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Oxygen Targeting in Preterm Infants: A Physiologic Interpretation

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Oxygen therapy in preterm infants must balance the benefits of tissue oxygenation and growth with the risks of oxygen toxicity[1]. Tissue oxygenation and oxygen toxicity depends ultimately on the amount of oxygen delivered to, and the amount extracted by the tissues. Oxygen delivery to the tissues depends on the cardiac output, the oxygen content (which in turn depends on the hemoglobin concentration, the oxygen saturation, and the partial pressure of dissolved oxygen), and on the position of the oxygen dissociation curve [2]. Oxygen extraction is measured as the difference between arterial and venous oxygen content[3]. Pulse oximetry is now the most commonly used method of monitoring oxygenation. However, the range of optimal saturation by pulse oximetry (SpO_2) in preterm infants receiving supplemental oxygen has remained controversial [4, 5]. To identify such a range, five large multicenter, masked, randomized control trials – SUPPORT (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial)[6], COT (Canadian Oxygen Trial)[7] and three BOOST II (Benefits of Oxygen Saturation Targeting) studies[89] were recently conducted that together enrolled nearly 5000 preterm infants less than 28 weeks postmenstrual age (PMA) at birth. These studies followed a predetermined design and compared low target SpO_2 (85–89%) versus high target SpO_2 (91–95%). The conclusions of these trials, especially those of SUPPORT and BOOST II, have been stated in simple terms as "maintaining an oxygen saturation target of 85 – 89% leads to a lower risk of retinopathy of prematurity (ROP) but a higher risk of mortality". Because of the reported increased mortality with the lower target range, SUPPORT investigators have been thoroughly criticized by public advocacy agencies and subsequently defended by many neonatologists through expert opinions[10, 11, 12, 13, 14, 15, 16] and a public hearing[17]. These trials were very well planned, designed and executed. However, the methods and interventions used in these trials had physiologic, technical, and implementation concerns that raise questions about the

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external validity and practical application of the findings. In this review we list these concerns and discuss how they weaken the conclusions of the studies, thereby leaving us with a persistent uncertainty regarding the ideal oxygen saturation target range and the best way to monitor oxygenation in preterm infants. We group our concerns into two categories:

A. Problems with the use of pulse oximetry in these studies.

B. Methodological issues.

A. PROBLEMS WITH THE USE OF PULSE OXIMETRY

Problems with using pulse oximetry to determine oxygenation status can arise from several sources:

- The technology used
- The location of probe placement
- The relationship between SpO_2 and arterial oxygen saturation (SaO_2)
- The relationship between SaO_2 and partial pressure of oxygen (PaO_2)

Pulse oximetry technology

Pulse oximeter reading is a transcutaneous, non-invasive estimate of SaO_2. It is based on the principle that oxyhemoglobin and deoxyhemoglobin differentially absorb red and near-infrared light. The pulsatile component of red to infrared light modulation ratio is calculated. A microprocessor in pulse oximeters has an algorithm that uses this ratio to determine the percentage of hemoglobin bound to oxygen (SpO_2) based on a calibration curve generated in healthy volunteers [18].

Are pulse oximeters accurate in preterm infants?

Preterm infants have a high concentration (70–90%) of fetal hemoglobin (HbF) at birth [19]. Fetal hemoglobin has a fairly similar absorbance pattern compared to that of adult hemoglobin (HbA) leading to similar functional SpO_2 measurements[20, 21, 22]. In 22 preterm infants, Rajadurai et al did not observe any significant impact of HbF on SpO_2 measurements [23]. Based on these observations, it appears that the SpO_2 values obtained by pulse oximetry in preterm neonates is similar to that in older children and adults.

How accurate is the Masimo pulse oximeter in neonates?

The product manual for Masimo Radical 7 pulse oximeter[24], which uses signal extraction technology (SET)[25] states that the algorithm's accuracy in neonates was established in 79 samples from 16 neonates (NICU patients - 7 to 135 days old and weighing between 0.5 to 4.25kg). Testing was conducted over the SpO_2 range of 70–100% with a resultant accuracy of 2.9%. Johnston et al report that this variation equals ± 1SD[26]. So, if the displayed SpO_2 is 88%, true SaO_2 may be in the 85–91% range in 68% of subjects[26] (figure 1) and 82–94% range in 95% of the subjects[4].

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What was the error in the original algorithm in Masimo pulse oximeters?

Manufacturers of the pulse oximeter originally generated an algorithm curve referring to SpO_2 in the high range[26]. In 2002, as SpO_2 targets in preterm infants were trending lower, the manufacturers added a lower curve (corresponding to SpO_2 in the 70s to 80s range – figure 2B). The lower curve was free of "upward adjustment" [26]. The effect of this dual curve was that the SpO_2 values in the region of 87–90% (at the junction of the lower and higher algorithm curves, figure 2B) were shifted upwards.

The SUPPORT trial enrolled infants from February 2005 through February 2009 and used this original algorithm. The COT trial enrolled patients between December 2006 and August 2012. The BOOST-II trial enrolled infants from March 2006 until December 2010. During the BOOST-II trial, investigators in UK audited data from standard, unmodified Masimo SET pulse oximeters[26]. SpO_2 data gathered from 176 oxygen dependent preterm infants between August 2006 and April 2009 undergoing standard care revealed a lower frequency of SpO_2 readings in the 87–90% range than expected[26]. The Masimo Corporation after investigation as cribed the finding to the "dual curve" in the calibration algorithm used by the oximeter described above (figure 2B and the difference between the solid black line and hyphenated black line shown by an arrow in figure 3). This lead to an artificial elevation of SpO_2 readings that was maximal at a displayed value of 90% and was around 1.6% higher (2% since only whole numbers are displayed – figure 3). Masimo Corporation supplied new software with a revised algorithm that relied on a calibration curve with a uniform slope (diagrammatically shown in figure 2B). This was installed in all trial oximeters in UK and Australia (New Zealand had completed enrollment) between December 2008 and May 2009 and in the COT trial between February and June 2009. Since pulse oximeters from this manufacturer were used in the SUPPORT trial, it is possible that this discrepancy existed (but was unrecognized). As seen in figure 3, the difference in SpO_2 readings between the original algorithm and revised algorithm is minimal. The change in median SpO_2 in COT and BOOST-II trials was $\leq$ 1% following revision of the algorithm (supplementary figure 1)

What was the impact of modification/revision of the pulse oximeter software algorithm?

Meta-analysis of mortality data from infants on pulse oximeters with revised software (death at discharge for BOOST II – UK and Australia and death before 18 months for COT trial) showed a relative risk of 1.41 (1.14–1.74), favoring the high SpO_2 group [27]. The time spent at <85% SpO_2 among patients on supplemental oxygen with revised algorithm was significantly higher in the low target group (21.5%) compared to the high target group (10.7%). From a physiologic perspective, severe hypoxemia can increase mortality. Therefore, for mortality to increase after revision of the algorithm, one would expect a significant increase in proportion of time spent with severe hypoxemia.

The proportion of time spent with SpO_2<85% decreased slightly in both BOOST-II (UK/Australia) and COT trials following revision of the algorithm (supplementary figure 1) and should have had minimal effect on mortality. The revision of pulse oximeter algorithm did not significantly alter mortality at 18 months in the COT trial (from 17.4 to 16.8% in the lower target group and a decrease from 17.9 to 14.1% in the high target group)[7]. In sharp contrast, mortality before discharge significantly increased in the 85–89% SpO_2 target group

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from 15.6 to 23.1% following revision of the algorithm in BOOST-II trial [9] (supplemental figure 1). A recent editorial[5] pointed out a puzzling reversal in the direction of the observed treatment effect on mortality at discharge in BOOST-II (UK) following installation of the revised algorithm (supplemental figure 2). This increased mortality cannot be explained solely on the basis of shift in displayed SpO_2.

While the etiology of increased mortality in the low SpO_2 target arm in BOOST-II is not clear, we offer the following speculations. It is possible that the pulse oximeter algorithm revision had a minimal effect on oxygenation. Intermittent hypoxemia probably had a bigger role in etiology of higher mortality at discharge[28] in the low target arm[29] (figure 2E). The time spent in <85% SpO_2 in the low target group in BOOST-II trial was nearly twice the time spent in >95% SpO_2 (24.2 vs. 12.5% respectively, supplemental figure 1). The time spent in <85% SpO_2 in the low target group in COT trial was only slightly higher than the time spent >95% SpO_2 (19.3 vs. 16.3% respectively, supplemental figure 1). This may be secondary to lack of a mandated/standardized low alarm setting in some of the BOOST-II protocols and a protocol-defined limit with monthly feedback to centers in COT [5]. Secondly, the overall incidence of death before discharge was higher in UK (21.8%) compared to Australia (16.05%) and New Zealand (13.23%) (Supplemental figure 3). There were more infants enrolled in UK after revision of the pulse oximeter algorithm compared to Australia and New Zealand (New Zealand completed its recruitment prior to algorithm revision). However, even within the BOOST-II Australian subjects, revision of the algorithm increased mortality (supplemental figure 2) and is difficult to explain. Finally, the impact of stopping the BOOST-II UK and Australian trials early on the validity of the results needs further evaluation [30, 31].

Location of Probe Placement

Since pre-ductal oxygen content represents oxygen delivery to the brain, oxygen saturation targeting trials should ideally compare preductal oxygen saturations. However, the site of study pulse oximeter probe placement was not specified in these trials. Beyond the first few days of life, the ductus arteriosus is often closed in most patients and if open, oxygenated blood usually shunts from left to right. In these conditions, in theory, there should not be a significant difference between preductal (right upper extremity) and postductal (lower extremity) SpO_2 values. We recently compared concurrent preductal and postductal SpO_2 values in preterm infants, that were obtained using Masimo pulse oximeters, as part of critical congenital heart disease (CCHD) screening [32] in the NICU. Based on their clinical status and on follow-up, none of these infants had critical congenital heart disease or an open ductus arteriosus. Among 96 preterm infants born at < 28 weeks gestation, the SpO_2 recording before discharge (at 95 ± 26 days of postnatal age) was identical in the preductal and postductal extremity in forty two (44%) infants. In 36% of preterm infants, postductal SpO_2 was higher than preductal SpO_2 (range 1–4% higher). In 20% of infants, preductal SpO_2 was higher than postductal SpO_2 (range 1–3%) – (see supplemental figure 4). The difference between preductal and postductal SpO_2 may be ≥ 3% in 10% of and ≥ 2% in 28% of preterm infants < 28 weeks PMA at birth even at the time of discharge. Therefore, it is possible that the lack of specification of the site of probe placement in these 5 trials may

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have further contributed to variation in preductal PaO_2 at each displayed SpO_2 level (figure 1).

Relationship between SpO_2 and SaO_2

The standard manufacturers' claim of accuracy of detection of SaO_2 using the SpO_2 measured by pulse oximeters is ± 2–3% over the range of 70–100% SpO_2. [33] In addition, sensor misalignment, light interference [34], a functional error in the electrical circuitry in the sensor or emission spectra different from the specification may cause an error in estimation of oxygen saturation [33]. Rosychuk et al reported that umbilical arterial SaO_2 was lower than postductal SpO_2 in preterm infants by −1.84 (95% CI −7.6 to 3.9%) [35]. In the same study postductal SpO_2 of 85–89% was associated with umbilical arterial SaO_2<85% in 39% of samples (and <80% in 10% of samples). In our laboratory we have prospectively evaluated preductal SaO_2 values from 520 right carotid arterial and mixed venous blood gas samples (from a main pulmonary arterial catheter) in 58 preterm lambs (127–134 d gestation, term ~ 147 d) and compared them with concurrently obtained preductal SpO_2. Preductal SpO_2 of 85–89% was associated with a right carotid arterial SaO_2<85% in 16% of samples (and <80% in 2%). A significant increase in SaO_2 and mixed venous SvO_2 (both obtained from a Radiometer blood gas analyzer, Radiometer ABL825, Westlake OH) was observed with increasing SpO_2 but there is considerable divergence/discrepancy of these two values in some zones, especially at the extremes of oxygenation (supplementary figure 5 and table 1).

Relationship between Oxygen Saturation and PaO_2

Oxygen toxicity and oxygen delivery to the tissues are determined by the local concentration of oxygen in the tissue which in turn depends on PaO_2, hemoglobin concentration, oxygen content of the blood and blood flow (figure 1). While SpO_2 and SaO_2 are reasonable surrogate markers for PaO_2, the relationship between SaO_2 and PaO_2 is asymptotic and SaO_2 is a poor estimator at high values of PaO_2. Right carotid arterial and simultaneous mixed venous (pulmonary arterial) PO_2 values from preterm lambs is shown in supplementary figure 6. The arterial values and variability observed in the preterm animal model is similar to that described in preterm neonates[36]. Studies in neonates have shown that monitoring transcutaneous PO_2 results in less time spent with high oxygen tension, low oxygen tension and less variability in oxygen tension compared to SpO_2 monitoring[37]. A given displayed SpO_2 value may be associated with a wide range of PaO_2, oxygen content, oxygen delivery and extraction (figure 1). In addition, the type of hemoglobin (adult – HbA vs. fetal –HbF) alters the relationship between SaO_2 and PaO_2 (see below). Therefore, even though trials have targeted different ranges of SpO_2 in the two groups, there may have been considerable overlap in the true PaO_2 to which these groups were exposed.

What is the effect of transfusions on PaO_2 – SpO_2 relationship in preterm infants?

Emond et al have demonstrated that extremely preterm infants (26.4 ± 1.4 weeks PMA at birth) have a high concentration of HbF (70–90%) and cord blood has a P50 (partial pressure of oxygen at which blood saturation is 50%) of 18.3 ± 1.9 mmHg [19]. The P90 of cord blood (PO_2 at 90% oxygen saturation) was 40.8 ± 3.6 mmHg. Following transfusion of packed red blood cells (PRBC - mean volume – 26.9 ml/kg), HbF decreased from 92.9 ± 1.1% to 42.6 ± 5.7% during the first week of postnatal life in extremely preterm infants. This decrease was

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associated with an increase in P50 from 18.5 ± 0.8 to 21 ± 1 mmHg[38]. In preterm infants with BPD at 42.2 ± 4.7 weeks PMA, P50 was 25.1 ± 2.7 mmHg (similar to an adult value of 26–27 mmHg)[39]. Hence transfusions significantly increase the percentage of adult hemoglobin in the blood. A PaO_2 range of 50–75mmHg is associated with SpO_2 of 96–97% with HbF and only 85–94% with HbA[40]. Presence of HbA markedly increases PaO_2 required to achieve the same SpO_2 and alters the balance between oxygen content/delivery and oxygen toxicity (figure 1 – case D)[38]. Therefore, in these 5 trials, PRBC transfusions may have altered oxygen tension and content for a specific SpO_2 range and further contributed to the variability in the SpO_2-PaO_2 relationship.

Why do the mortality curves of the lower SpO_2 target and high target groups separate *after* the first couple of weeks of postnatal age?

With increasing postnatal age, the cumulative total volume of transfused PRBC to preterm infants increases resulting in a high percentage of HbA in the blood[2, 38]. An interesting observation in all the trials is that the difference in mortality between low target SpO_2 group and high target group appears after a few weeks of postnatal age[6, 7, 9]. This phenomenon can be explained by a unique, paradoxical relationship between oxygen delivery, arterial PO_2 and fetal hemoglobin[41]. It is often assumed that oxygen delivery is decreased in the presence of HbF because of its increased affinity to oxygen. It is true that when PaO_2 is maintained at a high value, better oxygen delivery would exist if the oxygen dissociation curve is shifted to the right with adult hemoglobin. However, a leftward shift in the hemoglobin-oxygen dissociation curve resulting from high levels of HbF may better maintain oxygen delivery during episodes of severe hypoxemia[41]. Wimberley et al calculated that during hypoxemia, the infant would achieve better oxygen delivery with fetal oxygen dissociation curve than with an adult curve[42]. In a subgroup of SUPPORT patients, such episodes of intermittent hypoxemia ($SpO_2 \leq 80\%$) increased in both groups over the first 3 weeks of life followed by a decrease in the high target group compared with a plateau in the low target group[28]. In addition, as pointed out by Vento, it may take some time before the consequences of intermittent hypoxemia are translated into clinical vulnerability[1]. The reduced frequency of intermittent hypoxemic episodes and relatively better oxygen delivery due to high fetal hemoglobin levels and lag in manifesting clinical consequences of hypoxemiamay explain lack of difference in mortality between the two groups during early postnatal period.

Is there a significant difference in oxygenation between 85–89% and 91–95% SpO_2 target range?

Table 1 shows the difference in various parameters of oxygenation in preterm lambs at ≤84%, 85–89%, 91–95% and ≥96% SpO_2. There is a statistically significant increase in PaO_2, and mixed venous PO_2 with increasing SpO_2. There was no significant difference in arterial oxygen content or oxygen extraction ratio (OER = arterial oxygen content – venous oxygen content as a percentage of arterial oxygen content) between 85–89% and 91–95% SpO_2 groups. However, arterial oxygen content significantly decreased and oxygen extraction significantly increased when SpO_2 decreased below 85% (table 1). Pulmonary vascular resistance (PVR) is similar between 91–95% and 96–100% SpO_2 range. There is a significant increase in PVR in the ≤84% and 85–89% groups (table 1 and supplementary figure 7). These results indicate a significant difference in oxygen delivery, extraction and

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PVR especially during episodes of desaturation below 85%. Such intermittent hypoxemic episodes were observed more frequently in the low SpO_2 target group in the SUPPORT trial [28] and time spent <85% was significantly higher in the low SpO_2 target group in the COT and BOOST-II trials (supplementary figure 1). We speculate that during periods of SpO_2 below 85%, preterm infants may have suboptimal oxygen delivery to the tissues increasing the risk of pulmonary hypertension and necrotizing enterocolitis (NEC). This may explain some of the findings of the trials and the metanalysis[27].

B. METHODOLOGICAL ISSUES

How were pulse oximeters altered to mask the target SpO_2 range?

To maintain masking, electronically altered pulse oximeters were used that showed saturation levels of 88 to 92% for both targets of oxygen saturation with a maximum variation of 3%. For example, a displayed reading of 90% corresponded to true level of 87% in the group assigned to lower oxygen saturation (85–89%) and 93% in the group assigned to the higher saturation (90–95%). The oxygen saturation reading changed and reverted to actual values when it was less than 84% or higher than 96% in both groups (figure 3). Similar masking was successful in the first BOOST trial [43].

What was the impact of masking algorithm on titration of oxygen therapy?

Schmidt et al reported an interesting observation related to rapidity of change in displayed SpO_2 values secondary to masking [44] and is shown in figure 3 (modified from figure 1 in reference [44] and BOOST-II UK protocol). The masking algorithm achieved a 3% increase (in the low SpO_2 target arm) and a 3% decrease (in the high SpO_2 target arm) in displayed values. The displayed values returned to true values atSpO_2 ≤84% and ≥96% (figure 3). Above 84%, the displayed values began to deviate from true values. Oximeters designed for the lower SpO_2 target rapidly established a +3% display offset as the true SpO_2 increased from 84 to 85%, then maintained this offset until a true SpO_2 of 93%, equivalent to a displayed SpO_2 of 96%. The displayed SpO_2 remained constant at 96% between true SpO_2 values of 93% and 96% as the +3% offset was reversed. When the true saturation decreased from 85% to 84% (1% drop), the displayed SpO_2 decreased from 88% to 84% triggering the lower limit alarm in the process (figure 3 – zone of instability). Caregivers had a tendency to maintain saturations above this zone of instability by potentially increasing inspired oxygen. The opposite phenomenon occurred in oximeters designed for the higher target group. When true saturations increased from 95 to 96%, displayed SpO_2 jumped from 92 to 96% triggering the higher limit alarm in the higher target group (zone of instability). This may have led to a tendency to decrease inspired oxygen in the higher target group[44]. This differential management reduced the separation between the median true SpO_2 between the two groups (figures 3 and 2). A similar phenomenon has possibly occurred in BOOST-II and SUPPORT trials as well. The net effect is a reduced separation and SpO_2 overlap between the two arms (figure 2).

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What is the impact of true separation in SpO_2 obtained between the two groups and morbidity and mortality?

As mentioned previously, the meta-analysis of these trials demonstrated increased mortality at discharge, decreased severe ROP and increased necrotizing enterocolitis (NEC) in the low target SpO_2 (85–89%) group compared to the high SpO_2 group (91–95%)[27]. Although a 6% separation in SpO_2 (85–89 vs. 91–95%) was intended between the restricted and liberal oxygen groups while on supplemental oxygen, only 1.54 to 2.67% separation in median SpO_2 was achieved between the groups in these studies[44]. It is interesting and concerning that in spite of poor separation between the two groups, the metaanalysis showed differences in mortality, ROP and NEC. If better separation were achieved between the groups, would the mortality and incidence of NEC be higher in the 85–89% target SpO_2 group?

Figure 4 is redrawn superimposing the saturation distributions in the intervention and control groups from SUPPORT, COT and BOOST-II trials to illustrate the true difference in saturations. It is difficult to demonstrate a “dose effect” on mortality, NEC or severe ROP based on SpO_2 achieved while on supplemental oxygen. COT trial achieved better separation between the 2 groups and even here, the majority of infants in the low saturation target group had a median oxygen saturation ~ 90% both in the first 3 days of life and thereafter. The BOOST II separation graphs with the original and the revised algorithm reveal improved separation with the revised algorithm. Tighter compliance, mandated lower displayed SpO_2 alarm limits and wider separation likely reduced exposure to extreme SpO_2 levels more effectively in COT (supplementary figure 1).

The investigators of COT performed a *post hoc* subgroup analysis on the effects of targeting higher versus lower SpO_2, looking at the difference between centers with more or less separation between median SpO_2 and outcomes(presented as an abstract at Pediatric Academic Societies 2014 - abstract # 1400.5 on http://www.pas-meeting.org/abstracts/default.asp). They found that the overall separation was 2.5% and that paradoxically, the centers with greater separation observed lower rather than higher rates of death and disability at 18 months in the 85–89% group (50% with more separation and 54% with less separation) than the 91–95% group (55% with more separation and 44% with less separation), consistent with their previous finding of no significant harm with the lower SpO_2 target. There was no significant difference in death before 18 months with more separation in SpO_2 between the two arms (17% with more separation and 16% with less separation in 85–89% arm and 18% with more separation and 12% with less separation in 91–95% arm). Therefore, better separation between the lower and higher target groups may not increase the difference in mortality between the two groups.

What is the impact of intermittent hypoxemia or hyperoxemia?

Di Fiore et al analyzed data derived from the SUPPORT trial and demonstrated that the lower SpO_2 target range was associated with increased incidence of intermittent hypoxemia[28]. This may be another factor that may alter the risk of poor outcomes in the low oxygenation group if saturation targets were not strictly applied which may represent the reality in many busy neonatal units. Similarly, in the COT trial there was a significant difference in time spent <85% and >95% in both groups [7] (supplementary figure 1).

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Decrease in SpO_2 below 85% increases PVR (supplementary figure 7) and reduces oxygen delivery to tissues and increases oxygen extraction (table 1). Obtaining data on time spent <85% and >95% in individual patients and linking that to outcome may enhance our understanding of differences in outcomes between the two groups.

Conclusion

Although these trials had a similar design, there is variation between the trials in the separation of oxygen saturation achieved between the 2 arms, and the variable influence of the software algorithm modification in the trials. It is difficult to explain the findings of these five studies using physiological principles of gas exchange and oxygen transport. Multiple factors outlined in this article influence the results of these studies. As pointed out by Bateman and Polin,[29] it is not clear to what extent individuals who experienced death or ROP actually received the intended intervention. It is possible that individual patients who suffered severe ROP or NEC/death spent more time with SpO_2 above or below the intended range or had multiple episodes of brief hyperoxemia or hypoxemia. Better methods of assessing oxygenation, such as simultaneous SpO_2 and tissue oxygen saturation by near-infra red spectroscopy (NIRS)[45] or transcutaneous oxygen tension monitoring[37] may be necessary but are not practical for continuous monitoring. Automated closed-loop control of inspired oxygen based on SpO_2 may enable clinicians to effectively maintain oxygen saturations in the target range[46]. Sola et al, in a recent elegant review have suggested using a wider intermediate target sch as 88 to 94% to avoid extremes of hypoxemia and hyperoxemia[4]. The BOOST II trial (UK and Australia) follow-up results and the planned individual patient-data level metaanalysis of these studies will hopefully shed light on these associations and help us provide the best care for our tiny and most vulnerable patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

1. Randomized controlled trials evaluating low target oxygen saturation (SpO_2:85–89%) versus high target SpO_2 (91–95%) have shown variable results regarding mortality and morbidity in extremely preterm infants.
2. Because of the variation inherent to the accuracy of pulse oximeters, the unspecified location of probe placement, the intrinsic relationship between SpO_2 and SaO_2 and between SaO_2 and PaO_2 (differences in oxygen dissociation curves for fetal and adult hemoglobin), the two comparison groups could have been more similar than dissimilar.
3. The SpO_2 values were in the target range for a shorter period of time than intended due to practical and methodological constraints. So the studies did not truly compare “target SpO_2 ranges”.
4. In spite of this overlap, some of the studies did find signficant differences in mortality prior to discharge, necrotizing enterocolitis and severe retinopathy of prematurity. These differences could potentially be secondary to time spent beyond the target range (SpO_2<85% or >95%) and could be avoided with an intermediate but wider target SpO_2 range (87–93%).
5. In conclusion, significant uncertainty persists about the desired target range of SpO_2 in extremely preterm infants. Further studies should focus on studying newer methods of assessing oxygenation and strategies to limit hypoxemia (<85% SpO_2) and hyperoxemia (>95% SpO_2).

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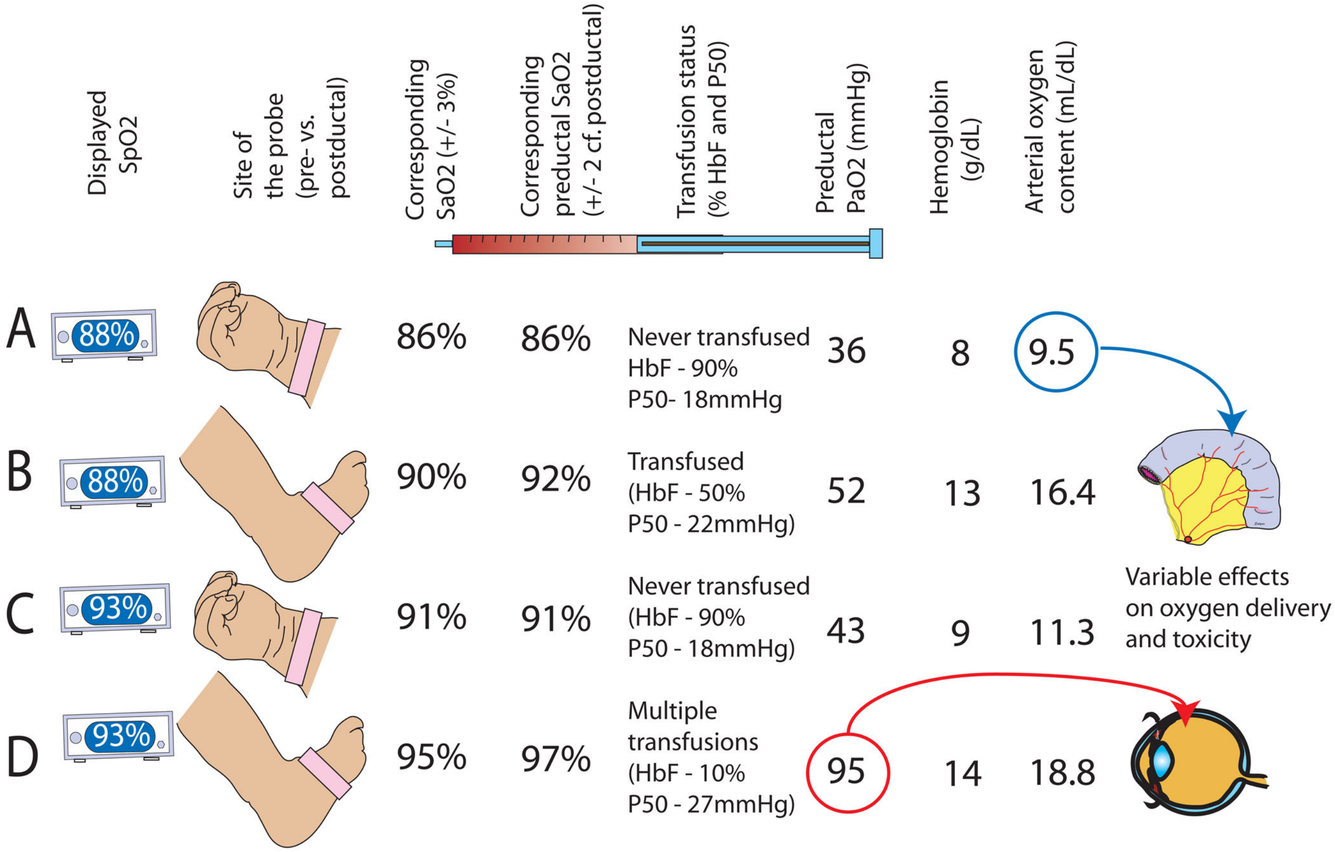

Figure 1. Variables that influence oxygen delivery (based on arterial oxygen content) and oxygen toxicity (based on PaO_2)

This figure illustrates the variation in the arterial oxygen content based on variation in the factors that contribute to it. Each row represents an infant with a specific combination of variables. The oxygen content can vary two fold with a 5% difference in displayed SpO_2 on the pulse oximeter, and an infant with a lower SpO_2 (88%) can actually have a higher oxygen content than one with a higher SpO_2 (93%).

Infant A has a preductal SpO_2 of 88% which can correspond to a SaO_2 range of 85 to 91% in approximately two-thirds of subjects (± 3% variation with pulse oximeters). If the corresponding preductal SaO_2 is assumed to be 92%, and she has never received a transfusion, her hemoglobin F (HbF) concentration is > 90%[2, 38]. The corresponding preductal PaO_2 is 36 mmHg. If this infant has a hemoglobin (Hb) concentration of 8g/dL, her arterial oxygen content will be approximately 9.5 mL/dL.

Infant B has a postductal SpO_2 of 88% which can correspond to a SaO_2 range of 85 to 91% in approximately two-thirds of subjects. If postductal SaO_2 is assumed to be 90%, the corresponding preductal SaO_2 may be 92%. If this baby had received two transfusions, her hemoglobin F (HbF) concentration is approximately 50%[2, 38] and the corresponding preductal PaO_2 is 52 mmHg. If this infant has a Hb concentration of 13g/dL, her arterial oxygen content will be approximately 16.4 mL/dL.

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Infant C, who has never been transfused with blood and with a preductal pulse oximeter probe with a displayed SpO_2 of 93% and a PaO_2 of 43 mmHg and at significantly reduced risk of oxygen toxicity compared to infant B in spite of a higher displayed SpO_2.
Infant D has the same displayed SpO_2 as infant C (93%). However, his pulse oximeter is located on his left foot (postductal) and he has received blood transfusions. His PaO_2 is considerably higher (95mmHg) compared to infant C (43mmHg) putting him at risk for oxygen toxicity. A higher hemoglobin concentration results in higher arterial oxygen content.

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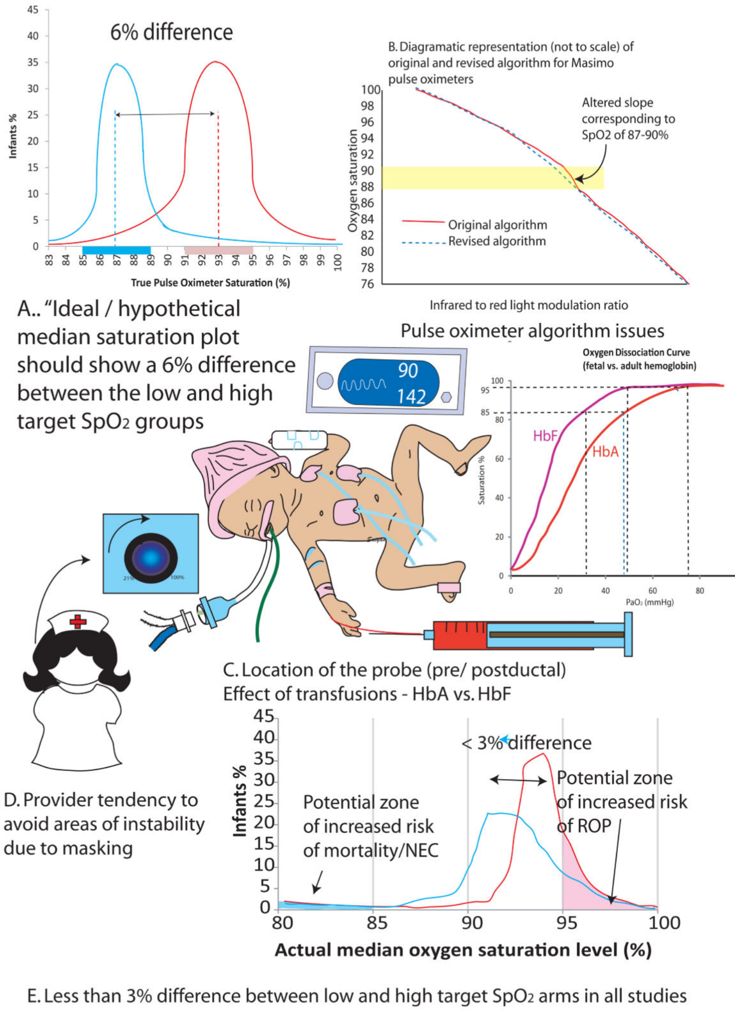

Figure 2.

Infographic showing an overview of reasons for decreased separation between the low and high target SpO_2 arms in SUPPORT, BOOST-II and COT trials. The intended separation between the two groups during periods of oxygen supplementation was 6% (A). The original Masimo algorithm had a steeper slope in the infrared to red light modulation ratio curve corresponding to 87–90% SpO_2 resulting in a maximal increase in 2% point increase in displayed SpO_2 around this range (B). The effect of location of the probe (preductal vs. postductal and gradual increase in hemoglobin A with transfusions might have altered the relationship between SpO_2 and PaO_2 in the retinal (and intestinal) circulation (C). Instability secondary to masking possibly led to a tendency to increase FiO_2 in the low target group and decrease FiO_2 in the low target group when displayed SpO_2 was in the unstable zone (D – see figure 3). The end result was a lower than intended separation between the two SpO_2 target zones (E).

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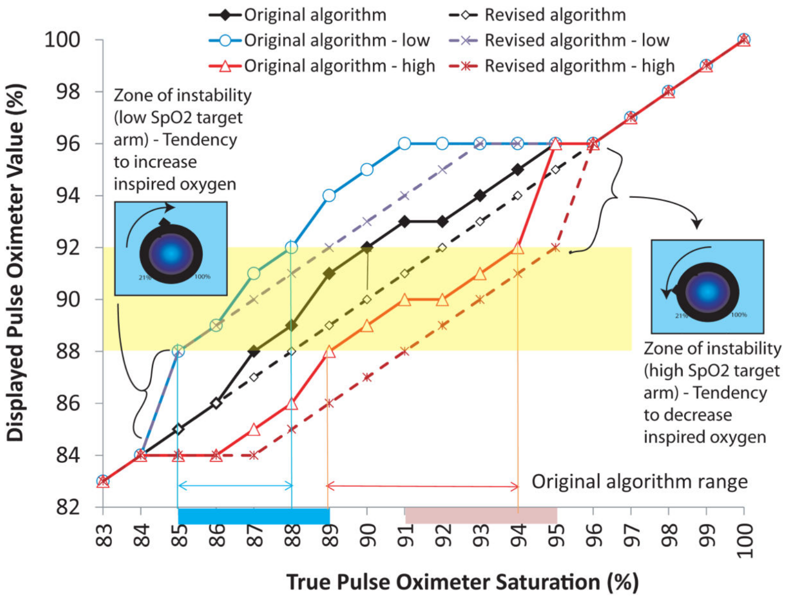

Figure 3. Effect of pulse oximeter algorithm and masking on SpO_2 target range

This graph shows SpO_2 based on the revised algorithm on the X-axis (“true” saturation) and displayed SpO_2 values on the Y-axis. The dark black line with closed diamonds approximately correlates to increased SpO_2 values in the 87–90% range in the original algorithm (i.e., SpO_2 of 90% would be advanced by 1.6% to read as 91.6 or rounded to 92%). The yellow horizontal bar represents the SpO_2 range recommended by the protocol for bedside providers during the study period. The blue open circles represent the display from pulse oximeter units modified to the low SpO_2 arm (85–89%) using the original algorithm. The blue vertical lines show that the “true” target in these infants was approximately 85 to 88% based on the revised algorithm. The red open triangles represent the display from the pulse oximeter units modified to the high SpO_2 arm (91–95%) using the original algorithm. The red vertical lines shows that the “true” target in these infants was approximately 89 to 94% on the revised algorithm reducing the separation between the low and high SpO_2 arms. The purple and crimson crosses represent the display from pulse oximeter units modified to low and high SpO_2 arms respectively based on the revised algorithm. The display of 88–92% to the bedside providers using the revised algorithm corresponded to 85–89% in the low arm and 91–95% in the high arm (blue and pink bars along the X-axis). The instability in displayed SpO_2 between 84–88% on the Y-axis in the low SpO_2 target group possibly led to a tendency to increase FiO_2. Similarly, the instability of displayed SpO_2 between 92 and 96% in the high SpO_2 target group might have led to a tendency to decrease FiO_2. The net effect of the algorithm change and the effect of masking was decreased separation between the two groups (see text for details; modified from BOOST II protocol and reference [44]).

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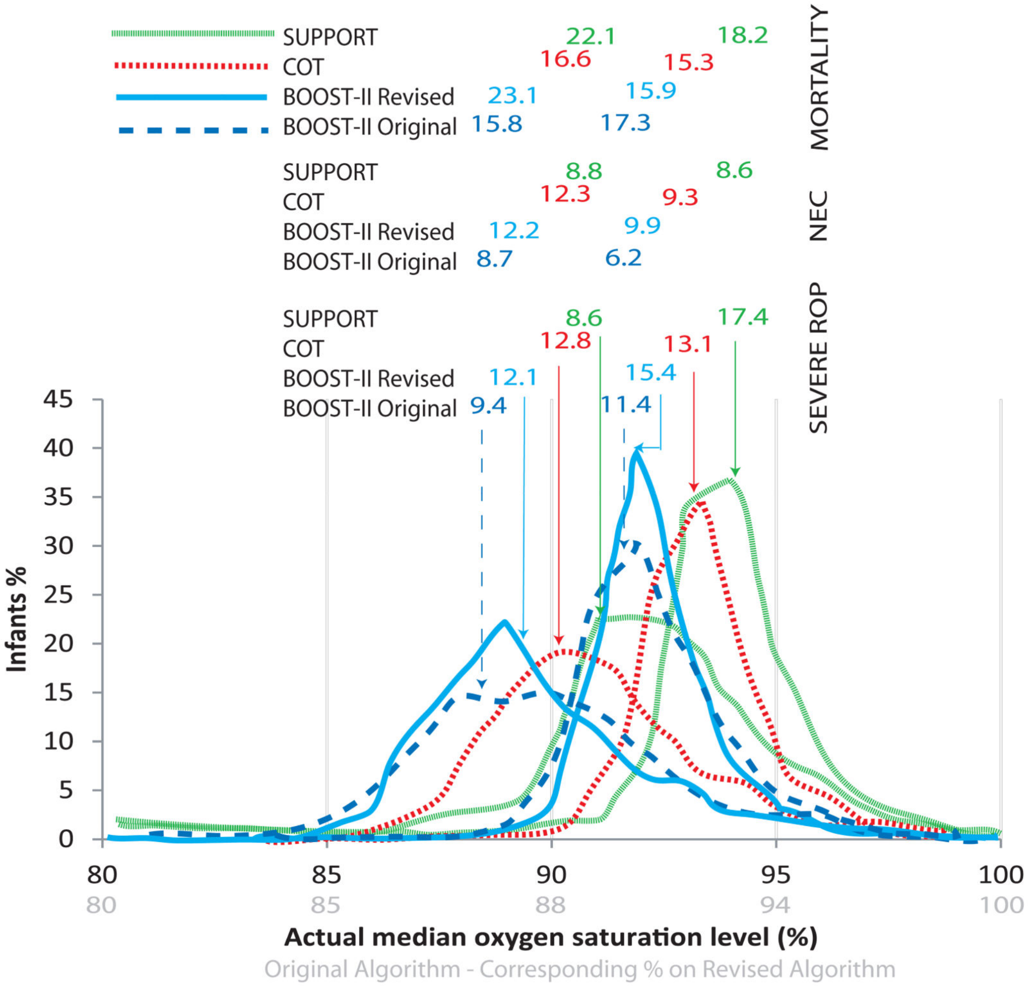

Figure 4.

Distribution of actual median oxygen saturation in the low SpO_2 (85–89%) and high SpO_2 (91–95%) arms in SUPPORT (green), COT (dotted red) and BOOST-II (revised algorithm – solid blue and original algorithm – hyphenated blue) studies: Mortality numbers currently available are shown as % (note that 18–22 month mortality numbers are currently not available for BOOST-II UK and Australia trials and reflect mortality at discharge). Currently available numbers for the incidence of severe ROP and NEC are shown. Since SUPPORT and original algorithm BOOST-II data are reported using the original algorithm, corresponding SpO_2 numbers on the revised algorithm are shown in grey color. A saturation of 90% in the original algorithm corresponds to a saturation of 88% on the revised algorithm.

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Table 1

Values of variables related to oxygenation status at different ranges of oxygen saturation in preterm lambs

SpO_2 range (%)	**60–84**	**85–89**	**91–95**	**96–99**
N (samples)	**96**	**89**	**117**	**218**
Hemoglobin (g/dL)	12.7 ± 1.3	12.4 ± 1.4	12.7± 0.9	12.5 ± 1
P_aO_2 (mmHg)	49 ± 56[†*]	50 ± 10[†*]	85 ± 76[¶*]	123 ± 105[¶†]
Preductal SpO_2 (%)	74 ± 8[¶†*]	87 ± 1[†*]	92 ± 2[¶*]	98 ± 1.5[¶†]
SaO_2 (%)	75 ± 19[¶†*]	87 ± 6[†*]	92 ± 4[¶]	94 ± 4[¶]
Pulmonary Art SO_2 (%)	64 ± 17[¶†*]	79 ± 8[†*]	83 ± 6[¶]	85 ± 6[¶]
PVR	1 ± 0.6[¶†*]	0.8 ± 0.4[†*]	0.5 ± 0.2[¶]	0.5 ± 0.2[¶]
Q_p (ml/kg/min)	63 ± 31[†*]	67 ± 39[*]	78 ± 22	82 ± 22[¶]
$P_{pa}O_2$ (mmHg)	25 ± 2	28 ± 3	33 ± 5	36 ± 7
CaO_2 (mL/dL)	12.9 ± 3.3[¶†*]	14.8 ± 2.2[*]	15 ± 2.6[*]	16.3 ± 2.1[¶†]
OER (%)	12.8 ± 10.7[†*]	11.5 ± 7.1	9.6 ± 7	8.8 ± 5.4

Data are shown as mean ± SD; derived from 520 simultaneous right carotid arterial and mixed venous (pulmonary arterial) blood gases.

PaO_2 – partial pressure of oxygen in the arterial blood

PVR – pulmonary vascular resistance

Qp – Left pulmonary arterial blood flow per kg body weight

$P_{pa}O_2$ – Mixed venous/main pulmonary arterial partial pressure of oxygen

CaO_2 – arterial oxygen content in mL/dL

OER – oxygen extraction ratio = (arterial oxygen content – venous oxygen content) × 100/arterial oxygen content

[¶] p< 0.01 compared to 85–89%

[†] p< 0.01 compared to 91–95%

[*] p < 0.01 compared to 96–100%