Retinopathy of Prematurity and the Oxygen Conundrum

Lessons Learned from Recent Randomized Trials

Brian W. Fleck, MD, FRCOph[a,*], Ben J. Stenson, MD[b]

KEYWORDS

- Oxygen supplementation • Retinopathy of prematurity • Preterm infants
- Neonatal Oxygenation Prospective Meta-analysis (NeoPROM) collaboration

KEY POINTS

- Retinopathy of prematurity (ROP) was first recognized as oxygen supplementation was introduced into neonatal care in the 1940s.
- Oxygen was quickly recognized to have an important role in the causal chain.
- Randomized controlled trials have consistently shown that restricting oxygen results in a lower incidence of severe ROP but at a cost of increased mortality.
- Present evidence suggests that it is unwise to target oxygen-saturation values less than 90% in preterm infants born before 28 weeks' gestation.
- Implementing this evidence is likely to result in a small increase in severe ROP.
- New approaches to the prevention of ROP are required.

HISTORICAL BACKGROUND

When Joseph Priestly first described oxygen more than 200 years ago he raised caution about possible toxicity, commenting that, if breathed by a healthy person, it may cause them to live out too fast. Oxygen rapidly came into use in the care of preterm infants in the 1940s. Seventy years later, the optimal balance of administration to avoid the consequences of both hyperoxia and hypoxia remains unknown.

Terry[1] first described retrolental fibroplasia (RLF), now known as retinopathy of prematurity (ROP), in 1942. Campbell[2] suggested a link with oxygen treatment in 1951. Patz and colleagues[3] published a small clinical trial 1952, which showed that higher levels of inspired oxygen were associated with a higher risk of cicatricial RLF. Ashton[4,5] showed toxic effects of oxygen on retinal blood vessel development in a kitten model. His work further emphasized the toxic effects of oxygen on developing

[a] Department of Ophthalmology, Princess Alexandra Eye Pavilion, Chalmers Street, Edinburgh, EH3 9HA, UK; [b] Neonatal Unit, Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh, Edinburgh, EH16 4SA, UK
* Corresponding author.
E-mail address: Brian.Fleck@ed.ac.uk

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retinal blood vessels, and he recommended that "only the minimal amount consistent with the infant's survival" should be used.

Askie and colleagues[6] summarized the results of oxygen trials in preterm infants in the 1950s in a Cochrane Review. The largest study was published in 1956: the cooperative study of retrolental fibroplasia and the use of oxygen. Reduced (curtailed) oxygen therapy resulted in a lower incidence of RLF than giving 50% oxygen for 28 days of postnatal (routine) oxygen therapy, which was the standard of care at that time.[7] Both vascular RLF and cicatricial RLF occurred more frequently in the routine-oxygen-therapy group. The power calculation for the study was based on the incidence of RLF, not on mortality, and no significant difference in mortality was found between the groups.

INCREASED MORTALITY AND MORBIDITY WITH OXYGEN RESTRICTION

Following publication of the cooperative study, a policy of restricted oxygen therapy was universally adopted. It was anticipated that RLF could be prevented by this approach.[8] However, an excess mortality among preterm infants on the first day of life was clearly shown by Cross[9] using epidemiologic data in 1973. It was estimated that for every case of blindness prevented, 16 infants died.[9] The optimal level of oxygen therapy was unknown, and Cross[9] called for increased resources for the intensive care of preterm infants.

ARTERIAL BLOOD GASES AND TARGET RANGES FOR P_{O_2}

In the 1960s and 1970s it became possible to measure arterial P_{O_2} by sampling blood from umbilical arterial catheters and thus to titrate oxygen against intermittent measurements of P_{O_2}. Initial practice was to aim for the P_{O_2} of healthy older individuals. Observational data did not link the development of ROP to exposure to any particular P_{O_2} level,[10,11] but prospective trials of different P_{O_2} target ranges were not performed. The introduction of transcutaneous P_{O_2} electrodes enabled oxygen to be titrated against P_{O_2} continuously rather than against infrequent blood samples. Bancalari and colleagues[12] asked whether using continuous monitoring of transcutaneous oxygen tension (TcP_{O_2}) would reduce the incidence and/or severity of ROP. The target range for P_{O_2} was 50 to 70 mm Hg (6.7–9.3 kPa). The overall incidence of retinopathy was 51% in the transcutaneous group versus 59% in the standard-care group. Mortality was 32% in the continuous-monitoring group versus 24% in the standard-care group. Neither difference was statistically significant. With an 8% absolute reduction in ROP associated with continuous monitoring but also an 8% increase in mortality, it is regrettable that the trial was not larger because, with the benefit of hindsight, 25 years ahead of the recent trials, this study may represent the first evidence from the era of targeted oxygen therapy that more stringent control of oxygen against measures of oxygenation reduces ROP but at a cost of increased mortality. In a post-hoc analysis of the TcP_{O_2} levels during oxygen therapy in the infants in the continuous-monitoring group, there was a statistically significant relationship between time spent with TcP_{O_2} greater than 80 mm Hg (10.6 kPa) and the incidence and severity of ROP.[13] It became increasingly common practice to target a P_{O_2} range of 50 to 80 mm Hg and this was recommended in clinical guidelines.[14]

OXYGEN-SATURATION MONITORING

From the 1990s, oxygen-saturation (Sp_{O_2}) monitoring became increasingly popular as the main guide to supplemental oxygen administration in neonatal units, which was an

important change in approach. Po_2 and Spo_2 are not linearly related, and the many factors influencing hemoglobin/oxygen affinity mean that the Po_2 associated with a given Spo_2 varies within and between infants. As a result, target Po_2 ranges cannot readily be converted to target Spo_2 ranges. Trials were not done to determine whether this move to Spo_2 monitoring would be associated with improved clinical outcomes compared with $TcPo_2$ monitoring or to determine the optimal Spo_2 range to target. In a randomized crossover study in preterm infants comparing transcutaneous $TcPo_2$ monitoring with saturation Spo_2 monitoring, oxygenation was more variable while using Spo_2 than when using $TcPo_2$.[15] A case control cohort study had previously shown that $TcPo_2$ oxygen variability during the first 2 weeks of life was associated with an increased risk of severe ROP.[16] Clinical practice in terms of Spo_2 target range varied widely between neonatal units.[17,18] In the absence of high-quality evidence defining the boundaries, clinicians were attempting to steer a middle way between possible complications of hyperoxia and of hypoxia. Most current research now relates the risks and benefits of different approaches to oxygen administration to measures of Spo_2.

PATHOGENESIS OF ROP: UNDERSTANDING THE EFFECTS OF OXYGEN SUPPLEMENTATION DURING THE TWO PHASES OF ROP DEVELOPMENT

In the past, the pathogenesis of RLF was understood in terms of the clinical oxygen supplementation regimens used in the early 1950s. Several weeks' exposure to high concentrations of inspired oxygen was followed by a rapid return to room air.[3] In a kitten model, this resulted in a vaso-obliteration phase during exposure to high concentrations of oxygen, and a vasoproliferation phase on return to room air.[5] However, understanding of the two phases of ROP development has altered with progress in clinical practice and with the development of better experimental models.

Human retinal blood vessel development normally occurs in a hypoxic environment in utero. The concept of physiologic hypoxia–driven, vascular endothelial growth factor (VEGF)–mediated angiogenesis[19] is central to the current understanding of early postnatal retinal blood vessel development in premature infants.[20] Preterm birth results in higher blood and tissue oxygen levels, which are further increased by oxygen supplementation. Physiologic hypoxia is reduced and retinal vascularization is delayed. In addition, serum levels of insulin like growth factor 1 (IGF1) are low at this time.[21] IGF1facilitates VEGF signaling,[22] and low serum levels of IGF1 contribute to delayed retinal vascularization: phase 1 of ROP development.[20] Clinical studies of oxygen therapy started soon after birth and continued during the first few weeks of postnatal life investigate this phase of ROP development.

Phase 2 of ROP development occurs when normal angiogenesis is overtaken by pathologic angiogenesis. The peripheral avascular retina continues to grow, and VEGF secretion into the vitreous increases. At the same time, serum IGF1 levels increase,[21] facilitating the effects of VEGF on retinal angiogenesis.[22] Abnormal blood vessels grow out of the retina, toward the high concentrations of VEGF in the vitreous. Extraretinal growth of vascular tissue is termed stage 3 ROP. It has been postulated that increased oxygen supplementation may be beneficial during phase 2 of ROP development: increased tissue oxygen may reduce VEGF levels and arrest progression to severe ROP. Clinical studies of oxygen therapy performed during this phase, typically after 32 weeks gestational age, may be expected to produce different effects on retinal blood vessel development than studies performed in the earlier postnatal period.

THE SUPPLEMENTAL THERAPEUTIC OXYGEN FOR PRETHRESHOLD RETINOPATHY OF PREMATURITY TRIAL

The concept that relative hypoxia in the peripheral avascular retina is responsible for the pathologic angiogenic response in the second phase of ROP, and that this response might be mitigated by increased supplemental oxygen, was tested in the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial, published in 2000.[23] This trial differed from other oxygen trials in that it was designed to test a possible treatment of acute, severe ROP, rather than to prevent the development of severe ROP.

Infants with prethreshold ROP in at least 1 eye, who had an oxygen saturation less than 94% in room air, were randomized at a mean postmenstrual age of around 35 weeks to oxygen therapy that resulted in 89% to 95% saturation (conventional oxygen), or 96% to 99% saturation (supplemental oxygen). Forty-eight percent of infants on conventional oxygen and 41% of infants on supplemental oxygen progressed to threshold ROP. After adjustment for baseline factors, there was no significant difference between the groups. At 3 months after term, there was no difference in the structural outcome of the retina (4.8% abnormal in the conventional group and 4.1% in the supplemental group). The supplemental-oxygen group had worse systemic outcomes, with pneumonia or worsening chronic lung disease in 13.2% versus 8.5% in the conventional-oxygen group.

COHORT STUDIES OF REDUCED-OXYGEN THERAPY

Several cohort studies published during the 2000s pointed toward reduced-oxygen treatment producing fewer cases of severe ROP.[17,18,24] Chow and colleagues[24] described a single-center historical comparison, with reduced severe ROP following the adoption of a policy of reduced and more stable oxygen therapy. Tin and colleagues[17] measured the rate of severe ROP in several treatment centers that used differing oxygen therapy policies. They found an association between reduced rates of severe ROP and the use of low-oxygen-saturation protocols. There was no identifiable increase in other morbidities or mortality with lower Spo_2 targets. Anderson and colleagues[18] reported a survey of 142 neonatal treatment centers in North America. Again, there was an association between reduced rates of severe ROP and the use of low-oxygen-saturation protocols.

THE BENEFITS OF OXYGEN SATURATION TARGETING STUDY

The Benefits of Oxygen Saturation Targeting (BOOST) study[25] was performed in Australia, and was published in 2003. The hypothesis behind the study was that chronic hypoxemia in preterm neonates would result in poor growth and development. The power calculation for the study was based on postnatal weight gain and the rate of major developmental abnormality at 12 months of age. Infants born at less than 30 weeks' gestation, who remained oxygen dependent at 32 weeks postmenstrual age, were randomized to standard-saturation oxygen therapy to maintain Spo_2 in the range of 91% to 94%, or high-saturation oxygen therapy with Spo_2 in the range of 95% to 98%. A major innovation in the trial design was the use of specially modified Nellcor N-3000 oximeters that had been internally offset by the manufacturers to read 2% higher or 2% lower than the true Spo_2 so that the intervention could be properly masked, which meant that, if caregivers used an allocated trial oximeter to target the displayed Spo_2 range of 93% to 96%, the patient would have an actual target range of either 91% to 94% or 95% to 98%. Spo_2 data were downloaded from the trial

oximeters to measure the actual achieved Spo_2 ranges of the two groups and this was plotted in the form of pooled frequency distributions, as shown in **Fig. 1**. The study methodology resulted in different Spo_2 distributions between the two randomization groups.

The study found no significant differences in the primary outcomes of growth or major developmental abnormality at corrected age 12 months. There was no significant difference in the rates of ROP, of any stage, between the two groups. There was no significant difference in the proportion of infants who needed treatment of acute ROP in the two groups: 20/178 (11%) in the standard-saturation group and 11/180 (6%) in the high-saturation group ($P = .09$). All infants treated for ROP had a gestational age at birth of less than 28 weeks. The proportions of infants of gestational age at birth of less than 28 weeks who needed treatment of acute ROP was 20/124 (16%) in the standard-saturation group, and 11/132 (8%) in the high-saturation group ($P = .06$).

The timing of oxygen therapy intervention is important when interpreting the results of the first BOOST trial. The oxygen interventions were started at 32 weeks' gestation, consistent with the timing of phase 2 of ROP development. This timing may account for the (nonsignificant) reduction of severe ROP in the high-oxygen-saturation group, as also occurred in the STOP-ROP trial.

NEONATAL OXYGENATION PROSPECTIVE META-ANALYSIS COLLABORATION

Following completion of the first BOOST trial, it was recognized that, although individual oxygen treatment trials could show moderate to large differences in mortality and morbidity between groups, a large number of subjects is needed to show a smaller, but clinically significant, difference in mortality or severe disability.[26] A sample size of 5000 infants is needed to detect a 4% difference in death or severe disability.[26] A collaboration of 5 national multicentre randomized controlled trials was formed (**Box 1**), with harmonized study protocols and advance agreement to perform a meta-analysis of the studies.[26] The opposing concerns to be studied were that infants exposed to lower levels of oxygen (<90% saturation) during the first few weeks of life

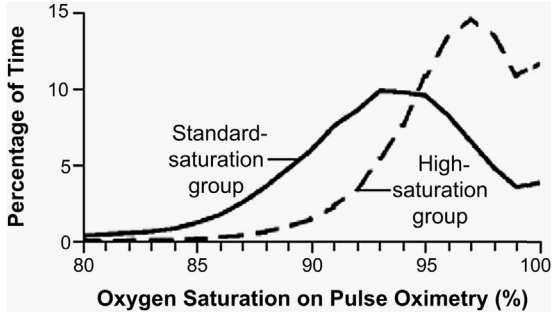

Fig. 1. Pooled frequency distribution curves of time spent at each oxygen saturation in the two groups in the first BOOST trial. The saturation values were sampled every 10 seconds during intermittent downloads performed approximately twice weekly and lasting 8–24 hours each. The median oxygen saturation was 93% in the standard-saturation group (interquartile range, 90%–96%) and 97% in the high-saturation group (interquartile range, 94%–98%). (*From* Askie LM, Henderson-Smart DJ, Irwig L, et al. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003;349(10):963; with permission. Copyright © 2003, Massachusetts Medical Society.)

Box 1
Trials include in the NeoPROM prospective meta-analysis collaboration

Name of Trial	Country	Planned Sample Size
Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)	United States	1310
BOOST II	Australia	1200
BOOST II	New Zealand	320
BOOST II	United Kingdom	1200
Canadian Oxygen Trial (COT)	Canada	1200

may be at greater risk of death, cerebral palsy, patent ductus arteriosus (PDA), pulmonary vascular resistance, and apnoea,[27–29] whereas infants exposed to higher levels of oxygen (>90% saturation) may be at greater risk of ROP[17,18,24] and chronic lung disease. The (negative) hypothesis of the Neonatal Oxygenation Prospective Meta-analysis (NeoPROM) collaborative meta-analysis is that, compared with a target range for Spo_2 of 91% to 95%, targeting Spo_2 of 85% to 89% within 24 hours of birth until 36 weeks postmenstrual age is associated with less than 4% absolute risk difference in mortality and major disability by 2 years of age.

As in the first BOOST study, the 5 NeoPROM trials used specially offset oximeters to mask the intervention. Masimo Radical oximeters were modified by the manufacturers so that, within the Spo_2 range 85% to 95% they displayed a reading that was either 3% higher or 3% lower than the monitored reading. By targeting a range of 88% to 92%, infants cared for with trial oximeters would thus be targeted to a range of either 85% to 89% or 91% to 95%. Outside the range of 85% to 95%, the oximeters transitioned gradually back to an unmodified reading. Infants born before 28 weeks' gestation were included and the allocated treatment was commenced within 24 hours of delivery. The study interventions were continued until 36 weeks gestational age.

The prospective meta-analysis of data from these 5 trials will take place once each individual trial has reported its primary outcome data. At this time, all of the trials have stopped recruiting infants. Follow-up has been completed in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), the New Zealand BOOST II trial, and the Canadian Oxygen Trial (COT) and is ongoing in the UK and Australian BOOST II trials.

NEOPROM TRIALS: AN UNFORESEEN PROBLEM WITH THE OXIMETER CALIBRATION ALGORITHM

After the NeoPROM trials had started, it was shown in a separate investigation by the UK trial investigators that standard Masimo Radical oximeters returned fewer Spo_2 values from 87% to 90% than expected.[30] Spo_2 values were downloaded from the oximeters used in the routine care of 176 oxygen-dependent preterm infant in 35 UK and Irish Neonatal Units. The downloaded Spo_2 data were pooled and plotted as a frequency histogram similar to that published in the first BOOST trial. There was a dip in the histogram, with fewer values than were expected in the Spo_2 range of 87% to 90% (**Fig. 2**).

Because this could affect the lower and higher Spo_2 randomization groups in the oxygen trials differently and might therefore affect the trial results, it was investigated further with assistance from Masimo. A systematic shift up in the oximeter calibration curve between 87% and 90% reduced the frequency of displayed Spo_2 values

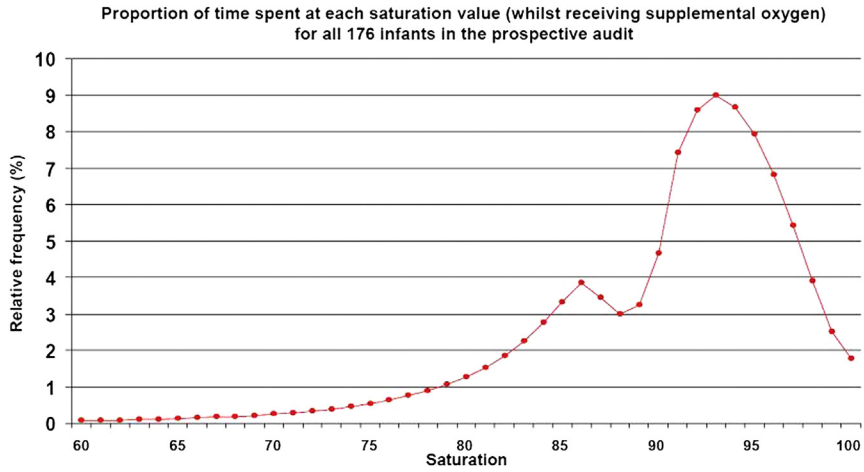

Fig. 2. Pooled frequency distribution curve of time spent at each oxygen saturation while receiving supplemental oxygen in 176 oxygen-dependent preterm infants monitored using standard Masimo Radical oximeters. CI, confidence interval. (*From* Johnston ED, Boyle B, Juszczak E, et al. Oxygen targeting in preterm infants using the Masimo SET Radical pulse oximeter. Arch Dis Child Fetal Neonatal Ed 2011;96:F430; with permission.)

between 87% and 90% and caused Spo_2 values more than 87% to read up to 2% higher, with this increase maximal at an Spo_2 of 90% and becoming smaller at higher values such that it disappeared at Spo_2 values more than 96%. The shift up in the calibration curve has the effect of narrowing the available target range of the lower target group but not the high target group. An increase of the SPo_2 values in the high target group means that their actual values were lower, effectively narrowing the difference between groups.

Masimo supplied software with a revised calibration algorithm that eliminated the unwanted effect and, in direct within-patient comparisons in oxygen-dependent preterm infants, this performed similarly to commonly used oximeters from other manufacturers.[30] The revised calibration algorithm was installed into the trial oximeters in the UK and Australian BOOST II trials between December 2008 and May 2009 and all infants recruited after this time were managed with the revised oximeters. Investigation of the Spo_2 patterns of infants recruited to the trials before and after the change showed that the Spo_2 distributions of the infants were affected by the change and that clearer separation of saturation patterns between the randomization groups was achieved with the new oximeter calibration algorithm than with the original oximeters. It was considered that results obtained with the revised oximeters were likely to be more generalizable.

NEOPROM TRIALS: INITIAL RESULTS FROM THE SUPPORT TRIAL

SUPPORT was the first NeoPROM trial to complete recruitment and report hospital discharge outcomes.[31] The study recruited 1316 infants.[31] A two-by-two factorial design was used; testing 2 forms of ventilation (surfactant with ventilation vs continuous positive airway pressure), and 2 oxygen therapy saturation ranges (85%–89% vs 91–95%).

The primary composite outcome for the short-term analysis of the oxygen component of the study was severe retinopathy or death before 36 weeks' gestation,

although this was changed to severe retinopathy or death before hospital discharge before the initial analysis of the study was performed.[31] Severe retinopathy was defined as ROP that required ophthalmic treatment intervention. There was no significant difference between the groups for the primary composite outcome. However, 130 of 654 (19.9%) infants in the lower-oxygen-saturation group died before hospital discharge, compared with 107 of 662 (16.2%) infants in the higher-oxygen-saturation group (relative risk for lower saturation 1.27, 95% confidence interval [CI] 1.01–1.60, $P = .04$). The rate of severe retinopathy was lower in the lower-oxygen-saturation group (8.6% vs 17.9%, relative risk for lower saturation 0.52, 95% CI 0.37–0.73, $P<.001$). The published report recommended that caution should be exercised regarding a strategy of targeting oxygen-saturation levels in the low range for preterm infants because it may lead to increased mortality. These data were published while the other oxygen trials were still recruiting.

NEOPROM TRIALS: EARLY TERMINATION OF THE UK AND THE AUSTRALIAN TRIALS

In December 2010, the Data Monitoring Committees (DMCs) of the UK and Australian and New Zealand BOOST II trials undertook a joint interim safety analysis, pooling interim data from the 3 trials and considering them alongside the published data from the SUPPORT trial.[32] The sole outcome considered was survival to 36 weeks' gestation. The analysis considered data from 2315 infants in the UK and Australian and New Zealand BOOST II trials, plus 1316 infants in the SUPPORT trial. There were data for 1055 infants recruited to the UK and Australian trials after the revision of the oximeters. Guidelines for the analysis prespecified that the trial investigators would only be unblinded to the results if a difference in survival between groups for all infants, or for the infants treated using the new oximeters, exceeded 3 standard errors (equivalent to 99.73% CIs, or a P value <.003). Results of the analysis are shown in **Fig. 3**.

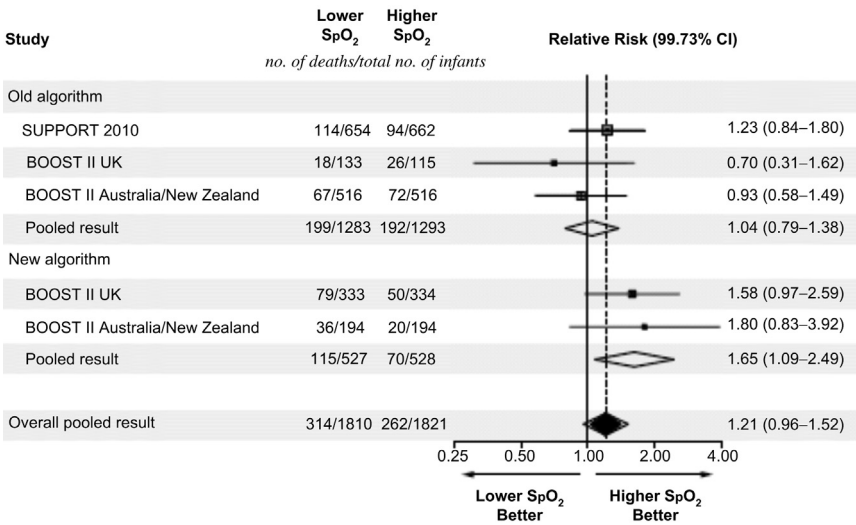

Fig. 3. Interim safety analysis performed by the Data Monitoring Committees of the United Kingdom, Australian, and New Zealand BOOST II trials, which included data from the SUPPORT study. (*From* Stenson B, Brocklehurst P, Tarnow-Mordi W, et al. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. N Engl J Med 2011;364(17):1681; with permission. Copyright © 2011, Massachusetts Medical Society.)

When all 3631 infants were included in the analysis, the infants randomized to Spo_2 of 91% to 95% had greater survival to 36 weeks. Mortality was 17.3% with the low target and 14.4% with the higher target ($P = .015$). Considering only the 1055 infants treated with the revised oximeters, there was a larger survival advantage to targeting higher Spo_2. Mortality was 21.8% in infants targeted to lower Spo_2 versus 13.3% in infants targeted to higher Spo_2 (relative risk for survival with higher Spo_2 1.65, 99.73% CI 1.09–2.49, $P<.001$). A test of interaction was highly significant, suggesting that the treatment effects observed with the original and revised oximeter calibration algorithms were significantly different ($P = .006$). In view of the substantial survival advantage associated with targeting higher Spo_2, recruitment to the BOOST II trials in the United Kingdom and Australia was halted. The other NeoPROM trials had already completed recruitment. It was concluded that, pending the results of longer term follow-up, it was prudent not to target Spo_2 of 85% to 89% in preterm infants.

Considering only the results obtained before the revision of the oximeter calibration algorithm, in the 2576 infants recruited to the 3 BOOST trials and the SUPPORT trial, mortality was not different between Spo_2 treatment groups. The revision of the oximeter calibration algorithm eliminated an unphysiologic artifact and the results obtained after this revision are likely to be more generalizable to clinical practice than the earlier results. If the oximeters had not been revised, it is possible that an incorrect conclusion that targeting Spo_2 less than 90% had no effect on mortality would have been reached, potentially repeating the errors from earlier in the oxygen story.

NEOPROM TRIALS: SUPPORT TRIAL OUTCOMES AT 18 TO 22 MONTHS

The SUPPORT trial has recently published follow-up data to 18 to 22 months.[33] The primary composite outcome for the longer term analysis was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months corrected age.[33] There was no significant difference between the higher-oxygen-saturation group and the lower-oxygen-saturation group for the primary composite outcome. However, mortality was higher in the lower-oxygen-saturation group (22.1% vs 18.2%, relative risk for lower saturation 1.25, 95% CI 1.00–1.55, $P = .046$).

Five of 479 (1.0%) infants in the lower-oxygen-saturation group and 6/511 (1.2%) infants in the higher-oxygen-saturation group were bilaterally blind (visual acuity <20/200) at 18 to 22 months' follow-up ($P = .86$). Thus, although the rates of acute, severe ROP were higher in the higher-oxygen-saturation group,[31] at 18 to 22 months' follow-up there were no differences between the two oxygen-saturation groups in the rates of blindness.[33]

Additional ophthalmic outcomes were available from the neurodevelopment assessments. Strabismus was found in 9.6% of infants in the lower-oxygen-saturation group and in 8.0% of infants in the higher-oxygen-saturation group ($P = .38$). These rates are similar to those reported in low-risk prethreshold cases in the Early Treatment of Retinopathy of Prematurity (ETROP) study, in which 9.6% of infants had strabismus during the first year of life.[34] Corrective lenses for both eyes were needed by 4.5% of infants in the lower-oxygen-saturation group and 4.1% of infants in the higher-oxygen-saturation group. Previous ophthalmic studies have shown a relationship between the severity of acute ROP and the subsequent development of myopia, and have shown progression of myopia over time.[35]

The results of the SUPPORT trial and the preliminary data from the three BOOST II trials show that targeting lower Spo_2 is associated with a significantly higher mortality risk. There is a need to await the follow-up data from all of the trials because, although there was no difference between groups in later neurodevelopmental impairment in

the SUPPORT trial, it is possible that this could still be observed in the other trials in infants treated with the revised oximeters.

Higher levels of oxygen saturation during the first few weeks of life result in an increased rate of severe ROP requiring treatment. However, effective treatment of most cases of severe ROP is now available,[36] so the clinical priority is survival. A small number of treatment failures continue to occur, as has been shown in previous ophthalmic treatment trials,[36] and in the SUPPORT study.[33]

FURTHER WORK

The full results of the studies in the NeoPROM collaboration are awaited. Further trials will be necessary. It is unlikely that the same Po_2 or saturation is ideal throughout gestation. It is unlikely that these trials have chanced on the approach that optimizes survival. It is important to recognize that, when oxygen was targeted to measurements of Po_2, the range in common use was 50 to 80 mm Hg. The historical switch to using Spo_2 monitoring that occurred with little supporting evidence was associated with a substantial shift downwards in Po_2. Spo_2 values less than 90% commonly permit Po_2 less than 40 mm Hg (**Fig. 4**).[15,37] A meticulous analysis of the oxygenation patterns over time that are associated with different adverse outcomes is required to inform the way forward. Any new interventions that affect oxygenation, such as closed-loop oxygen control systems should be evaluated carefully. The hope expressed in the 1950s

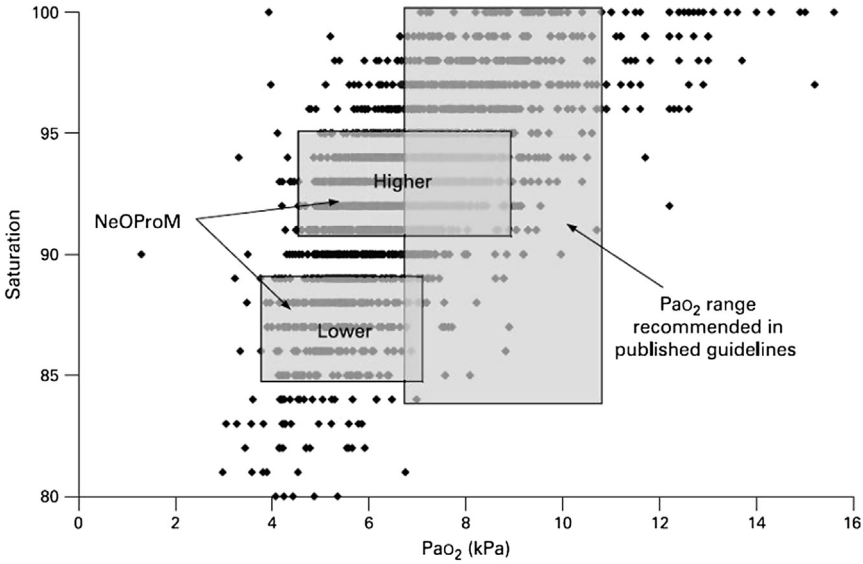

Fig. 4. Spo_2 plotted against Pao_2 from 2076 arterial blood gas specimens taken from oxygen-dependent preterm infants. At each Spo_2 the 95% CIs of Pao_2 for a given Spo_2 could be calculated. The smaller shaded boxes labeled higher and lower represent estimates of the likely 95% CI of Pao_2 for the Spo_2 values in the lower and higher Spo_2 groups in the NeoPROM trials. The larger shaded box shows the Pao_2 range 50 to 80 mm Hg as recommended in historical guidelines. (*From* Quine D, Stenson BJ. Arterial oxygen tension (Pao_2) values in infants <29 weeks of gestation at currently targeted saturations. Arch Dis Child Fetal Neonatal Ed 2009;95:F52(37), with permission; and *Data from* Myers TR, American Association for Respiratory C. AARC Clinical Practice Guideline: selection of an oxygen delivery device for neonatal and pediatric patients–2002 revision & update. Respir Care 2002;47(6):707–16.)

that ROP might be eliminated by oxygen restriction[8] must now be abandoned. Other approaches to reducing the incidence of severe ROP are needed.

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