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Oxygen Targeting in Extremely Low Birth Weight Infants

James J. Cummings, MD, FAAP, Richard A. Polin, MD, FAAP, COMMITTEE ON FETUS AND NEWBORN

abstract

The use of supplemental oxygen plays a vital role in the care of the critically ill preterm infant, but the unrestricted use of oxygen can lead to unintended harms, such as chronic lung disease and retinopathy of prematurity. An overly restricted use of supplemental oxygen may have adverse effects as well. Ideally, continuous monitoring of tissue and cellular oxygen delivery would allow clinicians to better titrate the use of supplemental oxygen, but such monitoring is not currently feasible in the clinical setting. The introduction of pulse oximetry has greatly aided the clinician by providing a relatively easy and continuous estimate of arterial oxygen saturation, but pulse oximetry has several practical, technical, and physiologic limitations. Recent randomized clinical trials comparing different pulse oximetry targets have been conducted to better inform the practice of supplemental oxygen use. This clinical report discusses the benefits and limitations of pulse oximetry for assessing oxygenation, summarizes randomized clinical trials of oxygen saturation targeting, and addresses implications for practice.

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INTRODUCTION

The discovery of oxygen is attributed to Polish scientist Michal Sędziwój in 1604, and a series of observations by John Mayow, Carl Wilhelm Scheele, and Joseph Priestley established the necessity of oxygen for life. In the early 1940s, Wilson et al[1] demonstrated that the use of 70% oxygen reduced periodic breathing in preterm infants. In 1949, investigators studying breathing irregularities in newborn infants recommended using 40% to 50% oxygen for all preterm infants immediately after birth for as long as 1 month.[2]

In 1951, two physicians, Kate Campbell in Melbourne, Australia, and Mary Crosse in Birmingham, England, suggested that unrestricted use of oxygen was associated with an increased risk of retrolental fibroplasia (now called retinopathy of prematurity [ROP]).[3,4] Several small clinical studies during the next few years confirmed this suggestion and recommended restricted use of supplemental oxygen.[5–9] In those studies, there was a trend toward increased mortality in the oxygen-restricted

infants, although it did not reach statistical significance.[5–7,9] Therefore, restricted oxygen use in preterm infants gained general acceptance, despite estimates of 16 additional deaths for every case of blindness prevented.[10]

Because measurement of arterial oxygen tension was not yet feasible clinically, none of the earlier studies of oxygen supplementation and ROP were able to correlate measures of blood or tissue oxygenation with increased risk of ROP. In 1977, a large, 5-center, prospective observational study could not demonstrate a correlation between high partial pressure of oxygen in arterial blood (Pao_2) and ROP but did find a strong association of ROP with cumulative supplemental oxygen exposure.[11] In 1987, a small randomized study of transcutaneous oxygen monitoring in infants with a birth weight <1300 g found a significantly lower rate of ROP in infants who were managed with continuous oxygenation measures versus standard intermittent oxygenation assessment.[12]

In the ensuing decades, numerous observational studies have indicated that the incidence of ROP and bronchopulmonary dysplasia could be reduced by restricted use of oxygen. In 2007, the *Guidelines for Perinatal Care* recommended an oxygen saturation range of 85% to 95%.[13] Recently completed randomized trials using nearly identical trial designs have now provided additional evidence regarding the effects of varying saturation targets in the NICU. The present clinical report discusses the benefits and limitations of pulse oximetry for assessing oxygenation, summarizes randomized clinical trials of oxygen saturation targeting, and addresses implications for practice.

PULSE OXIMETRY: ITS USES AND LIMITATIONS IN MONITORING OXYGEN DELIVERY

Principles of Pulse Oximetry

Pulse oximeters measure the differential absorption of red and infrared light by oxyhemoglobin and deoxyhemoglobin. In neonates and young infants, light is transmitted through a distal extremity and sensed by a detector placed on the opposite side of the extremity. Pulsatile blood flow results in fluctuations in blood volume, thereby changing the distance the light has to travel. Detecting this variable component of light transmission allows pulse oximeters to eliminate signals attributable to nonarterial blood elements, such as venous blood, skin, connective tissue, muscle, and bone, directly measuring the relative amounts of oxyhemoglobin and deoxyhemoglobin in arterial blood and reporting saturation (Spo_2).

Limitations of Pulse Oximetry for Monitoring Tissue Oxygenation

Device Limitations

Accuracy. The accuracy of pulse oximetry is determined by comparison of Spo_2 with the measured saturation of arterial blood (Sao_2). Most manufacturers report an SD of the difference between Spo_2 and actual Sao_2 of 3 points for neonates. However, because 1 SD on each side of the mean includes approximately 68% of the measurements, nearly one-third of the measurements will fall outside that range. For example, an Spo_2 reading of 88% could reflect an actual Sao_2 between 85% and 91% in 68% of infants but may fall outside a range of 82% to 94% in up to 5% of infants.

The accuracy of pulse oximetry also depends on the range of saturations being measured. Reports of increased inaccuracy at the lower ranges of saturation values commonly encountered in the NICU are of great concern. For oximetry saturation readings in the 85% to 89% range, early studies reported that actual arterial saturations were as much as 10 points lower.[14,15] These findings have been confirmed in the most recently developed devices using signal extraction technology to reduce motion artifact; in 1 study, 39% of oximeter readings in the 85% to 89% range had arterial saturations below that range, with 25% of those readings having an actual Sao_2 <80%.[16] This finding is consistent with a previous observation that using an 85% to 89% Spo_2 range resulted in Pao_2 values much lower than expected.[17] In addition, pulse oximeters are only calibrated down to 80%; saturations below this level are extrapolated and may therefore be subject to even greater error.

Averaging Times. Pulse oximeters do not give instantaneous readings of Spo_2 because aberrant signals can make the device response erratic. Modern devices use time-averaging (typically, from 2–16 seconds) over several heartbeats to smooth out the displayed readings. In general, longer averaging times result in a more stable value with fewer false alarms; however, longer averaging times are also less sensitive to brief deviations in saturation outside the targeted range. Longer averaging times not only reduce the detection of desaturations that are either brief (<30 seconds) or marked (<70%) but also overestimate the duration of some detected events by combining 2 or more shorter events.[18,19] Shorter averaging time will detect more events but result in more false alarms. Studies have not been able to demonstrate that averaging times alter the amount of time actually spent outside targeted ranges. However, a particular concern is the potential for delayed detection of hypoxemic events.

Pulse Oximeter Algorithms. Pulse oximeters do not measure oxygen saturation directly but derive

Spo_2 from an internal reference table generated from empirical measurements of Sao_2 in healthy adult subjects. No pulse oximeter uses calibration data derived from Sao_2 measurements in critically ill patients or even in well infants. Although the effect of age on pulse oximeter accuracy has not been studied, at least 1 study has shown that in critically ill adult patients, changes in Spo_2 tend to overestimate actual changes in Sao_2, and this discrepancy worsened with decreasing hemoglobin concentrations.[20]

Relationship Between Sao_2 and Pao_2

Oxygen delivery depends on 2 factors: oxygen content of the arterial blood and blood flow. Oxygen content is determined by hemoglobin-oxygen saturation and, to a much lesser extent, by dissolved oxygen; both hemoglobin saturation and dissolved content depend on the prevailing Pao_2. Although the relationship between Sao_2 and Pao_2 is reasonably linear at Sao_2 values <80%, the slope of that relationship changes at Sao_2 levels >80%, resulting in large changes in Pao_2 with small changes in Sao_2. This relationship is even more exaggerated in the presence of hemoglobin F, which shifts the oxyhemoglobin dissociation curve to the left. Given that Spo_2 is, at best, an estimate of Sao_2, Spo_2 measurements become poor predictors of actual Pao_2 levels, particularly when the infant is receiving supplemental oxygen.

Fetal Versus Adult Hemoglobin

Absent a history of intrauterine transfusion, all extremely low birth weight neonates have high concentrations (>95%) of hemoglobin F in their blood. Hemoglobin F has a higher affinity for oxygen than does hemoglobin A and enhances tissue oxygen delivery at lower Sao_2 levels. As the amount of hemoglobin A relative to hemoglobin F increases in the blood (eg, after a red blood cell transfusion), this ability diminishes. Because the absorption spectrum for hemoglobin F is similar to hemoglobin A, there is no effect on the correlation between Spo_2 and Sao_2.

Clinical Variables Affecting Oxygen Saturation Targeting

Few studies have examined ways to best target a specific oxygen saturation range in preterm infants. Manually maintaining oxygen saturation targets in a given range depends on several factors, including: (1) technology (ie, setting Spo_2 alarm limits); (2) personnel (bedside nurses); and (3) the clinical stability of the patient. Although automated, closed-loop systems of oxygen delivery have been developed, they are not approved for clinical use in the United States.[21]

Alarm Limits

Alarm limits must be distinguished from targets. Targets represent the clinical goal, and alarm limits are used to achieve that goal. In clinical practice, alarm limits typically are set at or slightly beyond the target range. Some monitoring systems allow the use of "alerts" or "soft" alarms, which are less disruptive (being either visual, or at a lower volume or frequency) but warn that a parameter is about to reach an alarm limit. In these cases, the alerts are set within the targets, and the alarm limits may be set wider.

From a human engineering perspective, there are 2 problems with the setting of alarm limits. First, the majority of alarms do not require intervention. Most are either false (eg, a displaced probe or electrode) or are so brief that an intervention is not required. Second, the sheer number of alarms that go off in a busy NICU in a single day can total in the thousands, leading to desensitization. Both issues can lead to disregard of alarms, either deliberately or unintentionally; this condition has been termed "alarm fatigue" and is one reason why providers change alarm limits from those ordered. Clucas et al[22] observed that in infants weighing <1500 g, the lower alarm limit was set correctly 91% of the time, but the upper alarm limit was set correctly only 23% of the time. This differential compliance with low versus high alarms could be attributable to an increased tendency for the high alarm limit to be reached, the assumption that hypoxemia is more detrimental than hyperoxemia, and/or the fact that many monitors automatically reset to a high alarm limit of 100% when first turned on.[23]

A balance must be struck between setting alarm limits too narrow (increasing the number of unnecessary alarms) or too wide (decreasing the safety margin for intervention). Studies have shown that matching the alarm limits with the target range is associated with more time spent within the target range.[24,25]

Personnel

In the multicenter COT (Canadian Oxygen Trial), study participants were maintained within the intended Spo_2 range between 68% and 79% of the time. Nurses from one of the centers identified several factors as important in targeting a specific saturation range, including: (1) education; (2) prompt response times; and (3) a favorable nurse-to-patient ratio.[26] Targets in the Canadian trial were achieved significantly more often than in other randomized studies,[25,27] even though those studies also used educational interventions and process algorithms.[24,28] Even in studies in which favorable nurse-to-patient ratios were believed to exist, infants spent 33% to 38% of the time outside their target ranges.[20,25] Maintaining infants in a given target range is an extremely labor-intensive process, as evidenced by studies showing that multiple manual

adjustments per hour only achieved target ranges approximately 50% of the time.[29] Using a fully automated oxygen-controlling system improved targeting by 7% over manual control.[30]

An additional concern is that manual documentation of hyperoxemic and hypoxemic episodes results in significant underreporting of such events.[31,32] Better tracking of saturation targeting can be accomplished by using third-party data extraction technology[33] or by using the histogram feature available on some monitoring equipment.[27,34]

Stability of the Saturation Signal in Clinical Settings

Preterm infants who require respiratory support are at increased risk of straying outside desired oxygen saturation targets, particularly if they are receiving supplemental oxygen. Because these infants often have desaturations during routine care (eg, repositioning, feeding, suctioning), it was once common practice to increase supplemental oxygen just before delivering such care (ie, preoxygenation). Preoxygenation also has been used commonly during intubation or other invasive procedures. Such practices may be harmful.[35] Instead, oxygen saturation values should be monitored closely, with measures to increase oxygenation used only as needed to maintain Spo_2 within the target range.

RANDOMIZED CLINICAL TRIALS OF OXYGEN TARGETING

The optimal saturation range for preterm infants in the NICU has remained elusive for more than 70 years. Although studies performed more than 50 years ago suggested an increased mortality associated with restricted oxygen administration,[36] observational trials performed in the era of continuous Spo_2 monitoring suggest that mortality is unchanged, with target Spo_2 ranges as low as 70%.[37] In addition, data from the Vermont Oxford Network indicate that the incidences of ROP and bronchopulmonary dysplasia are lower when a lower oxygen saturation range is targeted.[38] However, because these were observational studies, no cause-and-effect relationship can be inferred.

The first published randomized controlled trial (RCT) of differential targeting of oxygen saturations was the STOP-ROP (Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity) trial, published in 2000.[39] This study randomized infants to treatment when they reached "prethreshold" ROP, at an average postnatal age of 10 weeks. In this multicenter trial, 649 infants with prethreshold ROP were randomized to a saturation range of 89% to 94% (conventional arm) or 96% to 99% (supplemental arm). Progression to threshold ROP was not significantly different between groups in the total population; however, significant benefit was observed for infants in the high oxygen saturation arm who did not have "plus disease" (abnormal dilation and tortuosity of posterior pole blood vessels). On the negative side, infants in the high-oxygen saturation arm experienced an increased length of supplemental oxygen therapy and more often received diuretics at 50 weeks' postmenstrual age.

A second RCT that randomized infants to treatment at a later postnatal age was the BOOST (Benefits of Oxygen Saturation Targeting) trial (N = 358 infants), which hypothesized that maintaining higher oxygen saturation target ranges (95%–98% vs 93%–96%) would improve growth and neurodevelopmental outcomes.[40] The pulse oximeters in both groups were modified to read a targeted value in the range of 93% to 96%. The study reported no benefit to the higher saturation range but did find, similar to the STOP-ROP trial, that infants in the high-saturation arm had significant increases in length of oxygen therapy, supplemental oxygen at 36 weeks' corrected gestation, and home oxygen.

In 2003, an international meeting of clinical trials experts, statisticians, neonatologists, ophthalmologists, and developmental pediatricians was convened to harmonize the planned RCTs of different target saturation ranges to be able to conduct a prospective individual patient meta-analysis of the data after completion of the follow-up phase of the individual trials (NeOProM [Neonatal Oxygenation Prospective Meta-analysis]).[41] Investigators from all 3 planned studies agreed, including SUPPORT (Surfactant Positive Airway Pressure and Pulse Oximetry Trial), sponsored by the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development; the BOOST-II United Kingdom, Australia, and New Zealand study groups; and the COT trial. Although there were small differences in study design and outcome measures (Table 1), the studies were similar in terms of the population enrolled, methods, interventions tested, and outcomes collected. All studies were masked by the use of pulse oximeters that read 3% above or below the infant's actual saturation value within the 85% to 95% range. Outside the range of study saturation values ($\leq$84% and $\geq$96%), true saturation values were displayed. The primary outcome of the NeOProM study was a composite of death or disability at 18 to 24 months of corrected age. It was estimated that 5000 infants would be needed to detect a 4% difference in the rate of death or disability.[42]

The first of these 3 RCTs to be published was SUPPORT.[43] In this study, infants between $24^{0/7}$ weeks' and $27^{6/7}$ weeks' gestational age

TABLE 1 RCTs of Differing Pulse Oximetry Targets

Study	Primary Outcome	Primary Outcome Results	Other Findings
STOP-ROP[39]	Rate of progression to threshold ROP (89%–94% vs 96%–99%) *N* = 649	No significant differences	• Higher saturation range exhibited worsening of chronic lung disease and longer duration of hospitalization
BOOST[40]	Growth and developmental outcomes (91%–94% vs 95%–98%) *N* = 358	No significant differences	• Higher saturation range required oxygen for a longer period of time, dependence on oxygen at 36 wk postmenstrual age, and need for home oxygen
SUPPORT[43,44]	Death, severe ROP, or both (85%–89% vs 91%–95%) *N* = 1316	No significant differences	• Severe ROP significantly more common in the higher $Sa0_2$ range • Increased mortality in the lower $Sa0_2$ range at 18–22 mo of corrected age • No significant difference in the composite outcome of death or neurodevelopmental impairment at 18–22 mo
BOOST II[45–48]	Death or neurodevelopmental impairment at 18–22 mo of corrected for prematurity (85%–89% vs 91%–95%) *N* = 2448	No significant differences in a pooled analysis of all 3 trials[47] No significant difference in individual trial analyses[46,48] In a post hoc analysis combining 2 of the 3 trials, the primary outcome occurred in 492 (48.1%) of 1022 in the lower target group versus 437 (43.1%) of 1013 in the higher target group (RR, 1.11 [95% CI, 1.01–1.23]; *P* = .023)[46]	• Change in oximeter algorithm during the study • Study stopped before complete enrollment • Severe ROP significantly more common in the higher $Sa0_2$ range • Significantly increased necrotizing enterocolitis at the lower saturation range • Significantly increased mortality at hospital discharge in the lower $Sa0_2$ range with the revised oximeter algorithm
COT[49]	Death before a corrected age of 18 mo or survival with ≥1 of the following: gross motor disability, cognitive or language delay, severe hearing loss, and bilateral blindness (85%–89% vs 91%–95%) *N* = 1201	No significant differences	• Change in oximeter algorithm during the study • No difference in mortality • Targeting the lower saturation range reduced the postmenstrual age at last use of oxygen therapy

COT, Canadian Oxygen Trial; BOOST, Benefits of Oxygen Saturation Targeting; STOP, Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity; SUPPORT, Surfactant Positive Airway Pressure and Pulse Oximetry Trial.

(*N* = 1316) were randomized to the 2 different oxygen saturation ranges (85%–89% or 91%–95%) and also to either CPAP or intubation and surfactant, in a factorial design. Oxygen saturation targeting was initiated within 2 hours of birth. The primary outcome was a composite of severe ROP (defined as the presence of threshold retinopathy, need for surgical intervention, or the use of bevacizumab), death before discharge from the hospital, or both. The oximeters in SUPPORT used an older software algorithm that subsequently was updated for the other RCTs.

The composite primary outcome in SUPPORT did not differ significantly between the lower and the higher oxygen saturation groups (28.3% vs 32.1%; relative risk [RR], 0.90; 95% confidence interval [CI], 0.76–1.06). However, death before discharge from the NICU was significantly different, occurring in 19.9% of infants in the lower oxygen saturation group and 16.2% of infants in the higher oxygen saturation group (RR, 1.27; 95% CI, 1.01–1.60), with a number-needed-to-harm of 27. In contrast, the rate of severe ROP among survivors was 8.6% in the lower saturation group versus 17.9% in the higher saturation group (RR, 0.52 [95% CI, 0.37–0.73]), with a number-needed-to-benefit of 11. At 18 to 22 months of corrected age, death or neurodevelopmental impairment occurred in 30.2% of infants in the lower oxygen saturation group and 27.5% of those in the higher oxygen saturation group (RR, 1.12 [95% CI, 0.94–1.32]).[44] Mortality remained significantly higher in the lower oxygen saturation group (22.1% vs 18.2%; RR, 1.25 [95% CI, 1.00–1.25]). No significant differences were detected in neurodevelopmental impairment, cerebral palsy, or blindness.

The next RCT published was BOOST-II, from the United Kingdom, Australia, and New Zealand.[45] Oxygen saturation targeting began in the first

24 hours of life but not as early as in the SUPPORT study. During these trials, investigators in the United Kingdom found that the standard oximeters (Masimo Corporation, Irvine, California) returned an unexpectedly low number of oxygen saturation values between 87% and 90%. They discovered that there was a shift-up in the oximeter calibration curve that caused values between 87% and 90% to read 1% to 2% higher. A new software algorithm was expected to improve oxygen saturation targeting, although that was not tested. The United Kingdom and Australian investigators began using oximeters with the new software approximately halfway through the trial. However, the New Zealand trial oximeters were not modified, because enrollment had already been completed. Of 2448 infants enrolled in BOOST-II, 1187 (48.5%) were monitored with oximeters incorporating the new software.

Because of the increased mortality in the lower oxygen saturation range in SUPPORT, the BOOST-II Data Safety and Monitoring Board conducted a safety analysis in December 2010.[50] In the 1187 infants monitored with the revised algorithm, those assigned to the lower target range had a significantly increased mortality rate at 36 weeks' gestational age (23.1% vs 15.9%; RR, 1.45 [95% CI, 1.15–1.84]). However, among the entire study population (N = 2448), there was no significant difference. The rate of ROP requiring treatment was reduced in the lower saturation group (10.6% vs 13.5%; RR, 0.79 [95% CI, 0.63–1.00]), and the rate of necrotizing enterocolitis requiring surgery or causing death was increased in that group (10.4% vs 8.0%; RR, 1.32 [95% CI, 1.02–1.68]). The rate of bronchopulmonary dysplasia was unaffected. Although a recent report combining outcomes for 2 of the 3 BOOST-II sites found a significant difference in the composite outcome of death or disability by 2 years of age in a post hoc analysis,[46] a pooled analysis from all 3 BOOST-II sites, as originally planned, showed no significant difference in this outcome between the 2 arms (46.8% in the lower vs 43.4% in the higher saturation group; P = .10).[47]

Two-year outcomes for the COT were published.[49] The primary outcome measure for this study was the rate of death (before 18 months of age) or survival with 1 or more disabilities (gross motor disability, severe hearing loss, bilateral blindness, and cognitive or language delay). Infants were randomly assigned to the lower saturation group or higher saturation group in the first 24 hours of life. Similar to BOOST-II, the calibration software for the oximeter was changed at the midpoint in the study. The number of infants enrolled was 1201, of whom 538 were monitored with oximeters using the new software. There was no difference in the primary composite outcome (51.6% in the lower vs 49.7% in the higher saturation range). Mortality was 16.6% in the 85% to 89% group and 15.3% in the 91% to 95% group. Infants in the lower saturation group had a shorter duration of supplemental oxygen but no changes in any other outcomes. Use of the revised oximeter software had no effect on the primary outcome or mortality.

Saugstad and Aune[51] published a systematic review of the 5 oxygen saturation trials. In total, 4911 infants were enrolled in the studies. At the time of this meta-analysis (in 2014), the composite outcome of death or severe neurosensory disability at 18 to 24 months of age was only available for SUPPORT and COT, and there was no difference in that composite outcome between groups. The RR of mortality using the original software in the BOOST-II and COT trials was 1.04 (95% CI, 0.88–1.22). With the revised software (COT and BOOST-II United Kingdom and Australia), the RR of mortality in the lower saturation arm was 1.41 (95% CI, 1.14–1.74). For all 5 trials (SUPPORT; BOOST-II United Kingdom, Australia, and New Zealand; and COT), the risk of mortality was increased (RR, 1.18 [95% CI, 1.04–1.34]). Severe ROP was significantly reduced in the low saturation group (RR, 0.74 [95% CI, 0.59–0.92]), and the risk of necrotizing enterocolitis was increased (RR, 1.25 [95% CI, 1.05–1.49]). The rates of bronchopulmonary dysplasia, patent ductus arteriosus, and intraventricular hemorrhage grades 2 through 4 were not significantly different.

A more recent systematic review[52] of the 5 oxygen saturation trials concluded that although infants randomly assigned to the more liberal oxygen target ranges had higher survival rates (relative effect, 1.18 [95% CI, 1.03–1.36]) to discharge, the quality of evidence (assessed by using the Grading of Recommendations Assessment, Development and Evaluation approach[53]) for this estimate of effect was low for 1 or more of the following reasons: (1) the pulse oximeter algorithm was modified partway into the study); (2) the distribution of Spo_2 values did not achieve the planned degree of separation (the median Spo_2 in the 85% to 89% groups was >90%); (3) the BOOST-II trials were stopped prematurely on the basis of this outcome; and (4) the COT trial did not report on this outcome explicitly. In addition, although the investigators noted that necrotizing enterocolitis occurred less frequently in the higher saturation arms, there were no significant differences in bronchopulmonary dysplasia, ROP, hearing loss, or death or disability at 24 months of age.[52]

The mechanism(s) by which maintaining lower oxygen saturation levels might increase the risk of death is unclear, as the data from these trials suggest that tissue hypoxia was unlikely to be a factor.[23] In particular, in the SUPPORT trial, the proportion of infants with median oxygen saturations <85% was no different between the low and high saturation groups.[43] Conversely, a post hoc analysis from the SUPPORT trial found a disproportionally higher mortality rate in small-for-gestational-age infants in the lower oxygen saturation target group, suggesting a possible interaction[54]; if this observation can be confirmed in the other oxygen saturation trials, and more importantly in the individual patient analysis, it would suggest that small-for-gestational-age infants may be more vulnerable to lower oxygen saturations.

In the 5 RCTs discussed in this report, the degree to which individual infants may have been harmed or benefited by the oxygen saturation targets to which they were assigned is not clear.[55] Specifically, it would be helpful to know whether an individual infant's outcome correlated with the amount of time he or she spent within, above, or below the target oxygen saturation range. This information is particularly relevant to ROP because avoiding hypoxemic episodes may be as important as avoiding hyperoxemic episodes.[56–59] The preplanned individual patient meta-analysis of these trials (NeOProM) may shed some light on these critical questions.

CONCLUSIONS

Establishing a target range for oxygen saturation in infants of extremely low birth weight has both clinical and practical considerations, and the ideal target range remains an elusive goal. Nevertheless, data from several well-designed RCTs can inform practice. Pending additional data, including the individual patient meta-analysis (NeOProM), the following can be concluded:

1. The ideal physiologic target range for oxygen saturation for infants of extremely low birth weight is likely patient-specific and dynamic and depends on various factors, including gestational age, chronologic age, underlying disease, and transfusion status.
2. The ideal physiologic target range is a compromise among negative outcomes associated with either hyperoxemia (eg, ROP, bronchopulmonary dysplasia) or hypoxemia (eg, necrotizing enterocolitis, cerebral palsy, death). Recent RCTs suggest that a targeted oxygen saturation range of 90% to 95% may be safer than 85% to 89%, at least for some infants. However, the ideal oxygen saturation range for extremely low birth weight infants remains unknown.
3. Alarm limits are used to avoid potentially harmful extremes of hyperoxemia or hypoxemia. Given the limitations of pulse oximetry and the uncertainty that remains regarding the ideal oxygen saturation target range for infants of extremely low birth weight, these alarm limits could be fairly wide. Regardless of the chosen target, an upper alarm limit approximately 95% while the infant remains on supplemental oxygen is reasonable. A lower alarm limit will generally need to extend somewhat below the lower target, as it must take into account practical and clinical considerations, as well as the steepness of the oxygen saturation curve at lower saturations.

LEAD AUTHORS

James J. Cummings, MD, FAAP
Richard A. Polin, MD, FAAP

COMMITTEE ON FETUS AND NEWBORN, 2014–2015

Kristi L. Watterberg, MD, FAAP, Chairperson
Brenda Poindexter, MD, FAAP
James J. Cummings, MD, FAAP
William E. Benitz, MD, FAAP
Eric C. Eichenwald, MD, FAAP
Brenda B. Poindexter, MD, FAAP
Dan L. Stewart, MD, FAAP
Susan W. Aucott, MD, FAAP
Jay P. Goldsmith, MD, FAAP
Karen M. Puopolo, MD, PhD, FAAP
Kasper S. Wang, MD, FAAP

PAST COMMITTEE MEMBERS

Richard A. Polin, MD, FAAP
Waldemar A. Carlo, MD, FAAP

CONSULTANT

Waldemar A. Carlo, MD, FAAP

LIAISONS

Tonse N.K. Raju, MD, DCH, FAAP — *National Institutes of Health*
CAPT Wanda D. Barfield, MD, MPH, FAAP — *Centers for Disease Control and Prevention*
Erin L. Keels, APRN, MS, NNP-BC — *National Association of Neonatal Nurses*
Thierry Lacaze, MD — *Canadian Paediatric Society*
James Goldberg, MD — *American College of Obstetricians and Gynecologists*

STAFF

Jim R. Couto, MA

ABBREVIATIONS

CI: confidence interval
Pao_2: partial pressure of oxygen in arterial blood
ROP: retinopathy of prematurity
RR: relative risk
Sao_2: measured saturation of arterial blood
Spo_2: pulse oxygen saturation

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