Oxygen in the First Minutes of Life in Very Preterm Infants

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Abstract

Even a few minutes of exposure to oxygen in the delivery room in very preterm and immature infants may have detrimental effects. The initial oxygenation in the delivery room should therefore be optimized, but knowledge gaps, including initial fraction of oxygen (FiO 2) and how FiO 2 should be changed to reach an optimal oxygen saturation measured by pulse oximetry (SpO 2) target within the first 5–10 min of life, remain. In order to answer this question, we therefore reviewed relevant literature.

For newly born infants with gestational age (GA) <32 weeks in need of positive pressure ventilation (PPV) immediately after birth, we identified 2 fundamental issues: (1) the optimal initial FiO 2 and (2) the target SpO 2 within the first 5–10 min of life. For newly born infants between 29 and 31 weeks of GA, an initial FiO 2 of 0.3 hit the target defined by the International Liaison Committee on Resuscitation (ILCOR) best. Newborn infants with GA <29 weeks in need of PPV and supplementary oxygen, we suggest starting with FiO 2 0.3 and adjusting the FiO 2 to reach SpO 2 of 80% within 5 min of life for best outcomes. Prolonged bradycardia (heart rate <100 bpm for >2 min) is associated with increased risk of adverse outcomes, including death. The combination of strict control of development of SpO 2 in the first 10 min of life and a heart rate >100 bpm represents the best tool today to achieve the most optimal outcome in the delivery room of very preterm and immature newborn infants.

Keywords

Delivery room · Oxygenation · Resuscitation · Very preterm

Introduction

The goals of oxygen therapy for newborn infants are to provide sufficient oxygen to the tissues to avoid anaerobic metabolism and promote optimal brain and somatic growth. Sufficient oxygen should also be given to prevent hypoxic pulmonary vasoconstriction while avoiding the adverse effects of oxygen [1, 2]. This dichotomy of oxygen is well known, especially in neonatology. Oxygen is critical for life but excess may lead to oxidative stress and injury to vital organs. Preterm and especially immature newborn infants are more vulnerable to oxidative stress than term infants due to a lower level of defense against oxidative stress. In addition, preterm infants are
more likely to be exposed to oxygen supplementation and inflammation than their term counterparts, further enhancing detrimental effects of oxidative stress. Oxidative stress due to hypoxia-reoxygenation also seems to play a role in regulation of cardiovascular systems, such as the ductus arteriosus and pulmonary blood flow [2–4], which implies that the right balance between too much and too little oxygen is especially crucial in the most immature newborn infants. To find the correct balance is, therefore, one of the most crucial goals in modern neonatology.

Although the potential negative effects of prolonged oxygen exposure on preterm infants have been acknowledged for 70 years [5], it is only in the last 20–25 years that brief exposure to oxygen immediately after birth was shown to possibly have lifelong consequences. This was understood, first of all when clinical studies in the 1990s and early 2000s demonstrated higher mortality in newborn term and near-term infants in need of intervention after birth, who were ventilated with pure oxygen compared to air. Newborns ventilated with oxygen also took their first breath significantly later than those ventilated with air [6–8]. These findings prompted a renewed interest in the natural development of oxygenation during the first minutes after birth, and subsequently, several papers were published on the development of SpO2 in normal healthy term and near-term infants in need of intervention after birth, who were ventilated with pure oxygen.

SpO2 development in 4 term newborn infants in need of PPV. The subsequent year, Maxwell et al. [21] reported results of many authors since 2010 was to follow the Dawson curves as closely as possible. However, for very preterm

In the last 10–15 years, more data have accumulated, and we summarize this information. We specifically discuss the optimal initial FiO2, and how the development of SpO2 within the first 10 min of life influences outcomes of newly born infants <32 weeks of GA needing PPV in the delivery room. Further, we examine how bradycardia especially in combination with low SpO2 in the first minutes of life affects outcome.

**Methods**

We included all relevant articles in this field we are aware of, including our own publications. Further, we examined all studies available in the field by searching PubMed with the following terms: “preterm infants,” “oxygen saturations,” “delivery room,” “oxygen,” “resuscitation,” and “respiratory support.”

**Results**

**Development of SpO2 after Birth**

In 1986, Harris et al. [9] presented post-ductal pulse oximetry data of newborn infants in the delivery room. Term infants born vaginally had an SpO2 of 61 ± 5% at 1 min, increasing to 82 ± 2% at 7 min. Infants born by cesarean section had lower SpO2 in the first 5 min of life [9]. In the same year, Sendak et al. [20] published data for SpO2 development in 4 term newborn infants in need of PPV. The subsequent year, Maxwell et al. [21] reported the development of SpO2 during the first minutes of life in 4 preterm infants (27–34 weeks of GA) in need of intervention. In 2006, we summarized 5 more studies published between 1986 and 2002 [10–15, 22]. The year after, Mariani et al. [23] presented the development of SpO2 in the first 15 min after birth in both pre- and post-ductal samples in healthy newborn infants of ≥37 weeks of GA. These authors found higher SpO2 values after vaginal birth compared to cesarean deliveries [23]. Later, as mentioned above, Dawson et al. [16] combined data from several authors to develop the pattern of SpO2 trajectories in the first 10 min. These curves included newborn infants.
recruited from several different cohorts. The data were stratified to study 3 different groups of healthy non-asphyxiated newly born infants: (1) ≥37 weeks of GA, (2) 32–36 weeks of GA, and (3) <32 weeks of GA. These studies confirmed that SpO2 is low immediately after birth, in the range of 60–70% at 1 min of age, reaching a median level of 80–85% within 4–5 min. However, the large variation in values is striking. The ILCOR, using data from the studies mentioned above, published the recommended SpO2 targets the first 10 min of life [17]. However, it is important to note that these recommendations are not evidence-based.

High versus Low Initial FiO2 and Outcome

Escrig et al. [24] showed in a prospective randomized trial of preterm infants 24–28 weeks of GA given initial low (0.3) versus high (0.9) FiO2 that FiO2 was different between the groups during the first 4 min only. After this, both groups needed an FiO2 of about 0.45 to achieve the prespecified SpO2 targets [24]. In the same cohort, Vento et al. [25] found significantly higher oxidative stress markers in blood and urine of infants given higher initial levels of oxygen, and these persisted until a week of age. Similar data were confirmed by Tataranno et al. [26] in infants <32 weeks of GA given 100% oxygen initially compared to 30% oxygen. However, Rook et al. [27], comparing infants <32 weeks of GA randomized to FiO2 0.3 or 0.65, did not find any difference in oxidative stress markers.

The To2rpido trial was a multicenter randomized study aimed to determine major disability or death at 2 years of age in infants <32 weeks of GA after delivery room resuscitation was initiated with either 21 or 100% oxygen [28]. There was no difference in mortality between the groups, although there was a tendency to lower mortality in the 100% oxygen group (RR 2.6; 95% CI 0.9–7.1, p = 0.06). However, when a post hoc analysis was carried out separately for infants <28 weeks of GA, mortality was significantly higher in the 21% than in the 100% oxygen group (RR 3.9; 95% CI 1.1–13.4). The reason for this remains uncertain. In a meta-analysis and systematic review of 677 newborn infants ≤32 weeks of GA randomized to a low (FiO2 0.21–0.30) or high (FiO2 0.6–1.0) initial oxygen supplementation for delivery room respiratory support, a borderline lower mortality was noted in those started with a low FiO2 (RR 0.62; 95% CI 0.37–1.04) [29].

Oei et al. [30] studied outcomes in relation to initial FiO2 in the delivery room from individual patient data from 504 infants <29 weeks of GA from 8 randomized studies that had compared lower (FiO2 0.21–0.30) to higher (FiO2 0.6–1.0) initial FiO2. There was no difference in mortality between the groups (RR 0.99; 95% CI 0.52–0.92), but mortality was lower in masked studies (clinicians unaware of treatment arm) in the low FiO2 arm (RR 0.46; 95% CI 0.23–0.92). These studies were also the most recent ones and could reflect an improved experience with SpO2 targeting in the delivery room [30].

In a Cochrane review, Lui et al. [31] summarized data from 10 studies including 914 preterm infants, most of them below <32 weeks of GA. There was no difference in mortality or neurodevelopmental outcome whether initial FiO2 was above or below <0.4. There was also no difference in risk of retinopathy of prematurity, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, chronic lung disease/bronchopulmonary dysplasia, patent ductus arteriosus, or postnatal growth. Furthermore, there were no subgroup differences in any outcome variables when the infants were stratified into ≤28 weeks GA versus >28–32 weeks GA [31].

Saturation Targets versus Initial FiO2

Oei et al. [32] published personalized data from 8 randomized controlled trials, in which 717 preterm infants <32 weeks of GA were ventilated in the delivery room with different initial FiO2 including 0.21, 0.30, 0.60–0.65, and 0.9–1.0. The data were stratified between 29 and 32 weeks of GA and <29 weeks of GA. For infants between 29 and 32 weeks of GA, FiO2 of 0.3 was the only group that hit the target defined by the ILCOR in 2010 [17] within 1–2 min. FiO2 of 0.21 was under and the other groups above this target. However, within 6–9 min, all groups had reached target SpO2. For those <29 weeks of GA, all groups except FiO2 0.9–1.0 failed to reach defined SpO2 targets until 7–9 min of age. Within 2 min of age, the 0.9–1.0 group reached the target and remained within SpO2 target ranges for rest of the observation period of 10 min [32].

Clinical Associations with SpO2 Development

These authors also demonstrated an association between development of SpO2 the first 5 min of life and adverse outcomes. Infants who did not reach an SpO2 of 80% within 5 min of life had a higher risk of severe (grade 3 or more) intraventricular hemorrhage (OR 2.04; 95% CI 1.01–4.11) [32]. Survivors of the To2rpido study between 28 and 32 weeks of GA who had not reached a SpO2 of 80% within 5 min also had a lower cognitive score at follow-up (mean 95.4; SD 12.4 vs. 100.8; SD 12.5, p = 0.02) [33].
Target SpO2 of 80% within 5 min of Life

Based on these data, a target SpO2 of 80% by 5 min appears to be an important clinical variable related to outcome. Time to reach this target appears to be crucially dependent on GA. The median time according to the Dawson curves to reach an SpO2 of 80% was 2.5 min for healthy newborn infants ≥37 weeks of GA. For those between 32 and 36 of GA, time required was 3.2 and 3.6 min for those <32 weeks GA. In the study of Mariani et al. [23], SpO2 of 80% was reached 1.4 min earlier in pre-versus post-ductal samples. In the cohort followed by Oei et al. [32], 46% did not reach a target of 80% within 5 min and 42% exceeded the upper target of 85%. Therefore, only 12% of infants reached optimally defined SpO2 ranges of 80–85% within 5 min even under strict trial conditions. Infants were less likely to reach target ranges if they were started on lower rather than higher initial FiO2 (59 vs. 32%, OR 2.63; 95% CI 1.21–5.74). Infants with SpO2 ≤80% at 5 min were more preterm and had lower birth weights than infants with SpO2 >80%. Infants with 5-min SpO2 ≤80% were more likely to die (OR 2.70; 95% CI 1.58–4.61) and develop intraventricular hemorrhage (OR 1.82; 95% CI 1.20–1.75), but there was no difference in rates of bronchopulmonary dysplasia. Regression analysis taking confounders into account showed SpO2 ≤80% was associated only with increased risk of intraventricular hemorrhage (OR 2.04; 95% CI 1.01–4.11) [32].

In a cohort of newborn infants <32 weeks of GA, Veneto et al. [34] found that CPAP in the delivery room reduced the time to reach SpO2 80% by 1 min, and girls reached this target 0.9 min earlier than boys. In the cohort of Oei et al. [33], median time to reach 80% saturation was 6 min for those <29 weeks of GA. Recently, Padilla-Sánchez et al. [35] demonstrated a significantly reduced time after birth to reach a target SpO2 of 80% in vaginally born healthy term infants with delayed cord clamping ≥60 s. Therefore, the time to reach a target SpO2 of 80% is dependent on several factors in addition to disease severity, such as GA, gender, CPAP or not, and early versus delayed cord clamping, however early bonding did not play a significant role [36]. In some, but not all, studies, mode of delivery played a role with faster increase after vaginal delivery versus cesarean section.

Significance of Heart Rate and SpO2 in the First Minutes of Life

Oei et al. [32] found in their cohort that bradycardia at 5 min was associated with increased risk of death (OR 4.6; 95% CI 1.62–13.98). Kapadia et al. [37] demonstrated in the same cohort that bradycardia (heart rate <100 bpm) was associated with adverse outcomes. During the first 5 min of life, mortality increased fairly linearly with duration of bradycardia being 5% after 1 min and 30% if bradycardia had lasted 6 min or more. Prolonged bradycardia (heart rate <100 bpm for 2 min or more) increased the risk of death before discharge (OR 3.79; 95% CI 1.55–9.28). When prolonged bradycardia was combined with an SpO2 <80% in the first 5 min of life, risk of death before discharge increased dramatically (OR 18.6; 95% CI 4.3–79.7).

High or Low Initial FiO2?

Data we have accumulated so far strongly indicate a better outcome in newborn infants <32 weeks of GA if their pre-ductal SpO2 reaches 80% or more within the first 5 min of life. Recent data from the study of Binder-Heschl et al. [38] demonstrated that FiO2 is not significantly different during the first 2–3 min of life between those reaching and those not reaching SpO2 of 80% within the first 5 min of life. In addition, SpO2 is not clinically significantly different between these 2 groups at 2 min of age [38]. This means there is a very short window, if any, in time to adjust FiO2. In the clinical setting, therefore, it might be impossible in the first 2–4 min after birth to identify those who are not going to reach the saturation target. Therefore, in order to ensure this target is reached, there have been suggestions that starting with higher FiO2, for example, 0.9 or even 1.0 and titrating FiO2 down according to development of SpO2, instead of starting low (e.g., FiO2 of 0.3) and titrating FiO2 up, may be better for reaching SpO2 targets [39].

Dekker et al. [40] randomized infants between 24 and 30 weeks of GA needing PPV in the delivery room to 30 or 100% oxygen. FiO2 was adjusted by 0.1 up or down every 30 s to keep SpO2 between the 25th and 90th percentiles of the Dawson curves [16].

Not surprisingly, the low group had less exposure to oxygen in the first 5 min of life. The group that started low had lower minute volume and longer duration of mask ventilation compared to the group started high. Further, they had a longer duration of hypoxemia and lower SpO2 at 5 min of age. There was, however, no difference in duration of hyperoxemia or oxidative stress markers, measured at 24 h. SpO2 at 5 min of age was 92% in the high versus 76% in the low FiO2 group. These authors, therefore, argued that it might be better to start high and titrate FiO2 down instead of starting low and titrating up [40].

However, in the study of Dekker et al. [40], mean SpO2 in the FiO2 group of 0.3 was substantially lower than that in the similar group in the cohort of Oei et al. [32], espe-
cially in the first 4 min of life. For instance, at 2 min of age, mean SpO₂ was 38% in the study of Dekker et al. [40] versus 57% in the data of Oei et al. [32] (Fig. 1). Further, during the first 3 min of life, SpO₂ values in the FiO₂ group of 1.0 in the study of Dekker et al. [40] were very similar to those in the FiO₂ group of 0.3 described by Oei et al. [32], 69 versus 64% (Fig. 1). This indicates that how FiO₂ is titrated might be as important for development of SpO₂ as initial FiO₂.

**Discussion**

In recent years, a significant body of knowledge has accumulated to inform the best strategy to achieve stable pulse oximetry and to reach target SpO₂ in the first few minutes of life. However, the optimal initial FiO₂ for preterm newborn infants needing PPV in the delivery room, especially those of GA <29 weeks, and the best way to titrate FiO₂, remains unknown.

It seems that those very preterm infants who do not reach an SpO₂ of 80% within 5 min have worse outcomes compared with those who attain 80% or higher. They are more likely to have severe intraventricular hemorrhage and higher mortality, although at least part of this is due to a lower GA and birth weight. Almost half of this population does not reach an SpO₂ target of 80% within 5 min. In fact, only 12% of the cohort was within a target of 80–85% within 5 min of age. In addition, follow-up studies suggest an association between a lower cognitive score and slower increase of SpO₂. We do not know if lower SpO₂ is detrimental per se or whether a slower development of SpO₂ is due to underlying illness or less maturity.

However, based on the present data, we strongly recommend that efforts be made to adjust FiO₂ to target SpO₂ of at least 80% within 5 min of life in very preterm and immature infants. We suggest an upper target of 85%.

How this should be reached is a matter of discussion. Data for GA between 29 and 32 weeks indicate that an initial FiO₂ between 0.21 and 0.30 is acceptable; however, more data are needed. Even for late preterm infants between 32 and 36 weeks of GA, more data on initial FiO₂ are needed.

Dekker et al. [40] suggest starting with a high initial FiO₂ of 1.0 and titrating down. They found a higher minute volume and reduced need for mask ventilation when compared to an initial FiO₂ of 0.3. However, when examining the data of Dekker et al. [40], it is clear that the group started with initial FiO₂ 0.3 had substantially lower SpO₂ than the similar group in the study published by Oei et al. [32] In fact, the FiO₂ group 0.3 in the study of Oei et al. [32] had almost identical SpO₂ levels as the high initial FiO₂ group in the study of Dekker et al. [40] in the first few minutes of life. It, therefore, seems that how adjustments of oxygen are performed during the first 10 min of life may be as important as which initial FiO₂ is chosen. Dekker et al. [40] did not find differences in oxidative stress between the low and high FiO₂ groups, in contrast to data from Vento et al. [25] and Tataranno et al. [26]. The duration of follow-up by Dekker et al. [40] was also considerably shorter compared to Vento et al. [25], who found increased oxidative stress a week after birth in infants <29 weeks of GA started with an FiO₂ of 0.9 versus 0.3.

Previous clinical and experimental data demonstrated that even a brief exposure to hyperoxia in the first minutes after birth may lead to detrimental outcomes, but this may be in infants without significant lung pathology, such as more mature infants. We, therefore, do not recommend an initial FiO₂ above 0.30 for immature infants. Still, we have to admit at the present stage that we do not know the optimal initial FiO₂ for such babies needing PPV. Some of them may benefit from starting higher than FiO₂ of 0.3, perhaps it should be 0.4 or even higher. We need more studies to examine this important issue [39].

The combination of bradycardia and low and slow increase of SpO₂ seems to aggravate the risk of poor outcome. Death before discharge is increased in babies with prolonged bradycardia (2 min or more) during the first minutes of life.

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**Fig. 1.** Development of SpO₂ in the first 10 min of life in 2 different cohorts of immature infants. Initial FiO₂ was 0.3 versus 0.9–1.0 or 1.0. Data are from Oei et al. [32] and Dekker et al. [40].
The data summarized in this article illustrate the importance of stabilizing immature newborn infants within the first 5 min of life. SpO₂ should be targeted to at least 80% by 5 min by adjusting FiO₂ and efforts should be made to increase heart rate to >100 bpm as rapidly as possible. To avoid oxidative stress, and before further information is available, we recommend starting respiratory support of preterm infants <30 weeks of GA with FiO₂ of 0.30 and titrating to aim for SpO₂ for instance as described by data from Oei et al, or perhaps even somewhat faster (see Fig. 1).

**Conclusion**

Based on data, first of all from the To2rpido trial, we do not recommend an initial FiO₂ of <0.3 for infants below 29 weeks of GA needing PPV in the delivery room. For infants between 29 and 32 weeks of GA in our opinion, data at this stage do not clearly demonstrate whether to start with air or 30% O₂. Our data indicate that FiO₂ of 0.3 better fits with the recommended targets than FiO₂ of 0.21. For newborn infants above 31 weeks of GA, PPV should be initiated with air. However, infants with pulmonary disease may need higher FiO₂. We, therefore, recommend that regardless of GA, FiO₂ should be adjusted according to pulse oximetry readings, provided a pulse oximeter is available in the delivery room [41]. Currently, the Dawson curves represent the best available data. However, we need more data to stratify curves for SpO₂ targets according to GAs. By combining strict control of development of SpO₂ during the first 10 min of life combined with a heart rate >100 bpm, we have the best tool today to achieve the most optimal outcome of very preterm and immature newborn infants.

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**Conflict of Interest Statement**

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**Author Contributions**

O.D.S., V.K., and J.O. contributed substantially to the conception and design of the work, interpretation of data for the work, drafting the work, and revising it critically for important intellectual content. All authors approved the final version and are accountable for all aspects of the work.

**References**

1. Vali P, Underwood M, Lakshminrusimha S. Hemoglobin oxygen saturation targets in the neonatal intensive care unit: is there a light at the end of the tunnel? *Can J Physiol Pharmacol*. 2019;97:174–82.
2. Perez M, Robbins ME, Revhaug C, Saugstad OD. Oxygen radical disease in the newborn, revisited: oxidative stress and disease in the newborn period. *Free Radic Biol Med*. 2019;142(142):61–72.
3. Saugstad OD, Gluck L. Plasma hypoxanthine levels in newborn infants: a specific indicator of hypoxia. *J Perinat Med*. 1982;10(6):266–72.
4. Clyman RI, Saugstad OD, Mauray F. Reactive oxygen metabolites relax the lamb ductus arteriosus by stimulating prostaglandin production. *Circ Res*. 1989;64(4):1–8.
5. Campbell K. Intensive oxygen therapy as a possible cause of retrolental fibroplasia; a clinical approach. *Med J Aust*. 1951;2(2):48–50.
6. Saugstad OD, Rootwel T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. *Pediatrics*. 1998;102(102):e1.
7. Tan A, Schulze A, O’Donnell CP, Davis PG. Air versus oxygen for resuscitation of infants at birth. *Cochrane Database Syst Rev*. 2005;2005(2):CD002273.
8. Saugstad OD, Ramji S, Soll RF, Vento M. Resuscitation of newborn infants with 21% or 100% oxygen: an updated systematic review and meta-analysis. *Neonatology*. 2008;94(94):176–82.
9. Harris AP, Sendak MJ, Donham RT. Pulse oximetry in newborn infants in the delivery room. *J Pediatr*. 1986;109:117–9.
10. House JT, Schultetus RR, Gravenstein N. Continuous neonatal evaluation in the delivery room by pulse oximetry. *J Clin Monit*. 1987;3(3):96–100.
11. Dimich I, Singh PP, Adell A, Hendler M, Sonnenklar N, Jhaveri M. Evaluation of oxygen saturation monitoring by pulse oximetry in neonates in the delivery system. *Can J Anaesthes*. 1991;38(8):985–8.
12. Toth B, Becker A, Seelbach-Göbel B. Oxygen saturation in healthy newborn infants immediately after birth measured by pulse oximetry. *Arch Gynecol Obstet*. 2002;266(266):105–7.
13. Rabi Y, Yee W, Chen SY, Singhal N. Oxygen saturation trends immediately after birth. *J Pediatr*. 2006;148(5):590–4.
14. Kamlin CO, O’Donnell CP, Davis PG, Morley CJ. Oxygen saturation in healthy infants immediately after birth. *J Pediatr*. 2006;148(148):585–9.
15. Rao R, Ramji S. Pulse oximetry in asphyxiated newborns in the delivery room. *Indian Pediatr*. 2001;38(7):762–6.
