COMMENTARIES

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Is Oxygen More Toxic Than Currently Believed?

ABBREVIATIONS. ROP, retinopathy of prematurity; CLD, chronic lung disease; CI, 95% confidence interval.

Scheele and Priestley discovered oxygen independently of each other in 1772 and 1774, respectively. It was quickly realized that this gas is not only life-giving but might be poisonous as well. However, what man has known for only 2 centuries nature itself has known for some 700 million years. One of the biggest leaps forward in evolution occurred when blue–green-like algae developed enzymes that scavenge the superoxide radical enabling them to live in an oxygen-rich atmosphere.

Shortly after its discovery, oxygen was used for medical purposes. In 1780 France’s Chaussier experimented giving oxygen to newborn infants who failed to establish normal breathing. In 1928 Flagg described a detailed procedure for intubation and intermittent positive pressure insufflation using a mixture of oxygen and carbon dioxide for resuscitation of asphyxiated newborns. Oxygen therapy for newborn infants was introduced in the United States in the 1930s and 1940s although the Finnish pediatrician Ylppo in 1917 had already recommended intragastric administration of oxygen, a practice that continued a surprisingly long time, into the mid-1950s. Not before the discovery of its relation to retrolental fibroplasia (retinopathy of prematurity [ROP]) were questions raised concerning the use of oxygen. The rest of the story is well-known: in the 1950s and 1960s the oxygen concentration was turned down in many incubators apparently resulting in a reduction in ROP but probably increased mortality.

In the 1970s the transcutaneous electrodes were introduced—first the oxygen and subsequently the carbon dioxide electrode. Such electrodes should be a means to strict control of the oxygenation of the neonate, and it was thought that the problem related to ROP was solved. Or perhaps it was not? One problem was that the skin of the most immature infants often could not tolerate the heated electrodes. Further, it became clear that these electrodes, however accurate and sensitive they are, in many cases give values that are too high or too low. During the 1980s many centers reported an increasing incidence of ROP, mainly attributable to the fact that more immature infants survived. However, it became clear that ROP is not only attributable to exposure of oxygen. Oxidative stress per se because of oxygen exposure and high oxygen content in the blood, increased oxidative stress mediated through inflammations, or reduced antioxidant defense might be important contributing factors.

In the 1980s pulse oximeters were introduced in neonatal intensive care units. Now arterial oxygen saturation could be followed continuously without any dermal harm even in the tiniest infants. These devices are noninvasive, easy to use, do not require calibration or heating of the skin, and give almost immediate information regarding changes in arterial oxygenation. Several problems related to the use of pulse oximeters were, however, revealed. They have a relatively high rate of false alarms, often caused by motion artifacts. They are also light-sensitive. Different models use different techniques. For instance, oximeters that display functional oxygen saturation show a somewhat (1.5%–3%) higher saturation than those recording so-called fractional saturations. But perhaps more importantly, if the saturations are too high, for instance >95%, the pulse oximeters do not give sufficient information about the oxygen tension, which could be very high.

Bronchopulmonary dysplasia or chronic lung disease (CLD) has also been recognized as a disease related to oxidative stress. A high oxygen concentration in inspired air therefore might be detrimental. Today we know that the truth is more complicated and that both barotrauma and volutrauma play roles. Still, oxidative stress seems to be an important factor triggering this condition.

The other side of the coin is that too low saturations increase pulmonary resistance, increase airway resistance, limit somatic growth, and perhaps also increase the risks of sudden death in infants with CLD.

Very recently at least 2 reports have explored whether a high saturation of oxygen may elevate the risks of lung and/or ophtalmologic injuries. The STOP-ROP trial tested whether a regime aiming at a high arterial oxygen saturation (96%–99% vs 89%–94%) for at least 2 weeks reduced further development of ROP once prethreshold retinopathy had been detected. No reduction in progression of ROP in the high-saturation group was found but there was a tendency for pneumonia and/or exacerbation of CLD to occur in more infants in the high- rather than in the low-saturation group (13% vs 8%). The need for supplemental oxygen at 50 weeks postmenstrual age was also lower in the low-saturation group (37% vs 47%; P = .02). In another study by Van Marter et
al a high concentration of inspired oxygen was found in infants developing CLD. A fraction of inspired oxygen of 1.0 the first day of life almost doubled the risk of CLD. In contrast, oxygen saturations were equivalent for those who developed and those who did not develop CLD.12

In a study by Tin et al13 the effect of 4 different oxygenation policies were studied in infants born between 23 to 27 weeks of gestation in the Northern England in 1990–1994. A total of 295 of these infants who survived infancy had been treated in 5 nurseries and monitored with pulse oximetry at least 4 weeks of their life. The policy regarding oxygen saturation was ascertained retrospectively and it became clear that 4 different regimes could be identified, namely supplemental oxygen given to maintain arterial oxygen saturations with alarm limits between: 1) 70% to 90%; 2) 84% to 94%; 3) 85% to 95%; and 4) 88% to 98%. It seemed that the nursing staff aimed at the upper range of these levels. For instance, in the first group with the lowest limits saturations were typically kept between 80% and 90%. Saturation was monitored using the Critikon (Critikon, Tampa, FL), Nellcor (Mallinckrodt Inc, Pleasanton, CA), Ohmeda (Datex-Ohmeda, Tewksbury, MA), or Radiometer (Radiometer, Copenhagen, Denmark) pulse oximeters throughout the time the infants were in supplemental oxygen, that is pulse oximeters depending on different techniques and therefore giving slightly different values. At 1 year of age there were no differences in either survival (44%–55%) or in incidence of cerebral palsy (15%–17%) among the groups. However, among the 126 infants with oxygen saturation limits between 70% and 90% only 6% (95% confidence interval [CI]: 1.7%–15%) had threshold retinopathy versus 28% (95% CI: 17%–40%) in infants aiming at oxygen saturations in the upper ranges, i.e., 88% to 98%. In the 2 groups between 14% and 16% of infants developed threshold retinopathy, respectively. When infants with the lowest saturations were compared with those with the highest saturations they required significantly shorter duration of both supplemental oxygen (40 vs 96 days) as well as artificial ventilation (14 vs 31 days).

Birth weights 940 (855–1074) g vs 910 (810–1018) g, gestational age 27.1 (26.2–27.3) weeks vs 26.4 (25.8–27.3) weeks and gender (46% vs 55% male) did not seem to differ between the low- and high-saturation groups. However, more infants in the highest than in the lowest saturation group had arterial lines in for >1 week (49 vs 2 infants). The high saturation infants also received more blood transfusions. Weight centiles fell more in the high than in the low-saturation group, and 45% of the former and 17% of the latter had a weight less than the third centile at discharge. The study by Tin et al has several obvious shortcomings that have been commented on by Marlow.14 First, it was not a randomized study. Although the patients were collected in a prospective collaborative observational study the different policies in the nurseries were assessed retrospectively. Different pulse oximeters were used in the different units and as mentioned above this could account for a 1.5% to 3% difference in the saturations measured. It is also not clear from this report whether the saturations were monitored preductally or postductally. The exact oxygen levels were not given but in a later reply the authors state that PaO2 ranged between 5 and 11 kpa (38–83 mm Hg) in the low-saturation group.15 The rate of retinopathy also seems to be extremely high in the highest oxygen saturation group compared with other centers in the United Kingdom.14 Could it be that the differences in outcomes found between the high-saturation and low-saturation groups mainly reflect differences in disease severity? Thus, the sicker infants were maintained at a higher oxygen saturation, required more arterial lines for longer time periods, needed more blood transfusions, and also had a slower weight gain? Although this might not be likely this and other questions as mentioned above can only be sorted out fully in a prospective, randomized study. Still the data presented by Tin et al are thought-provoking.

It has been acknowledged for 5 decades that oxygen might be harmful to premature infants, is it still possible that toxic reactions of oxygen are underestimated? Since we demonstrated that most newborn infants in need of resuscitation at birth can be resuscitated equally efficiently with room air as with 100% oxygen,16 2 more studies have shown that resuscitation with pure oxygen might have detrimental effects. Vento et al17 were able to show that newborn infants who were resuscitated with 100% oxygen have an increased oxidative stress for at least a month, in contrast to infants resuscitated with room air. Oxidative stress was assessed both by the ratio of reduced to oxidized glutathione in erythrocytes and oxidized mitochondrial DNA products in urine. Further, Temesvari and his colleagues found that 100% oxygen resuscitation of newborn piglets with pneumothorax had no advantage compared with room air. On the contrary, early neurologic outcome was significantly impaired in the oxygen resuscitated compared with room air resuscitated animals.18 This is in line with results from experiments with adult dogs with cardiac arrest where mortality was higher after resuscitation with 100% oxygen than with room air.19 The reason for this is not clear but it is evident that 100% oxygen resuscitation produces more oxygen-free radicals than room air resuscitation.20–23

If oxygen is a toxic substance even beyond our concept up to now perhaps it was correct as suggested by Sjostedt and Rooth 35 years ago that premature infants could be nursed in <21% oxygen? These authors found that growth and development apparently are normal in infants nursed in as low as 15%–16% oxygen.24 I don’t think this is the solution although this study shows us that it is possible to nurse premature infants at oxygen saturations <21%. A more recent study by Parkins et al25 showed that it is true that most healthy term infants at the age of 2 to 6 months of age could be nursed without any problems in 15% to 16% oxygen. However, in some of the infants, approximately 1 out of 8 severe and prolonged hypoxemia developed. It could not be determined in advance when the infants were in
room air which would develop hypoxemic episodes and which would not.

The study by Sjøstedt and Rooth as well as the recent one by Tin et al have taught us that the optimal arterial oxygen saturation of extremely premature infants the first weeks of life perhaps is not known. This is despite the fact that the normal oxygen saturation in both term and preterm infants during the first 24 hours of life has been studied extensively and found to be in median 98% with a range from 80% to 100%. During the first weeks of life both preterm and term infants seem to have a normal arterial oxygen saturation between 93% and 100% with mean/median values from 97% to 99%,26–29 The preterm infants in these studies ranged however between 30 and 36 weeks of gestation. In preterm infants with bronchopulmonary dysplasia Halliday et al have shown that a PaO₂ should be preferably >55 m Hg (7.3 kPa) to avoid pulmonary hypertension. The infants of that study were, however, not followed longitudinally.9

Do we know what the optimal arterial oxygen saturation of growing extremely premature infants is? Probably not. Although several recommendations exist, they are probably valid for the more mature premature infants only. These recommendations vary from keeping the saturation between 89% and 92% to values >92% in infants with CLD, and >94% if the child is on oxygen therapy.10 Perhaps new recommendations are needed for the most extreme premature infants with gestational ages between 23 and 27 weeks? Perhaps these infants should be nursed with lower oxygen saturations than used by mainstream nurseries up to now, at least the first few days of life? As mentioned above it seems that even a hyperoxic exposure during a few minutes after birth may increase the oxidative stress for weeks. Because oxidative stress influences apoptosis and cell growth, this may have long-term consequences on growth and development.30 If this is the case, there is a urgent need for well-controlled, multicenter trials testing out the optimal arterial oxygen saturation at the different days postpartum in our most tiny patients. However, as commented by Marlow as well,14 an arm testing out oxygen saturations climbing too high should be avoided and probably not accepted by ethical committees. Any such study needs long-term follow-up. If oxygen is toxic beyond present knowledge, we cannot wait with regard to getting these studies conducted.

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REFERENCES


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