

Pulse Oximetry in Very Low Birth Weight Infants



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KEYWORDS

• Oxygen saturation • Neonatal • Resuscitation • Intensive care

KEY POINTS

- During neonatal care, pulse oximetry is readily used to target oxygen saturation (SpO_2) during delivery room resuscitation, in situations associated with an increased risk of hypoxemia, in prevention of hyperoxia, and for screening of congenital heart disease.
- The optimal SpO_2 for very low birth weight infants remains a moving target, because uncertainty still exists as to the most appropriate range.
- Randomized clinical trials have demonstrated that 21% oxygen is as effective as 100% oxygen for resuscitation of term and late preterm infants and is associated with lower mortality.
- Although controversial, for resuscitation of infants less than 32 weeks it is recommended to choose initial inspired oxygen between 30% and 90% and titrate it to achieve the recommended SpO_2 value ranges.
- In the management of preterm infants receiving supplemental oxygen a single target SpO_2 range that minimizes mortality and severe ROP remains undetermined; however, data from clinical trials suggest that use of a higher oxygen saturation target range than previously recommended (eg, 90%–95%) is prudent.

INTRODUCTION

The development of pulse oximetry is arguably one of the most important advances in clinical monitoring during the past three decades. Its introduction in clinical practice has led to a revolutionary advancement in patient assessment and monitoring because it allows for a simple, noninvasive, and reasonably accurate estimation of arterial oxygen saturation. Pulse oximeters have become available for widespread application in neonatal care, and oxygen saturation has even been proposed as the “fifth vital sign.”¹ In neonatal care, pulse oximetry is readily used to target oxygen saturation (SpO_2) during delivery room resuscitation, in situations associated with an increased risk of hypoxemia (eg, during intubation), in prevention of hyperoxia, and

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Clin Perinatol 41 (2014) 1017–1032
<http://dx.doi.org/10.1016/j.clp.2014.08.018>

perinatology.theclinics.com

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for screening of congenital heart disease. Accumulating evidence from large, blinded, randomized, controlled trials in neonates now shows that relatively small differences in SpO_2 target ranges can have a surprisingly strong influence on important clinical outcomes.²⁻⁶ The optimal SpO_2 for very low birth weight (VLBW) infants remains a moving target, because uncertainty still exists as to the most appropriate range. This article describes the historical perspective, physiologic principles, and the use of pulse oximetry in targeting different oxygen ranges at various time-points throughout the neonatal period (at delivery, early weeks, later period) in VLBW infants.

HISTORICAL PERSPECTIVE

The theoretic background for noninvasive assessment of blood oxygenation was set in the early 1900s when it was observed that spectral changes of light absorbance in vivo are related to tissue perfusion.⁷ In the 1930s and 1940s, photo cells permitted German, English, and American physiologists to build ear oximeters with red and infrared light, requiring calibration. In 1940, Squire⁸ reported on a blood-oxygen meter for use on the hand that computed saturation based on changes of red and infrared light transmission caused by pneumatic tissue compression. In 1942, Millikan⁹ coined the word "oximeter" for a portable ear device that read energy absorption in the red and infrared light spectra. Subsequently, Wood¹⁰ used this approach to compute absolute saturation continuously from the ratios of optical density changes with pressure in an ear oximeter by interrupting tissue perfusion. However, all these early oximeters relied either on compression and reperfusion of the measuring site or on the arterialization of capillary blood through heating and thus were inconveniently large, difficult to use, and, most importantly, inaccurate.⁷⁻¹¹ A true revolution in the development of noninvasive oximetry occurred with the work of the Japanese electrical engineer Aoyagi,¹² who was interested in measuring cardiac output noninvasively by dye dilution method using commercially available ear oximetry. He balanced the red and infrared signals to cancel the pulse noise, which prevented measuring the dye washout accurately. He discovered that changes of oxygen saturation voided his pulse cancellation and realized that these pulsatile changes could be used to compute saturation from the ratio of ratios of pulse changes in the red and infrared. His ideas and equations led to the development of the first pulse oximeter in late 1974. Over the next two decades, after the explosive development of technologies in light emission and signal processing, pulse oximeters underwent astonishing improvements and became available for widespread application throughout medical practice.¹¹⁻¹³

PHYSIOLOGIC PRINCIPLES OF PULSE OXIMETRY OPERATION

Conceptually, it is most useful to view the pulse oximeter waveform as measuring the change in blood volume during a cardiac cycle in the region being studied. Pulse oximetry is based on two physical principles: the presence of a pulsatile signal generated by arterial blood (AC component), which is relatively independent of nonpulsatile arterial blood, venous and capillary blood, and other tissues (DC component); and oxyhemoglobin (O_2Hb) and reduced hemoglobin (Hb) have different absorption spectra.¹⁴ Currently available oximeters use sensors placed around a hand or foot with two light-emitting diodes that emit red and infrared light, most commonly at wavelengths of 660 and 940 nm, respectively. Light is detected on the other side using a photo diode. These two wavelengths are used because O_2Hb and Hb have different absorption spectra at these particular wavelengths. In the red region, O_2Hb absorbs less light than Hb, whereas the reverse occurs in the infrared region. Therefore, any change in light absorption should be attributed to the variations of the arterial blood volume

related to the cardiac cycle.^{12,15–17} By obtaining the ratio of light absorption in the red and infrared spectra and then calculating the ratio of these two ratios (ratio of absorption ratios), the SpO₂ can be calculated as follows¹²:

$$\text{SpO}_2 = f(\text{AC}_{\text{red}}/\text{DC}_{\text{red}})/(\text{AC}_{\text{infrared}}/\text{DC}_{\text{infrared}})$$

where, *f* is the calibration constant that is manufacturer specific.

In addition to the digital readout of SpO₂, most pulse oximeters display a photoplethysmogram resulting from surges in arterial blood volume and subsequent increased light absorption that occur with each heartbeat. The peaks in the photoplethysmographic waveform coincide with each heartbeat and are used to generate a pulse rate, and the waveform display can also help clinicians distinguish an artifactual signal from the true signal.

OXYGEN SATURATION TARGETS DURING RESUSCITATION

Michal Sedziwoj (1566–1636), a Polish scientist and alchemist, is credited with the discovery of oxygen. By heating saltpeter, he concluded that air contained a life-giving substance (later shown to be oxygen). More than 170 years later Mayow, Scheele, and Priestly reached a similar conclusion, but none of them realized that the “life-giving” substance was oxygen. Ultimately it was Lavoisier who named the gas “oxygine” and recognized it as an element.¹⁸ Francois Chaussier (1746–1828) began using oxygen for neonatal resuscitation in 1780 and its use quickly spread throughout Europe. After William Little’s description of brain damage following asphyxia, the use of oxygen achieved even greater popularity. The development of the Apgar score further emphasized the importance of an infant’s “pink color” in determining the adequacy of resuscitation. As late as 2000, the American Heart Association (AHA) and the International Liaison Committee on Resuscitation (ILCOR) recommended 100% oxygen for resuscitation.¹⁹ However, over the past 15 years Saugstad and others have questioned the safety of 100% oxygen for neonatal resuscitation.^{20–26} Recent studies indicate that use of high concentrations of oxygen increases free radical production and inflammatory gene expression.^{27,28} Randomized clinical trials in humans have demonstrated that 21% oxygen is as effective as 100% oxygen for resuscitation of term and late preterm infants and is associated with lower mortality.^{21–26,29–31} Other benefits of using 21% oxygen for resuscitation (eg, reduced time to first breath or cry and improved Apgar scores) are controversial.^{21,23,26,29,30,32–34}

The clinical assessment of skin color is an imprecise way to detect cyanosis.³⁵ Furthermore, in healthy newborn infants, cyanosis is commonly observed in the minutes after birth, because the fetal oxyhemoglobin saturation values range between 40% and 50%.³⁶ Continuous pulse oximetry in the delivery room is considered standard of care and recommended by ILCOR/AHA for the following situations: when resuscitation is anticipated, when positive pressure ventilation is used for more than a few breaths, when supplementary oxygen is needed, or when cyanosis is persistent.²⁰ The pulse oximeter probe should be attached to a preductal site (right upper extremity). Studies suggest that data acquisition is quickest if the probe is attached to the infant before the probe is attached to the machine.³⁷ ILCOR guidelines recommend that a pulse oximeter be attached within 60 seconds of birth; however, a recent study by McCarthy and colleagues³⁸ suggested that goal is difficult to achieve even in a highly skilled tertiary facility.

In term and preterm infants who do not require any resuscitation (including oxygen), oxygen saturation values increase slowly following delivery and achieve values greater than 90% by 5 to 8 minutes of life.³⁹ Values in infants delivered vaginally rise more

quickly than those delivered by cesarean section.^{39,40} Dawson and colleagues⁴¹ published normative values for oxygen saturation (10th–97th percentile) in a large number of term and preterm infants (Fig. 1). ILCOR and the AHA recommend an oxygen saturation value in the interquartile range of preductal saturations measured in healthy term babies following vaginal birth at sea level (Fig. 2).³⁷ However, other countries have chosen different saturation targets and there are no data to decide which target is correct.⁴² Preterm infants receiving continuous positive airway pressure (CPAP) achieve reference oxygen values more quickly than spontaneously breathing preterm infants.⁴³ Oxygen saturation targets may be achieved by initiating resuscitation with air or blended oxygen. In term newborn infants, resuscitation should generally be initiated with room air; however, if the infant is still bradycardic (<60/minute) or saturation values do not increase as expected, the concentration of oxygen should be increased to 100%.³⁷ Given that cerebral blood flow is restored more quickly with 100% oxygen in animals with circulatory collapse we recommend that infants who are severely bradycardic or asystolic should receive 100% oxygen until the heart rate is restored.⁴⁴

The choice of an inspired oxygen concentration for resuscitation of infants less than 32 weeks is controversial.^{37,45–47} ILCOR recommends choosing initial inspired oxygen between 30% and 90% and titrating it to achieve the recommended saturation value ranges (see Fig. 2).³⁷ There have been several randomized clinical trials in preterm infants resuscitated with varying concentrations of oxygen. In each of the studies, the initial inspired oxygen concentration was titrated to achieve a predetermined target saturation value. Wang and colleagues⁴⁸ randomized 41 preterm infants (23–32 weeks gestation) to resuscitation with 21% or 100% oxygen. Saturation values remained significantly lower in infants resuscitated with room air than those receiving 100% oxygen. Furthermore, target saturation values could not be achieved by 3 minutes of life in the low inspired oxygen concentration group.⁴⁸ It is noteworthy that there were no significant differences in heart rate by 2 minutes of life. This suggests that cardiac output (and cerebral blood flow) were restored even though the saturation values

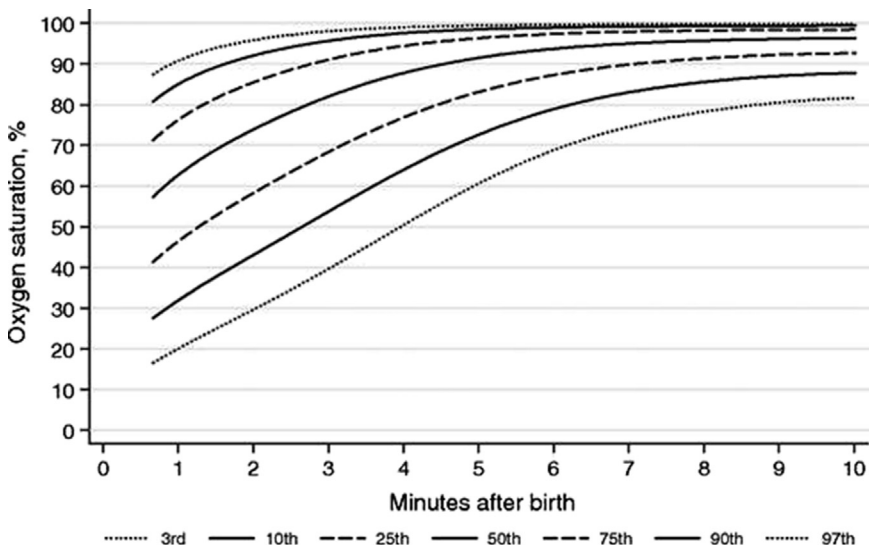


Fig. 1. The 3rd, 10th, 25th, 50th, 75th, 90th, and 97th SpO_2 percentiles for all infants with no medical intervention after birth. (From Dawson JA, Kamlin CO, Vento M, et al. Defining the reference range for oxygen saturation for infants after birth. *Pediatrics* 2010;125:e1344.)

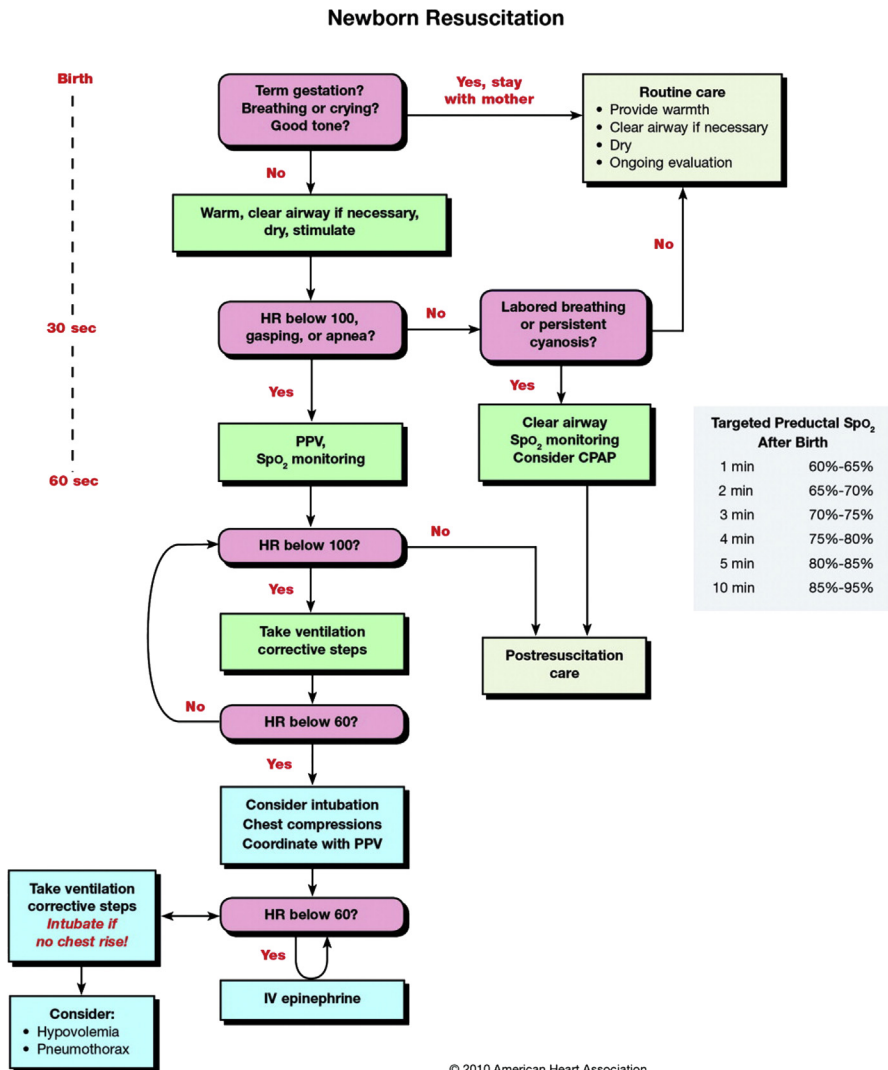


Fig. 2. Newborn resuscitation algorithm. CPAP, continuous positive airway pressure; HR, heart rate; IV, intravenous; PPV, positive pressure ventilation. (From Kattwinkel J, Perlman JM, Aziz K, et al. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010;122:S910; with permission.)

remained depressed. Escrig and colleagues⁴⁵ randomized 42 infants less than or equal to 28-weeks gestation to resuscitation with 30% or 90% oxygen. The target saturation value was 85%. In contrast to the prior study, there were no differences in oxygen saturation values at any time point. However, the probability of being ventilated with room air was significantly greater at 10 and 20 minutes of life in infants initially resuscitated with 30% oxygen.

Although the benefits of room-air resuscitation on mortality are clear, few studies have assessed the effect of oxygen on the risk of bronchopulmonary dysplasia

(BPD) or long-term neurodevelopmental outcomes. Two studies have addressed whether use of low or high inspired oxygen concentrations for resuscitation results in different pulmonary outcomes. Vento and colleagues⁴⁹ randomized 78 infants less than 1000 g to 30% or 90% oxygen. The low-oxygen group had less evidence of oxidative stress, required fewer days of oxygen and mechanical ventilation, and had a lower incidence of BPD. More recently Kapadia and colleagues⁴⁷ randomized 88 preterm infants 24- to 34-weeks gestation to 21% or 100% oxygen. Similar to previous studies, the inspired oxygen concentration was titrated to achieve the saturation values described in the 2010 AHA guidelines. The low oxygen group had less evidence of oxidative stress, fewer ventilator days, and a lower incidence of BPD. There has been a single meta-analysis of neurodevelopmental outcomes in infants ventilated with 21% or 100% oxygen. At 12 to 24 months of age, there were no differences in outcomes.³¹ However, 27% of the patients were lost to follow-up, there was considerable heterogeneity between the trials, and all of the studies were quasi randomized and unblinded.⁵⁰

Although ILCOR/AHA guidelines precisely define oxygen saturation targets, it is difficult to achieve them. Goos and colleagues⁵¹ demonstrated that during the resuscitation of preterm infants less than 30-weeks gestation there were large deviations from the European Resuscitation Council guidelines in the first 10 minutes after birth. To determine which oxygen resuscitation strategy was most effective at achieving and maintaining oxygen saturations of 85% to 92%, Rabi and coworkers⁵² randomized infants less than 32-weeks gestation to resuscitation with a static concentration of 100% oxygen or an oxygen titration strategy using 100% oxygen or 21% oxygen. At 8 and 10 minutes of life, the infants who were assigned to the oxygen titration strategy beginning with 100% oxygen spent a greater proportion of time in the targeted saturation range than the infants receiving a static concentration of 100% oxygen. Most recently, Gandhi and colleagues⁵³ investigated whether using a Transitional Oxygen Targeting System, which plots real-time saturation values, was better than standard saturation targeting at maintaining preterm infants between the 10th and 50th percentile oxygen saturation curves described by Dawson and colleagues.⁴¹ Saturation values were maintained within the specified target range for a significantly longer time in preterm infants resuscitated using the Transitional Oxygen Targeting System display.

OXYGEN SATURATION TARGETS DURING NEONATAL INTENSIVE CARE

The motivation for establishing a rational set of target limits for oxygen saturation in preterm infants receiving supplemental oxygen, and the persistent difficulty in doing so, cannot be understood outside the context of the epidemiology and pathogenesis of retinopathy of prematurity (ROP). That most neonatologists understand the story of this relationship as a “modern parable” or “cautionary tale,” replete with villains, heroes, unexpected plot twists, and avoidable tragedies, is because of the efforts of William Silverman (1917–2005), who used it to advocate evidence-based medical practice based on randomized controlled trials.^{54,55}

In 1942, Wilson and coworkers⁵⁶ recognized that periodic breathing observed in preterm infants could be abolished with oxygen. Wilson was cautious about advocating the therapeutic use of oxygen, but other investigators were more enthusiastic.⁵⁷ As oxygen use proliferated, an epidemic of blindness in preterm infants caused by retrolental fibroplasia (RLF) arose in the world’s developed countries, becoming within a single decade the most common cause of blindness in children.^{54,58} In the early 1950s, comparative observations in Britain and Australia noted a difference in rates of RLF

between nurseries that used oxygen liberally and those that did not.^{59,60} Early observations about the role of oxygen in the pathogenesis of RLF were augmented by clinical observations and laboratory models.^{61,62}

A randomized controlled trial begun in 1953 tested whether the incidence of RLF could be altered by exposure to restricted versus unrestricted levels of oxygen.⁶³ This trial, enrolling all infants with birth weight less than 1500 g in 18 hospitals, found that the incidence of cicatricial RLF was 3.5 times greater with unrestricted use than with use based on clinical need. The incidence of “active RLF” was twice as high. There was no difference in mortality noted. A smaller randomized trial performed at Bellevue Hospital found a 22% incidence of cicatricial RLF among preterm infants continuously exposed to “high” oxygen concentration (mean FiO_2 , 69% [standard deviation, 6.5%]) but none in infants in the “low” oxygen group (mean FiO_2 , 38% [standard deviation, 7.7%]).⁶⁴

During the next decade, the incidence of RLF declined sharply as oxygen use was curtailed. However, the restricted use of oxygen came with an unexpected cost. In 1960, a review of a series of autopsied preterm infants noted that deaths from hyaline membrane disease increased 2.5-fold during a 4-year period of restricted oxygen use (1954–1958) compared with a similar period (1944–1948) of routine oxygen use.⁶⁵ These observations were later confirmed epidemiologically.^{66,67} Reviewing data in the United Kingdom, Cross⁶⁷ estimated that each case of blindness prevented resulted in an excess of 16 deaths. The studies described previously were performed in an era when neither the technology to measure delivered oxygen (FiO_2) nor blood levels of oxygen (PaO_2 , Sao_2) were routinely available.^{68,69} Most of the devices related to oxygen that are now used became commercially available in the 1970s to 1980s.^{7,11,12,68,69} Therefore, infants in the 1960s nursed in a restricted oxygen environment likely experienced repeated episodes of cyanosis (and therefore low saturation values). Some of the increased mortality was almost certainly related to the severe restriction of oxygen that would not be tolerated in any modern neonatal intensive care unit (NICU).

In 1987, Bancalari and colleagues⁷⁰ performed a prospective observational study to determine whether continuous TcPo_2 monitoring reduced the risk of ROP in infants with birth weight less than or equal to 1300 g. Although they noted a reduction in ROP in infants with birth weight greater than or equal to 1000 g, they found no reduction in ROP in infants less than 1000 g, who had the greatest exposure to oxygen and were at highest risk for the disease. The investigators cautioned that, “...by continuously adjusting the FiO_2 in an attempt to keep the TcPo_2 within a specified range, oscillations in TcPo_2 are frequently amplified, thereby achieving an effect exactly the opposite of what is desired.”⁷⁰ In a second report based on this cohort, the investigators found that the adjusted odds ratio for each 12-hour period in which TcPo_2 exceeded 80 mm Hg was 1.9 (95% confidence interval, 1.2–3.0).⁷¹

Without a detailed understanding of the relationship between oxygen exposure and the pathogenesis of ROP on a cellular level, rational limits on the use of oxygen that minimized ROP in preterm infants could not be achieved. During 1990s, the relationship between premature birth, retinal oxygen status, insulin-like growth factor, vascular endothelial growth factor, and vascular growth and proliferation was gradually elucidated.^{43,57,72–74} This mechanism provided the rationale for the STOP-ROP trial, published in 2000.⁷⁵ The investigators reasoned that although hyperoxia might be responsible for intense vascular proliferation early in the disease, supplemental oxygen might actually downregulate neovascularization after ROP had become established. A total of 649 extremely low birth weight infants with prethreshold ROP and receiving supplemental oxygen were randomized to receive oxygen at a conventional

SpO₂ target range (89%–94%) or at a higher range (96%–99%). Although some measures of ROP severity improved in the high saturation group, there was no difference between groups in the rates of the primary outcome or progression to threshold ROP. Death rates were similar in both groups but worse pulmonary status was noted in infants randomized to the high-saturation group.

In Australia, another large multicentered trial, the Benefits of Oxygen Saturation Targeting (BOOST) trial, explored the possible benefit of higher levels of oxygen saturation.⁷⁶ This trial enrolled 350 infants with gestational age less than 30 weeks, randomized to a standard SpO₂ range (91%–94%) or a high SpO₂ range (95%–98%). The study found no differences in growth or neurodevelopmental outcome at 12 months corrected age and no difference in rates of death or ROP. However, it noted higher rates of BPD (supplemental oxygen need at 36-weeks postmenstrual age) and need for oxygen after hospital discharge in the high-saturation group. From these two randomized clinical trials, it became apparent that SpO₂ levels greater than or equal to 95% offered no benefit to small preterm infants.

By early part of this millennium, it was clear that the incidence of ROP was not decreasing, despite new monitoring technology and better understanding of ROP pathogenesis.⁷⁷ Several observations suggested that lower target SpO₂ range might decrease incidence of severe ROP and BPD in VLBW infants without causing harm.^{78–81} In a single NICU that set guidelines for a target SpO₂ range of 85% to 93% and imposed a strictly enforced protocol, the incidence of severe ROP (stage 3–4) decreased from 12.5% to 2.5% in a 5-year period (1997–2001).⁷⁸ During the same period, survival rates improved in this NICU. The severe ROP rate for infants in Vermont Oxford Network stayed about the same. These observations led to the widespread adoption of lower target saturation ranges and a subsequent decline in the incidence of severe ROP (Fig. 3). However, without guidance of a strong evidence base, advisory bodies were uncertain what saturation range to recommend. In the United States, the AAP suggested that a target SpO₂ range from 85% to 95% was

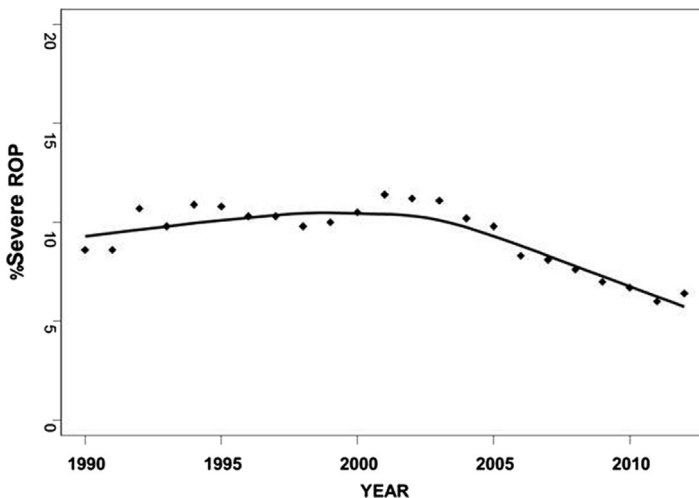


Fig. 3. Median incidence of severe ROP in member units of the Vermont-Oxford Network, 1990–2012. (From Vermont Oxford Network database of very low birth weight infants. Burlington (VT): Vermont Oxford Network; 2014. Nightingale Internet Reporting System. Accessed May 15, 2014; with permission.)

desirable.⁴⁸ In Europe, consensus guidelines suggested 85% to 93%.⁸² Both statements lamented the absence of data needed to support any recommendation.

The absence of solid evidence on which to base rational oxygen use led to calls for randomized controlled trials.^{55,83,84} By the mid-2000s, three large, double-blind, randomized clinical trials with similar design were launched in Europe, Australia, New Zealand, the United States, and Canada.^{3,4,6} These trials focused on infants less than 28-weeks gestational age. Common design features included two standardized target saturation groups: low ($SpO_2 = 85\%–89\%$) and high ($SpO_2 = 91\%–95\%$). Blinding in all three studies was attained using an altered pulse oximeter algorithm offset to read 88% to 92% for the specified target range. Composite outcomes were death or severe ROP, and death or neurodevelopmental disability 18 to 24 months. Death was included in these measures because it is a competing outcome.

The first of these trials, the SUPPORT trial,³ was a multicenter randomized trial involving 23 centers in the United States. It used a 2×2 factorial design, also testing two delivery room practices: initial CPAP without surfactant versus intubation and mechanical ventilation with surfactant. The trial enrolled 1316 infants 24- to 27-weeks gestational age who were randomized to one of the two SpO_2 target ranges noted previously, with blinding attained using the altered pulse oximeter. Results of the trial showed no difference in the composite primary outcome: death before hospital discharge or severe ROP (28% vs 32%; low vs high). However, the incidence of each of the component outcomes differed significantly: severe ROP was greatly reduced in the low- SpO_2 group (8.6% vs 17.9%), but the rate of death increased in the low-saturation group (19.9% vs 16.2%). No difference in rates of BPD or necrotizing enterocolitis (NEC) was noted.

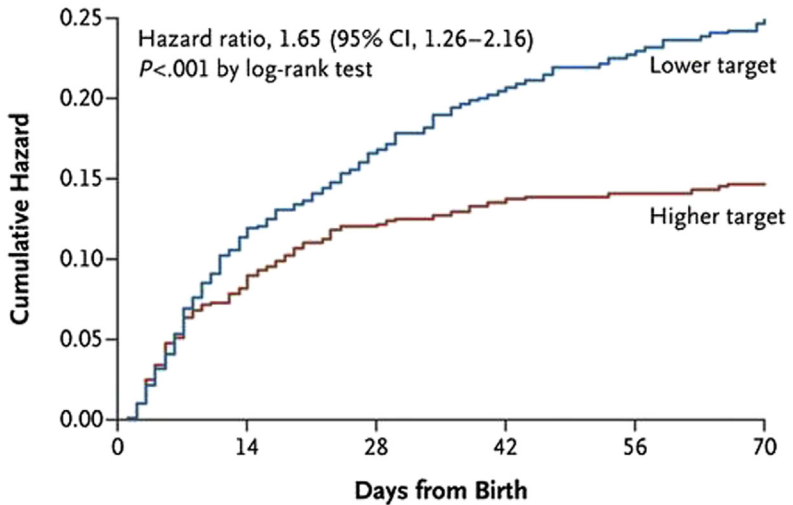
In a follow-up study of infants who participated in the SUPPORT trial, investigators found no difference in the composite outcome of death or neurodevelopmental impairment at 18- to 22-months corrected age among those assigned to a lower or higher target range of oxygen saturation.⁵ A significantly elevated mortality rate persisted in the low- SpO_2 group.

Interim results of the second trial, BOOST II,⁶ conducted in Australia, New Zealand, and United Kingdom, appeared in 2013. The report was based on the enrollment of 2448 infants less than 28-weeks gestational age. Halfway through the study, an error was discovered in the pulse oximeter algorithm that caused poor separation between the intended target saturation groups. Following introduction of a corrected algorithm, a higher death rate was noted in the low- SpO_2 target group (23% vs 16%). A decreased rate of severe ROP (11% vs 14%) and a higher rate of NEC (10% vs 8%) were also noted in the low- SpO_2 target group. The BOOST II trial was halted before completion by the study's safety committee. A report on the primary composite outcome (death or severe neurodevelopmental delay at 18–24 months) has not yet been published. **Fig. 4** shows the significantly elevated hazard ratio for death in the low- versus high- SpO_2 target groups obtained after the pulse oximeter algorithm was revised.⁶

The third study with similar design, the Canadian Oxygen Trial,⁴ found no difference in the composite primary outcome (death or neurodevelopmental impairment at 18 months), no difference in rates among the outcome components, and no difference in incidence of severe ROP. It did find a significantly longer duration of in-hospital oxygen need in the high-saturation group.

A retrospective meta-analysis that included results available for the three trials in late 2013 showed no difference between the low- and high-saturation groups in rates of death or severe neurosensory disability at 18 to 24 months with either the original or the revised algorithm.³⁰ Among secondary outcomes, the analysis found higher

Revised Algorithm



No. at Risk

Lower target	593	528	501	482	471	462
Higher target	590	543	523	515	512	509

Fig. 4. Cumulative hazard estimates for death before hospital discharge in the two oxygen saturation target groups for the revised oximeter algorithm, BOOST II trial. CI, confidence interval. (From Stenson BJ, Tarnow-Mordi WO, Darlow BA, et al. Oxygen saturation and outcomes in preterm infants. *N Engl J Med* 2013;368:2012; with permission.)

risk ratios (95% confidence interval) for mortality (1.41 [1.14–1.74]) and NEC (1.25 [1.05–1.49]) and a lower risk ratio for severe ROP (0.74 [0.59–0.92]) for low- versus the high-saturation groups. Risk ratios were similar for BPD, intra-ventricular hemorrhage (grades 2–4), and patent ductus arteriosus. A prospective meta-analysis based on individual patient data will be conducted when BOOST II follow-up results become available.⁸⁵

In summary, despite the efforts of three major international randomized trials, a single target saturation range that minimized mortality and severe ROP remained undetermined. However, data from these trials suggest that use of a higher oxygen saturation target range than previously recommended (eg, 90%–95%) is prudent in the management of preterm infants receiving supplemental oxygen.⁸⁶ The three randomized clinical trials leave many unanswered questions that may be fruitful areas of investigation. Recent studies have demonstrated the difficulty of maintaining the SpO_2 of VLBW infants receiving supplemental oxygen within any target range.^{2,87} In a study by Lim and colleagues,⁸⁷ a group of 45 infants less than 37-week gestational age on CPAP spent only about 30% of time with SpO_2 within the specified target range (89%–93%). The influence of these excursions on the incidence of ROP, mortality, and other outcomes is unknown.

Ethical Storm over the SUPPORT Trial Consent Form

In early 2013, the Office for Human Research Protection (OHRP) investigated allegations brought by the advocacy group Citizens United. At issue was whether the consent form used in the SUPPORT trial misled parents about the risks of participating in the study.

OHRP concluded that parents were indeed misled.⁸⁸ The University of Alabama at Birmingham (UAB), one of the SUPPORT study sites, was cited for “failure to describe the reasonably foreseeable risks of blindness, neurologic damage and death.” The letter contained a lengthy review of prior studies dating back to the 1950s, a review of SUPPORT outcome data, and extracts of the consent form used by UAB. It concluded, “Accordingly, we determine that the informed consent document for this trial failed to adequately inform parents of the reasonably foreseeable risks and discomforts of research participation.” Although the determination itself was confined to a criticism of the consent form used by UAB, it was clear that OHRP believed that increased mortality was a “reasonably foreseeable risk” of study participation and the conduct of the study could be considered unethical. That the investigators had acted unethically was asserted by the report and editorial in the *NY Times*.⁸⁹

In the weeks that followed the letter of determination, the conduct of the SUPPORT trial and the OHRP determination were vigorously defended.^{90–94} One defense of SUPPORT came from the National Institutes of Health,⁹¹ which had approved and funded the SUPPORT trial. Although acknowledging the deficiencies in UAB’s consent form and unequivocally supporting the role of the OHRP, the authors suggested that the OHRP ruling “has had the effect of damaging the reputation of the investigators and, even worse, casting a pall over the conduct of clinical research to answer important questions in daily practice.” Given the strong views expressed by opposing parties and the absence of clear standards, OHRP retreated from its original determination.⁸⁸ The issue remains under deliberation.

TECHNOLOGIC ADVANCES

Pulse oximetry has been proved to be an extremely useful tool in assessment and monitoring of VLBW infants as they receive neonatal care. However, its widespread use over the last three decades has also revealed some of its inherent limitations. Accurate determination of SpO_2 requires a high-quality arterial signal and is limited by errors resulting from motion, low perfusion, and dyshemoglobinemias. The theoretic model of conventional pulse oximetry assumes that the arterial blood is the only light-absorbing pulsatile component. However, this assumption has been challenged by SpO_2 readings during motion that fall below 85%. That should not be the case if these desaturations were merely the result of uncharacterized noise. The newest generations of pulse oximeters use improved algorithms of signal extraction technology, which assume that nonarterial absorbers also generate a pulsatile signal when motion occurs and that the ratio of absorption ratios should be considered a composite of arterial and nonarterial pulsatile signals, ultimately resulting in more accurate SpO_2 readings especially under critical conditions. These novel conceptual models are also applicable to situations of low signal-to-noise ratio, such as low-perfusion states.^{95,96}

Until recently, pulse oximeters have also been limited because they use two wavelengths of light to display SpO_2 , assuming that the only light absorbers in the blood are O_2Hb and Hb. This assumption is frequently violated, resulting in serious SpO_2 errors. The new multiwavelength Rainbow Technology pulse oximeters developed by Masimo Corporation (Irvine, CA) have permitted the noninvasive measurement of carboxyhemoglobin, methemoglobin, and total Hb.⁹⁷ Reflectance pulse oximeters that are based on absorption analysis of reflected rather than transmitted light have recently been introduced into neonatal clinical practice.⁹⁸ With the success of pulse oximetry and recent advances in digital signal processing, there is increasing research interest in the circulatory information derived from the photoplethysmographic

waveform. New plethysmograph-derived parameters, such as perfusion index and pleth variability index, have the potential to estimate tissue perfusion and intravascular volume noninvasively.¹⁶ Combined with improved understanding of the underlying physiology of the waveform it is easy to predict the emergence of multifunction pulse oximeters. The incorporation of these technologic advances into evidence-based clinical algorithms will improve the efficiency of this methodology in routine neonatal care. Clinical research is needed to define the utility of these technologies, and to identify new monitoring opportunities.

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