Optimizing Oxygenation of the Extremely Premature Infant during the First Few Minutes of Life: Start Low or High?

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One of the burning questions in contemporary neonatology is how to oxygenate preterm infants, especially the extremely preterm ones (<30 weeks of gestational age at birth) and in the first minutes of life. For term and near-term infants in need of stabilization/resuscitation at birth, there is agreement to start with air and titrate the inspired fraction of oxygen (FiO_2) according to the development of oxygen saturation (SpO_2) compared with the Dawson reference range curves, with the aim of reaching an SpO_2 of 80%-85%, corresponding to the 25th-50th percentiles of the Dawson reference range curves at 5 minutes of age.[1,2]

However, recent observations in extremely preterm infants have raised questions regarding optimal oxygenation of these infants. Ten years ago, randomized studies by Escrig et al[3] and Vento et al[4] showed that extremely preterm infants could be satisfactorily stabilized using 0.3 as the initial FiO_2. No differences in SpO_2 or heart rate were evident in the first 10 minutes when compared with infants initially stabilized with an FiO_2 of 0.9. Concomitantly, Wang et al launched a study with preterm infants randomized to an FiO_2 of 0.21 or 1.0 as needed in conjunction with artificial ventilation.[5] Infants who initially received room air had prolonged bradycardia and lower SpO_2 in the first 3-5 minutes after birth, and a significant number were switched to pure oxygen.

Recently, the TORPIDO study randomized infants <32 weeks of gestational age to air or 100% O_2.[6] For the entire study cohort, there was no difference in morbidity or mortality between the 2 groups; however, in a post hoc analysis, infants <28 weeks of gestational age had an almost 4-fold increased risk for mortality if initially started with air compared with 100% O_2 (relative risk, 3.9; 95% CI, 1.1-13.4).[6] In sharp contrast, in 2 blinded randomized trials comparing an initial FiO_2 of 0.3 vs 0.60 or 0.65, a tendency toward an increased survival rate was found in the group with the lower initial FiO_2.[4,7]

Further studies have shown that preterm infants <32 weeks of gestational age who did not achieve an SpO_2 of 80% within 5 minutes after birth independent of the initial FiO_2 had higher mortality, more severe intraventricular hemorrhage, and poorer neurodevelopmental outcome compared with those who achieved this SpO_2 level.[8] For this reason, aiming for an SpO_2 of 80%-85% within 5 minutes of life is recommended. But how should FiO_2 be initiated and titrated to achieve this aim? It has been shown that there is no difference in SpO_2 the first 2-3 minutes of life between infants who reach and those who do not reach an SpO_2 of ≥80% at 5 minutes of life.[9] This indicates that the window of opportunity to adjust FiO_2 to reach the 5-minute SpO_2 target of 80% is very limited. The reported optimal magnitude (ie, O_2 concentration as percentage) and frequency (ie, time in seconds when FiO_2 is changed in response to SpO_2 outside the target range) have varied among studies and needs further investigation. In addition, the optimal procedure for oxygen titration is not based on evidence.

Hypoxemia induces respiratory depression in preterm infants. Experimental studies in rabbits have shown that hypoxemia promotes glottis closure, and it has been hypothesized that this could also be the case in preterm infants.[10] It has been argued that because of the brief window of opportunity mentioned above, it may be better to start with an initial high FiO_2 and titrate down. However, in our view, more evidence from large, multicenter randomized trials is needed before any change in practice is widely implemented.

Figure 1 outlines the principles of oxygen supplementation during resuscitation as follows: (1) optimize ventilation of the lungs and establish functional residual capacity (to achieve this goal, adequate pressure may be needed to optimize lung liquid clearance and surfactant release); (2) promote glottic opening to maintain patency of the upper airway; (3) prevent hypoxic cerebral depression and stimulate spontaneous respiration; (4) promote pulmonary vasodilation, commonly associated with a change point of approximately 86% ± 10% SpO_2 in preterm animal models[11]; (5) achieve the target preductal SpO_2 of >80% and heart rate of >100 bpm by 5 minutes; and (6) avoid oxidative stress–induced injury.

Dekker et al randomized preterm infants <30 weeks of gestation to be stabilized at birth with either 30% or 100% oxygen (**Figure 2**) based on the Dawson curves.[1,12] When the initial FiO_2 setting was 0.3 and the SpO_2 was below the 25th percentile, the FiO_2 was titrated up to 0.5 and subsequently to 1.0. If the SpO_2 exceeded 90% with this initial setting, the FiO_2 was titrated down to 0.21 directly. When the initial FiO_2 setting was 1.0 and the SpO_2 exceeded 90%, the FiO_2 was titrated down to 0.5 and subsequently to 0.3 and 0.21. SpO_2 values were monitored

FiO_2	Fraction of inspired oxygen
SpO_2	Oxygen saturation

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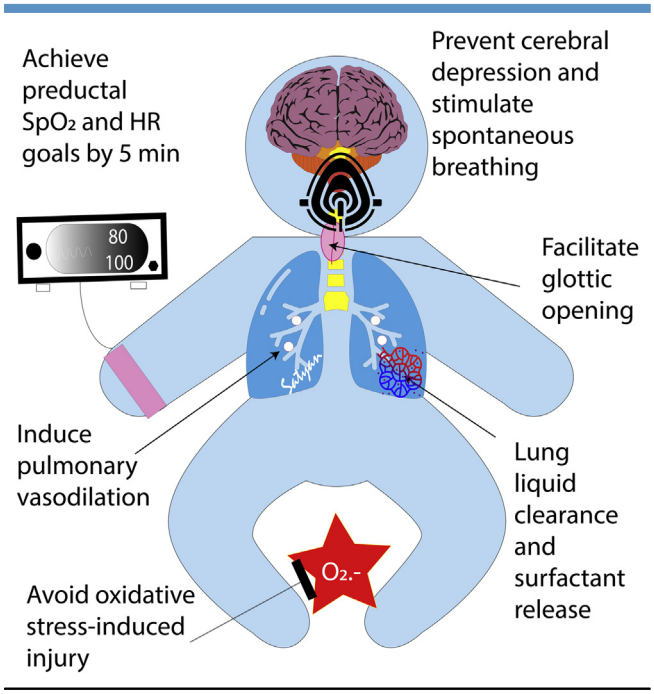

Figure 1. Principles of oxygen supplementation during resuscitation in extremely preterm infants. Stimulation of spontaneous breathing, glottic opening, establishment of functional residual capacity, and pulmonary vasodilation are crucial to achieve optimal oxygenation and heart rate. Simultaneously, oxidative stress–induced injury should be minimized. Copyright Satyan Lakshminrusimha. *HR*, heart rate.

continuously, and when values were outside the range, FiO_2 was titrated every 30 seconds. Cord clamping was performed after 30 seconds in infants with apnea and after 60 seconds in breathing infants. Respiratory support was provided using a T-piece resuscitator (Neopuff; Fisher & Paykel Healthcare, Auckland, New Zealand).

Out of 109 eligible infants, 26 infants were randomized to the 30% O_2 group and 24 were randomized to the 100% O_2 group. Six infants were excluded from the analysis owing to a lack of physiological measurements, leaving 44 infants for analysis. The mean birth weight was 931 ± 256 g in the 30% O_2 group and 992 ± 309 g in the 100% O_2 group. Only 52% of the infants in both groups received a full course of antenatal steroids.

The primary outcome of average minute volume in the first 5 minutes after birth was significantly higher in the 100% O_2 group compared with the 30% O_2 group (mean, 146.34 ± 112.68 mL/kg/minute vs 74.43 ± 52.19 mL/kg/min; $P = .014$). Average tidal volume was also significantly higher in the 100% O_2 group (4.8 ± 3.8 mL/kg vs 3.8 ± 3.7 mL/kg; $P = .006$), and the median duration of mask ventilation in the first 10 minutes after birth was shorter (23.6 seconds [range, 0-122.2 seconds] vs 108.3 seconds [range, 46.4-205.1 seconds]; $P = .021$).

Median SpO_2 in the first 5 minutes after birth was significantly higher in the 100% O_2 group (85% [range, 64%-93%] vs 58% [range, 46%-67%]; $P < .001$). In the first 5 minutes, infants in the 100% O_2 group had a significantly higher percentage of SpO_2 between 90% and 95%, whereas at 5-10 minutes after birth, there was no significant difference between the groups. An SpO_2 of 80% was reached more than 1 minute earlier in the 100% O_2 group (mean, 178 ± 70 seconds vs 261 ± 80 seconds after birth) and less time was spent with an SpO_2 <25th percentile of the reference ranges described by Dawson et al (median, 73 seconds [range, 0-189 seconds] vs 158 seconds [range, 116-184 seconds]; $P = .018$).[1]

Dekker et al report that initiating ventilation with 100% O_2 followed by careful oxygen titration led to a shorter period of hypoxemia without a longer duration of hyperoxemia. Importantly, the total oxygen load (described as the area under the curve for FiO_2) was not significantly different between the groups, and oxidative stress, as assessed by the level of 8-iso-prostaglandin F2α in cord blood and in blood at 1 and 24 hours of age, did not differ between the groups (**Figure 2**). Even though the number of patients was small, the rates of intubation (only 2 infants in the 30% oxygen group needed intubation in the delivery room), intraventricular hemorrhage grade ≥III, or death before hospital discharge did not significantly differ between the 2 groups.[12]

Based on these data, Dekker et al suggest "that oxygenation might be an important determinant in stimulating breathing and decreasing the need for positive-pressure ventilation," and argue that it is best to start with a brief pulse of high oxygen and titrate down, with the goal of avoiding any hypoxemia in the first minutes after birth. They also state that hyperoxia should be avoided during resuscitation of extremely preterm infants.[12]

We agree with Dekker et al that we currently do not know the optimal initial FiO_2 for immature infants, but we question whether this means that an FiO_2 of 1.0 should always be used instead of the recommended 0.3, and we believe that the data are insufficient to support such a conclusion. The study included a small population of selected infants, did not report separate data for those infants born at 24-26 weeks of gestation vs 27-29 weeks as stratified during allocation, and did not include neurodevelopmental outcomes.

We believe there are several arguments against beginning resuscitation with an FiO_2 of 1.0 and titrating down according to the Dawson SpO_2 curves. First, we do not know the optimal evolution of SpO_2 during the first few minutes after birth in extremely preterm infants. The Dawson curves are based mostly on term infants. We do not know whether the 25th percentile of Dawson curves represents a cutoff of hypoxemia in extremely preterm infants with respiratory depression or in spontaneously breathing preterm infants. Dekker et al argue that the total amount of oxygen exposure may even be less if resuscitation is initiated with higher FiO_2. Although this might be true, we do not know which is more detrimental—the total amount of oxygen exposure or the peak oxygen concentration.[4] Dekker et al measured oxidative stress only for the first 24 hours; however, even a brief (minutes) hyperoxic exposure immediately after birth has been shown to trigger increased oxidative and

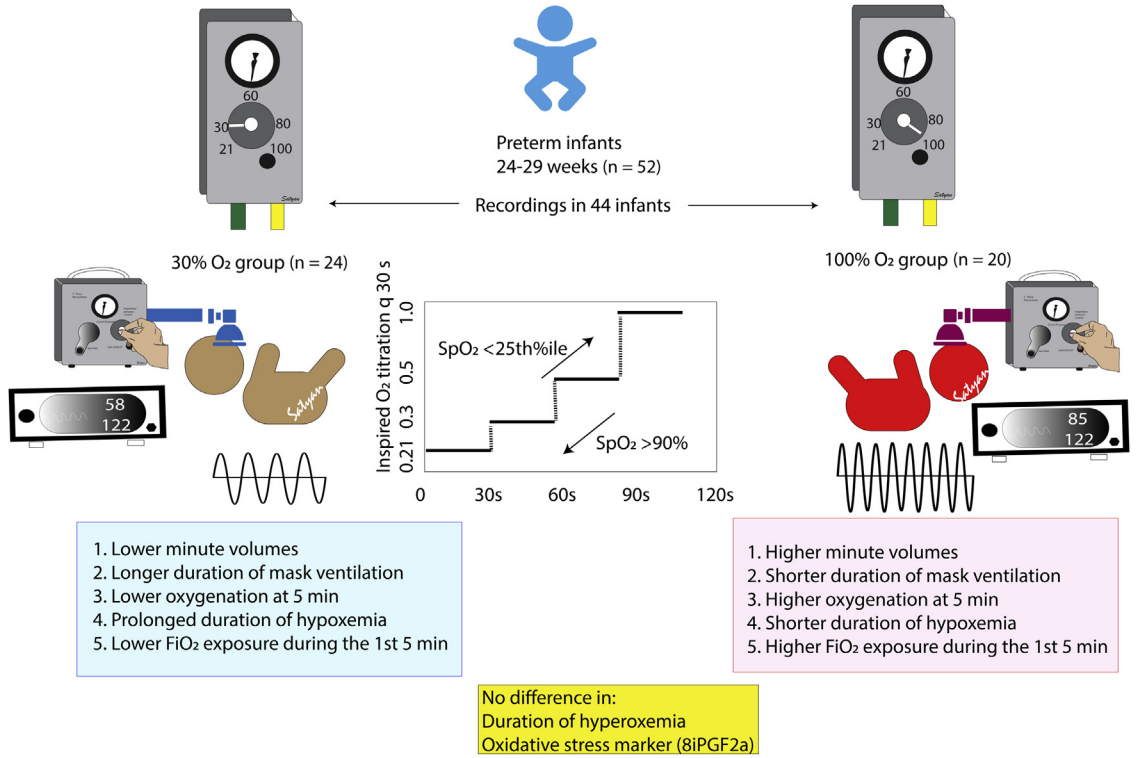

Figure 2. Graphic abstract of the study by Dekker et al on the effect of initial high vs low FiO_2 on breathing effort in preterm infants at birth. Copyright Satyan Lakshminrusimha.

inflammatory stress for at least several weeks.[4] In newborn hypoxic piglets, 30 minutes of exposure to 100% O_2 compared with 21% O_2 resulted in increased oxidative biomarkers of damage to proteins and DNA, peroxynitrite, fragmentation of hyaluronic acid, inflammation, and tumor necrosis factor-α and interleukin-1β expression in the lung.[13] It is known that hyperoxia may induce damage to cellular structures, impairment of oxidative phosphorylation and thus also of adenosine triphosphate production, increased inflammation and apoptosis for days or weeks, down-regulation of DNA protection and repair, and alterations in cell growth.[14-18] Moreover, from a practical standpoint, titration in the delivery room is difficult, especially in emergency situations, and achievement of the desired FiO_2 can be significantly delayed compared with titration in a strictly controlled research setting.[9,19] Thus, preterm infants started with a high FiO_2 would be at risk of receiving a higher oxygen load for a longer than desirable period.

So, which factors are most important, and how do we find a balance between these arguments? At a minimum, we need large randomized studies of contemporary populations of immature newborn infants. Several developments in the last decade have added complexity to the interpretation of previous randomized studies evaluating optimal oxygenation in preterm infants. Routine resuscitation of extremely preterm infants <24 weeks of gestational age, delayed cord clamping, and ventilation with an intact cord emphasize the need for new randomized trials evaluating initial oxygen concentration in extremely preterm infants. In addition, there is a need to precisely compare a wider range of initial FiO_2 settings at 0.21, 0.30, 0.40, and perhaps 0.60 to define the optimal initial FiO_2 in infants <32 weeks of gestational age. We need to determine the optimal development of SpO_2 over the first minutes after birth for very preterm infants and identify how to titrate oxygen to reach this target. Until such data are available, we do not recommend starting with an FiO_2 of 1.0 and titrating down, especially because the potential long-term adverse effects of such a practice are presently unknown. From the experience gathered with more than 500 infants monitored minute by minute in the first 10 minutes after birth, infants <26 weeks of gestation receiving noninvasive positive pressure ventilation need a higher initial FiO_2 than the recommended 0.30 to achieve an SpO_2 >80% and a heart rate >100 bpm within 5 minutes (**Figure 3**).[20] The aggressiveness of oxygen titration also may be influenced by the presence of bradycardia and the trend in heart rate. A steadily increasing heart rate >100 bpm may warrant a less dramatic titration of FiO_2, especially if the SpO_2 is close (within 5%) of the target range.

We acknowledge that our recommendations are also not completely supported by current evidence. More multicenter, randomized trials evaluating initial FiO_2, optimal SpO_2 targets, and the magnitude and frequency of FiO_2 titration during resuscitation of extremely preterm infants are warranted, and these should include long-term outcomes. Except for these situations in extremely preterm infants, we

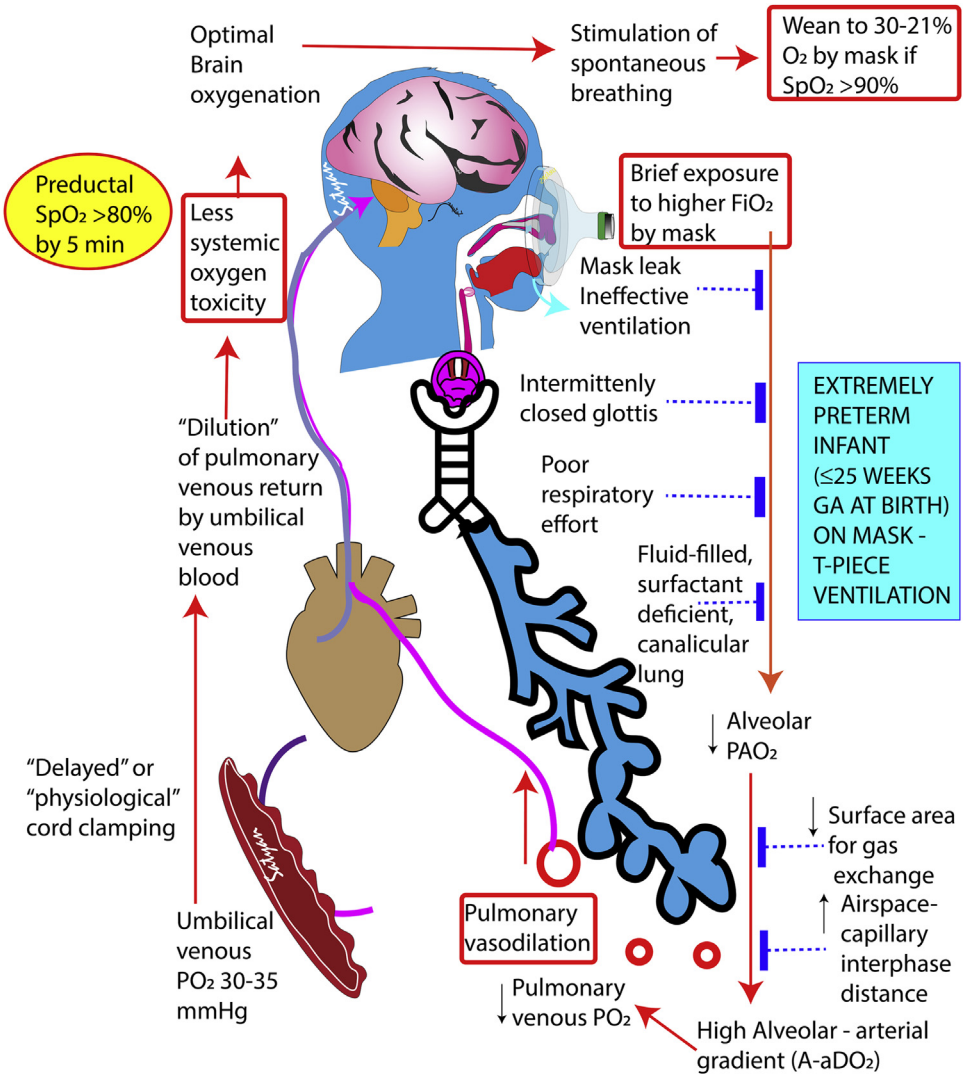

Figure 3. Potential effects of brief use of higher FiO_2 in the delivery room during mask and T-piece resuscitation of extremely preterm infants ≤25 weeks of gestational age at birth. Such factors as mask leak, intermittent glottic closure, lung liquid, and an immature surfactant-deficient canalicular lung reduce alveolar PAO_2. Reduced surface area for gas exchange and increased distance of the air space–capillary interphase increase the alveolar-arterial oxygen gradient (A-a DO_2) and reduce pulmonary venous PO_2. Persistent right-to-left shunts at the oval foramen and ductus arteriosus and also "dilution" by umbilical venous blood during delayed or physiological cord clamping further decrease PAO_2 and SpO_2. Once adequate oxygenation is achieved, inspired oxygen can be weaned and titrated to the desired SpO_2. Copyright Satyan Lakshminrusimha. *PaO_2*, arterial oxygen tension; *PO_2*, oxygen tension.

suggest following international guidelines recommending an initial FiO_2 of 0.21-0.30 for infants 28-31 weeks of gestational age, with the use of pulse oximetry to guide subsequent FiO_2 adjustments up or down. For infants <32 weeks of gestation, an SpO_2 of 80%-85% and a heart rate >100 bpm should be achieved within 5 minutes.[20] ■

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