiologically, but not physiologically, were lower in the low saturation target group. Whether or not growth restricted infants are worse off in the low saturation target is debatable [60]. However, based on these data, European and US guidelines recommend aiming for the high target. Recently there has been more focus not only on target saturations, but also on alarm limits [61,62]. The most recent European guidelines recommend targets of 90–94% and narrow alarm limits of respectively 89% and 95% [63]. However, very recent data from the SUPPORT trial indicate that the total amount of oxygen spent especially from week 1–5, and also to some extent from week 6–9, represents risk factors for developing severe ROP [64].

Therefore, when assessing oxygenation in immature infants beyond the delivery room it is relevant to assess saturation targets, alarm limits,

and total amount of exposure of oxygen as well, especially the first weeks after birth.

5.1. Genetic consequences of newborn hyperoxic exposure

In the lungs of newborn mice reoxygenated with hyperoxia (60 or 100% oxygen) differentially expression of several hundreds of genes was induced compared to reoxygenation with air. This effect was enhanced remarkably when hyperoxia followed hypoxia with almost a doubling of induced genes. Hyperoxia resulted in up-regulation of genes related to HIF-1 responsive genes, pathways related to cell cycling, nucleotide excision, nucleotide excision repair, mammalian target of rapamycin (mTOR) signaling pathway including genes related to growth (VegfC, Pgf) and signal transduction. DNA polymerase was down regulated by hyperoxia, hence reducing DNA replication [65–67].

In the mouse brain, hyperoxia down regulated genes related to DNA replication and to oxidative phosphorylation and increased cell death in the brainstem. In general, following hypoxia, hyperoxic reoxygenation induced a stronger brain inflammatory gene response than reoxygenation with air [68,69].

5.2. Epigenetic changes

Chen et al. found hyperoxia exposed rats exhibiting significantly lower total levels of four DNA methylated genes associated with hyperoxia-induced inhibition of alveolarization at day 14th [70]. By contrast, in a newborn mouse model given 80% oxygen for 14 days after birth the mean methylation level at 4 weeks of age was significantly higher in the hyperoxia than the air-breathing group, suggesting the presence of an overall DNA-hypermethylation effect of hyperoxia. These hypermethylated genes included *Tgfbr1*, *Crebbp,* and *Creb1*, which play central roles in the TGF-β signaling pathway and cell cycle regulation. In the normoxia control group no significant methylation differences were observed for specific genomic pathways [71]. A statistically significant enrichment of especially the TGF-beta signaling pathway was found. Studies performed in preterm newborn infants showed that the “oxygen load” received upon stabilization notably influenced the methylation pattern of DNA. Hypomethylation affected significant pathways such as cell cycle, antioxidant enzymes, DNA repair, Differences in sex and type of delivery were noted [72].

These studies indicate that long term hyperoxic exposure leads to DNA methylation of genes related to lung growth and development, lung morphogenesis, branching and alveolarization which are typical features of bronchopulmonary dysplasia. Epigenetic silencing may therefore potentially contribute to pathogenesis of bronchopulmonary dysplasia. Further, these data indicate, however not proven, that lifelong epigenetic changes may be induced after long term oxygen exposure.

6. Discussion

The optimal way to oxygenate newborn infants in need of oxygen supplementation is still not known. One reason for that is that we only have surrogate and approximate measures for the oxygen need available at the bedside. SpO_2 is presently the predominant measure of oxygenation status of the newborn. NIRS measuring the oxygen consumption and extraction in specific organs as the brain is available, but still mainly in research settings, and we need more clinical and follow-up data before this technique should be used routinely.

In the delivery room we have come a long way from the previous crude concept that every newborn in need of ventilator support at birth should be supplemented with pure oxygen. But we also know that one size does not fit all. Term and late preterm infants should be given air initially. For infants between 28 and 31 weeks' gestation air or 30% O_2 could be given. Based on available data we are unsure of the optimal initial FiO_2 for such infants. The same holds true for those < 28 weeks' gestation. However, data at this time seems to indicate that they need some supplementary oxygen initially, and we and others have suggested starting out with 30% O_2 [4]. There are also gender differences, as a more rapid increase in SpO_2 has been seen in premature girls than in boys during the first minutes of life [48].

For all groups FiO_2 should be adjusted according to SpO_2, if a pulse oximeter is available. One challenge is that we don't know exactly which saturations we should aim for at which time of life. However, so far it seems that a saturation of 80% should be reached within 5 min to optimize outcome.

Regarding oxygenation beyond the delivery room we have few solid data except for infants < 28 weeks' gestation after 24 h of age. A target of 91–95% as AAP suggests or 90–94% as the European guidelines recommend seems presently to be optimal [62,63]. Alarm limits should be tight to avoid fluctuations [63]. This seems to be most important the first few days/weeks after birth. Whether these targets should be adjusted with increasing post conceptional age or maturity is not known.

Oxygen therapy affects genes related to growth and development. Epigenetic changes might be lifelong. An association between oxygen exposure, even brief, at birth and childhood leukemia has been established. We still don't know if newborns exposed to oxygen at birth have increased risks of other malignancies later in life. We know however, that hyperoxia inflicts DNA damage and affects DNA repair mechanisms [73,74]. Thus there is a potential for negative long-term effects of oxygen therapy in the newborn period.

In spite of tremendous interest in, and emphasis on, oxygenation of the newborn, and in spite of substantial progress the last 30 years, there are still many unanswered questions. These questions can only be answered by large randomized studies.

6.1. Practice points

- Assessment of oxygenation is indirect only
- Hyperoxia leads to genomic and epigenetic changes
- Term and near-term newborns in need of ventilation at birth should be started in room air
- < 28 w GA beyond the delivery room: target SpO2 to 90/91–94/95 with tight alarm limits

6.2. Research directions

- Improve assessment of oxygenation
- Confirm the optimal oxygen saturation for immature infants the first 5 min of life
- Examine gender differences regarding oxygenation

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