ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803–5253

REVIEW ARTICLE

Hyperoxia in the term newborn: more evidence is still needed for optimal oxygen therapy

Ola Didrik Saugstad (odsaugstad@rr-research.no)

Department of Pediatric Research, Clinic of Women and Child Health, Oslo University Hospital, Rikshospitalet, University of Oslo, Oslo, Norway

Keywords
Air, Hyperoxia, Resuscitation, Term newborn infant

Correspondence
Ola Didrik Saugstad, Pediatrisk Forskningsinstitutt, Oslo Universitets sykehus, Rikshospitalet, PB 4950 Nydalen, 0424 Oslo, Norway.
Tel: +47 23072790/94 |
Fax: +47 23072780 |
Email: odsaugstad@rr-research.no

DOI:10.1111/j.1651-2227.2011.02546.x

ABSTRACT

It took more than 30 years from the first observations that oxygen may be toxic during resuscitation till international guidelines changed to recommend that term and near term newborn infants should be resuscitated with air instead of 100% oxygen. There are still a number of unanswered questions related to oxygen therapy of the newborn infant. The newborn brain, lungs and other organs are susceptible to oxygen injury, and newborns still develop injury caused by hyperoxia.

INTRODUCTION

Although it has been known for decades that oxygen is toxic, especially in newborns and premature infants, hyperoxic injury is still not uncommon in newborn infants. It took 30 years from our first description of a basic mechanism of so-called hypoxia-reoxygenation injury (1) until the international neonatology community realized that oxygen supplementation during resuscitation may be detrimental (2). The understanding 30 years ago that oxygen radicals are produced in excess during resuscitation with oxygen was based on two observations done almost 10 years earlier: (i) hypoxanthine accumulates in the blood of newborns during hypoxia (3) and increases exponentially the first minutes of resuscitation (4). (ii) Xanthine, and therefore hypoxanthine, is a potential free radical generator (5). Thus, it took almost four decades from the first observations till clinical practice was changed using air instead of 100% of oxygen in resuscitation of term newborn infants. Perhaps, this is what it takes and should take to change a paradigm in medicine?

Key notes

• The newborn lung and brain are vulnerable to hyperoxic injury. There is a window, the first week of life, in which the rodent brain is most vulnerable to hyperoxia. It is best to start resuscitation of term or near term infants with air and not oxygen. It took 30 years to change the oxygen paradigm. Still there are a number of unanswered questions regarding oxygenation of the newborn.

EFFECTS OF HYPEROXIA

Through the evolutionary process, the body tightly regulated its defence against low oxygen states. A master molecule, the transcription factor HIF-1α, is activated during hypoxia and transcribes a large number of genes which defend the organism against hypoxia. Among these are genes related to angiogenesis, erythropoiesis, increased breathing and glucose uptake resulting in reduced oxygen consumption and increased oxygen delivery. In normoxia and hyperoxia, HIF-1α is turned off and degraded (6,7).

In spite of the fact that man has less protection against hyperoxia induced for instant by medical treatment with supplemental oxygen, oxidative defence mechanisms have been developed through evolution. This fascinating part of

the evolutionary story is described and summarized by Lane in his book 'Oxygen, the molecule that made the world' (8). It is well known that already the first photosynthetic bacteria, the cyanobacteria, developed superoxide dismutase like enzymes, which were needed in order for life to survive in an increasingly hyperoxic atmosphere. The so-called Last Universal Common Ancestor of all known life was probably resistant to oxygen toxicity even before there was free oxygen in the air. How could this happen? It is hypothesized that life 4 billion years ago through evolution was forced through a 'radiation bottleneck' creating resistance not only to irradiations but also to oxygen and thus prepared eukaryotes to a life in an atmosphere high in oxygen (8). Another defence against oxygen was the origin of mitochondria which convert oxygen to water. In this way, the cells may take advantage of the highly efficient oxygen metabolism to produce ATP simultaneously reducing toxic oxygen to water. The early eukaryotes could thus inhabit water together with algae producing oxygen through photosynthesis.

The origin of multicellular organisms may have originated from a protection against oxidative stress. An example according to Lane (8) is the ciliate protozoa which has little resistance to oxygen. This species therefore swims towards water with low oxygen concentration. The higher the oxygen concentration, the faster they swim towards a lower oxygen area. However, when their surroundings are equally well oxygenated, they cannot escape and instead clump together in a mass, thus protecting the inner cells from a higher oxygen exposure. In accordance with this, the design, for instance of the human body, restricts delivery of oxygen to individual cells.

Although the primitive atmosphere was low in oxygen content, it gradually increased in oxygen level. The concentration of oxygen in the atmosphere has probably fluctuated and being higher than today, perhaps as high as 35%. Each rise in the oxygen concentration was followed by an expansion of life. The existence of giant plants and insects 270–320 million years ago may have occurred in periods with high oxygen concentration. Since then minor fluctuations probably found place until the present level of 21% (8). Therefore, life may have been adapted to higher oxygen levels than the present one.

Defence against hyperoxia may therefore have been developed not only through radiation but also by exposure to hyperoxia. Recently, it has been shown that *drosophila melanogaster* bred in for instance 90% oxygen for 13 generations could live, develop and reproduce in hyperoxia. The body weight increased, also with increased wing area, reaching a maximal weight in 70% oxygen (9).

WHY IS OXYGEN TOXIC?

In 1891, the Scottish chemist Sir James Dewar discovered that oxygen is magnetic (see 8). This results from the spin of unpaired electrons and makes it difficult for oxygen to form new chemical bonds owing to spin restriction. Oxygen can only receive single electrons with antiparallel spin to complete electron pairings. By feeding oxygen with one electron at a time for instance from iron the oxygen molecule is stabilized, this phenomenon explains the high affinity of iron to oxygen and the production of rust. During oxidative phosphorylation in the mitochondria, single electrons escape and join with 1–2% of the total oxygen consumed by the cells to form superoxide radicals; however, during physical exercise, this may increase to 10%.

By adding 2, 3 and subsequently four electrons to hydrogen peroxide, the hydroxyl radical and finally water are formed respectively. According to Lane (8), an average adult produces 1.7 kg of superoxide radicals each year.

It was in the 1950s that Gerschman and colleagues at the Manhattan project understood that hyperoxic injury and radiation injury share a common mechanism through free radicals (10), thus explaining how the evolution through the 'radiation bottleneck' as mentioned earlier, simultaneously prepared life to resist hyperoxia.

Oxygen radicals or reactive oxygen species (ROS) have a number of actions and oxidize free fatty acids, proteins and DNA. They have important physiologic properties as in the defence against microbes (11). They are also signalling substances, and redox processes probably are important for controlling growth and development. This was understood in the 1980s when several authors realized that ROS are the important regulators of the circulation (12,13) included the perinatal circulation (14,15).

Wright and Denery (16) recently reviewed other transcription factors than HIF-1α that play a role in hyperoxia:

1. NF-eryhtroid 2-related factor is activated by hyperoxia and activates antioxidant response element. This regulates detoxifying and antioxidant enzymes and increases expression of antioxidant enzymes. It is cytoprotective in type II cells of the lung and ameliorates O_2-induced lung injury in mice.
2. AP-1 controls genes regulating apoptosis, inflammation and oxidative stress.
3. NF-κB activates genes regulating apoptosis, inflammation and oxidative stress. It is activated by endotoxins and oxidative stress via Toll-like receptors in the cell membrane.
4. P53 regulates expression of target genes related to cell cycle arrest, cell death and DNA repair.
5. CCAT/enhancer-binding protein (CEBP) regulates cell proliferation and tissue development and is increased in the lung of rats exposed to hyperoxia.
6. STATs are polypeptides participating in signalling pathways and may be protective to hyperoxia by induction of heme-oxygenase, which is a highly inducible cytoprotective enzyme following exposure to hyperoxia.

TRANSITION FROM FOETAL TO POSTNATAL LIFE

The embryonic and foetal development occurs in a hypoxemic environment. This is a highly interesting observation and indicates that redox processes are of importance in regulating embryogenesis. In the foetus, the oxygen saturation of blood is around 50–60% (17). An important

question therefore is what the developmental consequences are when the redox status is changed in immature infants treated with oxygen to achieve a higher oxygen tension than in foetal life. This also shuts down HIF-1α in these babies (6,7).

EFFECTS OF OXIDATIVE STRESS ON THE NEWBORN BRAIN AND LUNGS

The neonatal brain is susceptible to oxidative stress because of its high content of polyunsaturated free fatty acids, its low antioxidative defence, presence of free iron, exposure to oxygen therapy and inflammations. Both neuronal and inducible nitric oxide synthetases (NOS) are high in the developing brain. Hypoxia activates NMDA receptors that lead to calcium influx and subsequent calmodulin activation of neuronal NOS. The presence of NO leads to the formation of peroxynitrite. This may initiate lipid peroxidation, but also exerts neuroprotection by inducing vasodilatation, angiogenesis and inhibition of platelet aggregation. Through its inhibition of cytochrome C release from mitochondria, peroxynitrite also has antiapoptotic actions. Activated microglia release both reactive oxygen and nitrogen species (18–20).

The immature and pre-oligodendrocytes are more vulnerable to oxidative stress than the mature oligodendrocytes (21). In rodents, it seems to be a sensitive window, the first week of life, when the brain is more easily injured by hyperoxia. For instance, in newborn rats at day 7 exposed to hyperoxia 24 h, there is induction of neuronal degeneration and apoptosis. A few days later, the brain is not so vulnerable to such exposure (22).

The lungs are directly affected by hyperoxia. Within a few days, type 1 cells disappear and are replaced by epithelial cells. The interstitium is thickened owing to oedema and influx of leucocytes. Growth is inhibited and so is protein synthesis. An oxygen-injured lung is therefore stiff with a low compliance (23–26).

WHY IS OXYGEN TOXIC DURING RESUSCITATION?

It had been known for decades that supplementation of oxygen after a period of lack of oxygen may be detrimental. Studies we did in Uppsala from 1973 lay a fundament to understand this process. With the help of my tutor, Gösta Rooth, I was able to construct a new method measuring hypoxanthine in small volumes of body fluids (27). Previously, it had been shown that hypoxanthine and other purines degraded from ATP during perfusion of hypoxic isolated organs as heart and kidney (28,29). We were able to show that hypoxanthine is increased in the blood of hypoxic newborn babies (3). McCord and Fridovich (5) had some years earlier demonstrated that the xanthine–xanthine oxidase system generates oxygen radicals, however, at that time not drawing the clinical consequences of this finding. We quickly understood and suggested that owing to the accumulation of hypoxanthine during hypoxia, it was probably not wise to add oxygen during the acute resuscitation period because of an explosive generation of oxygen radicals (1).

OXYGENATION IN THE DELIVERY ROOM

Recent international guidelines recommend starting resuscitation of term or near term babies with air instead of supplemental oxygen (2). This advice is based on animal studies and 10 clinical studies including more than 2000 babies resuscitated with either 21% or 100% oxygen (30). It seems that the use of 100% oxygen increases time to first breath approximately 30 sec and gives a less increase in Apgar score at 5 min and heart rate at 90 sec of life. More importantly is that resuscitation with air reduces relative risk of neonatal mortality approximately 30% (For review see 31).

It is therefore recommended to start ventilation with air and, if possible, use a blender so oxygen <100% could be given if the baby does not respond adequately (32). Adequate ventilation is essential before oxygen in case is supplemented. In babies with non-healthy lungs (for instance after meconium aspiration), oxygen supplementation may be needed, and no clinical data exist regarding optimal FiO_2 for such babies. In the rare event of the need of chest compressions of <1/1000 term or near term babies (33), it is not known which FiO_2 should be used. If a pulse oximeter is available, arterial oxygen saturations should perhaps aim at the 10th–50th percentile of the normal saturation limits recently published (34).

Instead of asking why it took so many years to change the practice and the guidelines recommending air instead of 100% oxygen for resuscitation of term or near term infants, perhaps, it is more important to ask why oxygen had been used without questioned for newborn resuscitation so many years. For instance in 1992, the American Heart Association's guidelines for newborn resuscitation stated that 100% O_2 should be used, it is not toxic, and there were no reason to be concerned (35).

Today, we know that was very wrong and that oxygen around birth is more toxic than understood up to that time (36). However, it was necessary that sufficient experimental and clinical data were accumulated before a change was recommended. Although the first clinical studies we carried out indicated that it is possible to resuscitate with air, neither our pilot study (37) nor Resair 2 (38) was strictly randomized and blinded. The quality of these studies therefore may have delayed the acceptance of room air resuscitation. However, these first studies were met with much of resistance, and funding was difficult. Resair 2 funding was limited to about 10 000$ only.

Further, in spite of the fact that there are indications that room air resuscitation may save several hundred thousand lives annually, none of the large general medical journals were willing to publish our data. New England Journal of Medicine not even considered our data for review, JAMA rejected our manuscript in spite of favourable review comments, and the Lancet never was willing to publish any original data. Even a meta-analysis we wrote was rejected;

instead, the Lancet preferred to publish data from a Cochrane review (39). However, the Lancet, in contrast to the other two journals mentioned, have shown interest in this topic and published three commentaries (31,40,41). By contrast, paediatric journals showed great interest in this topic and made it possible to publish the original clinical data.

There were therefore several reasons for the long process to change the practice from oxygen to air in newborn resuscitation. May be it is reassuring that it takes time for new ideas to be established into clinical practice? It definitely is important that the pendulum does not swing too far to the other side. We therefore always recommend that if available oxygen should be at hand and be used if heart rate is not normalizing provided, there is adequate ventilation.

In conclusion, oxygen was used uncritically in newborn babies up to our time. Oxygen is more toxic than understood until recently. Still there are a number of unanswered questions regarding the use of oxygen in the newborn period (42). The optimal FiO_2 for extremely low birth weight infants needing stabilization/resuscitation at birth is for instance not known.

CONFLICTS OF INTEREST

The author has declared no potential conflicts.

References

1. Saugstad OD, Aasen AO. Plasma hypoxanthine concentrations in pigs. A prognostic aid in hypoxia. *Eur Surg Res* 1980; 12: 123–9.
2. Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, et al. Part 11: neonatal resuscitation: 2010 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 2010; 16 Suppl 2: S516–38.
3. Saugstad OD. Hypoxanthine as a measurement of hypoxia. *Pediatr Res* 1975; 9: 158–61.
4. Aasen AO, Saugstad OD. Hypoxanthine in lethal canine endotoxin shock. *Circ Shock* 1979; 6: 277–83.
5. McCord JM, Fridovich I. The reduction of cytochrome c by milk xanthine oxidase. *J Biol Chem* 1968; 243: 5753–60.
6. Park AM, Sanders TA, Maltepe E. Hypoxia-inducible factor (HIF) and HIF-stabilizing agents in neonatal care. *Semin Fetal Neonatal Med* 2010; 15: 196–202.
7. Maltepe E, Saugstad OD. Oxygen in health and disease: regulation of oxygen homeostasis – clinical implications. *Pediatr Res* 2009; 65: 261–8.
8. Lane N. Oxygen: the molecule that made the world. Oxford: Oxford University Press, 2002.
9. Zhao HW, Zhou D, Nizet V, Haddad GG. Experimental selection for *Drosophila* survival in extremely high O_2 environments. *PLoS ONE* 2010; 5: e11701.
10. Gerschman R, Gilbert DL, Nye SW, Dwyer P, Fenn WO. Oxygen poisoning and x-irradiation: a mechanism in common. *Science* 1954; 119: 623–6.
11. Babior BM, Kipnes RS, Curnutte JT. Biological defense mechanisms. The production by leukocytes of superoxide, a potential bactericidal agent. *J Clin Invest* 1973; 52: 741–4.
12. Wei EP, Christman CW, Kontos HA, Povlishock JT. Effects of oxygen radicals on cerebral arterioles. *Am J Physiol* 1985; 248: H157–62.
13. Archer SL, Will JA, Weir EK. Redox status in the control of pulmonary vascular tone. *Herz* 1986; 11: 127–41.
14. Saugstad OD, Sanderud J. Circulatory effects of oxygen radicals. *Biomed Biochim Acta* 1989; 48: S20–4.
15. Clyman RI, Saugstad OD, Mauray F. Reactive oxygen metabolites relax the lamb ductus arteriosus by stimulating prostaglandin production. *Circ Res* 1989; 64: 1–8.
16. Wright CJ, Dennery PA. Manipulation of gene expression by oxygen: a primer from bedside to bench. *Pediatr Res* 2009; 66: 3–10.
17. Arikan GM, Scholz HS, Petru E, Haeusler MC, Haas J, Weiss PA. Cord blood oxygen saturation in vigorous infants at birth: what is normal? *BJOG* 2000; 107: 987–94.
18. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol* 2009; 8: 110–24.
19. Billiards SS, Haynes RL, Folkerth RD, Trachtenberg FL, Liu LG, Volpe JJ, et al. Development of microglia in the cerebral white matter of the human fetus and infant. *J Comp Neurol* 2006; 497: 199–208.
20. Haynes RL, Baud O, Li J, Kinney HC, Volpe JJ, Folkerth DR. Oxidative and nitrative injury in periventricular leukomalacia: a review. *Brain Pathol* 2005; 15: 225–33.
21. Back SA, Gan X, Li Y, Rosenberg PA, Volpe JJ. Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. *J Neurosci* 1998; 18: 6241–53.
22. Gerstner B, DeSilva TM, Genz K, Armstrong A, Brehmer F, Neve RL, et al. Hyperoxia causes maturation-dependent cell death in the developing white matter. *J Neurosci* 2008; 28: 1236–45.
23. Bhandari V. Hyperoxia-derived lung damage in preterm infants. *Semin Fetal Neonatal Med* 2010; 15: 223–9.
24. Bhandari V. Molecular mechanisms of hyperoxia-induced acute lung injury. *Front Biosci* 2008; 13: 6653–61.
25. Wilborn AM, Evers LB, Canada AT. Oxygen toxicity to the developing lung of the mouse: role of reactive oxygen species. *Pediatr Res* 1996; 40: 225–32.
26. Konsavage W, Zhang L, Vary T, Shenberger JS. Hyperoxia inhibits protein synthesis and increases eIF2α phosphorylation in the newborn rat lung. *Am J Physiol Lung Cell Mol Physiol* 2010; 298: L678–86.
27. Saugstad OD. The determination of hypoxanthine and xanthine with a PO_2 electrode. *Pediatr Res* 1975; 9: 575–9.
28. Berne RM. Cardiac nucleotides in hypoxia: possible role in regulation of coronary blood flow. *Am J Physiol* 1963; 204: 317–22.
29. Gerlache E, Deuticke B, Dreisbach RH, Rosarius CW. On the behavior of nucleotides and their phosphorylation degradation products in the kidney in ischemia and short-term post-ischemic re-establishment of blood circulation. *Pflugers Arch Gesamte Physiol Menschen Tiere* 1963; 278: 296–315.
30. Saugstad OD, Ramji S, Soll RF, Vento M. Resuscitation of newborn infants with 21% or 100% oxygen: an updated systematic review and meta-analysis. *Neonatology* 2008; 94: 176–82.
31. Saugstad OD. Resuscitation of newborn infants: from oxygen to room air. *Lancet* 2010; 376: 1970–1.
32. Vento M, Saugstad OD. Oxygen supplementation in the delivery room: updated information. *J Pediatr* 2011; 158 2 Suppl: e5–7.
33. Wyckoff MH, Berg RA. Optimizing chest compressions during delivery-room resuscitation. *Semin Fetal Neonatal Med* 2008; 13: 410–5.

34. Dawson JA, Kamlin CO, Vento M, Wong C, Cole TJ, Donath SM, et al. Defining the reference range for oxygen saturation for infants after birth. *Pediatrics* 2010; 125: e1340–7.
35. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Part VII. Neonatal resuscitation. *JAMA* 1992; 268: 2276–8.
36. Saugstad OD. Is oxygen more toxic than currently believed? *Pediatrics* 2001; 108: 1203–5.
37. Ramji S, Ahuja S, Thirupuram S, Rootwelt T, Rooth G, Saugstad OD. Resuscitation of asphyxic newborn infants with room air or 100% oxygen. *Pediatr Res* 1993; 34: 809–12.
38. Saugstad OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. *Pediatrics* 1998; 102: e1.
39. Davis PG, Tan A, O'Donnell CP, Schulze A. Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis. *Lancet* 2004; 364: 1329–33.
40. Tarnow-Mordi WO. Room air or oxygen for asphyxiated babies? *Lancet* 1998; 352: 341–2.
41. Hansmann G. Neonatal resuscitation on air: it is time to turn down the oxygen tanks [corrected]. *Lancet* 2004; 364: 1293–4. Erratum in: Lancet 2005; 365: 386
42. Saugstad O. New guidelines for newborn resuscitation – a critical evaluation. *Acta Paediatr* 2011; 100: 1058–62.