Air or 100% Oxygen in Neonatal Resuscitation?

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In 1897, De Lee\textsuperscript{1}, an obstetrician, published a seminal paper on neonatal asphyxia in which he stated that “there are three grand principles governing the treatment of asphyxia neonatorum: first, maintain the body heat; second, free the air passages from obstructions; third, stimulate respiration, or supply air to the lungs for oxygenation of the blood.” After more than a century, these principles are still the most important, and, in most cases, it really is that simple. When considering the gas to be supplied to the lungs, De Lee\textsuperscript{1} recommended exhaled air delivered by mouth-to-mouth insufflation with a tracheal catheter: “The catheter is inserted into the trachea, the operator fills his lungs and mouth with air, and applying the lips to the catheter, with the glottis closed, the air in the mouth, pure and warm, is forced gently by action of the cheeks into the lungs.”

In 1928, Henderson\textsuperscript{2} suggested that 5% or 6% carbon dioxide in oxygen was superior to oxygen alone because the latter “does not have a stimulating action on respiration,” although he acknowledged that “the real need is for oxygen; the carbon dioxide merely ensures that this gas is not washed out of the blood to so low a level as no longer to be a stimulus to the respiratory system.” As part of a campaign in the United States for “the practical application of the modern theory of respiration” to the treatment of adults overcome by asphyxiant gases such as carbon monoxide, cylinders filled with this mixture were brought into use (attached to a reducing valve and a water manometer—so-called inhalators) in coal mining companies, gas companies, chemical manufacturers, city fire departments, and ambulances\textsuperscript{2}.

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Gas under carefully controlled pressure was required to resuscitate infants using Henderson’s inhalator (3 inches water pressure) or Flagg’s apparatus (8 inches water pressure), and in the days before the invention of the self-inflating bag, this was most easily available in cylinders [2,3]. Oxygen and carbon dioxide mixtures were still the norm when Blaikley and Gibberd [4] described their experience with the “pharyngoscope” in 1935. The addition of carbon dioxide was soon recognized to be unnecessary, however, and for the last 60 years 100% oxygen has been confidently recommended for resuscitation of infants who have difficulty making the transition from intrauterine to extrauterine life. In recent years, evidence has emerged, however, to suggest not only that air alone may be just as effective as 100% oxygen [5], but also that high concentrations of oxygen, even for brief periods at birth, may be detrimental [6].

Oxygen toxicity

The fact that ionizing radiation is toxic has been known since the days of Marie Curie. The effect of ionizing radiation is to displace electrons from the atoms it encounters—ionizing them. Ionizing radiation damages body tissue in the same way. Stripping electrons off atoms within a complex organic molecule whose function depends on its three-dimensional shape or its charge is extremely destructive. Radiation does not need to attack complex molecules directly. The human body contains large amounts of water within and outside cells. If an electron is stripped off a water molecule, the result is a proton, a solvated electron, and an extremely unstable and reactive hydroxyl radical, which seeks to strip off an electron from any atom in its vicinity, which, in the right conditions, sets off a chain reaction of similar events.

Removal of a second electron from water produces hydrogen peroxide, and removal of a third results in a superoxide radical. Hydrogen peroxide is not very reactive, but should it diffuse into an area in the cell where it comes into contact with iron (or copper), perhaps as part of a complex protein, ferociously active hydroxyl radicals are formed—the Fenton reaction. During this process, the iron is oxidized to Fe$^{3+}$, which no longer can react with hydrogen peroxide in this way. A superoxide radical, otherwise not terribly reactive, can donate an electron to Fe$^{3+}$ to become oxygen and produce Fe$^{2+}$, which can participate in the Fenton reaction if hydrogen peroxide is present, producing more damaging hydroxyl radicals.

The idea that oxygen might be toxic was entertained by Priestley in 1775 and explored in some detail by Haldane at the beginning of the twentieth century. The fact that oxygen is toxic in high concentrations (ie, at high partial pressures) is well established. The suggestions that oxygen is slowly poisoning all living organisms even when breathed as air and that it is one of the major causes of aging have been appreciated only more recently. As can be seen in Fig. 1, the conversion of oxygen to water (and carbon dioxide), as happens in normal
Efficient defenses have evolved over millennia, and a cascade of antioxidants, so called because they block the potential chain reaction set off by the release of free radicals, is generated in all living cells. The system is not perfect, however, and a small percentage of free radicals does slip through to cause damage. If free radical production is increased, as in hyperoxia, or if antioxidant defenses are less well developed, as in prematurity, oxidative cell damage is increased. As the importance and complexity of these processes becomes better appreciated, the need to consider the possibility of serious unwanted effects from even quite limited exposure to high concentrations of oxygen becomes more urgent.

Perhaps it is necessary to reconsider the view of oxygen altogether. According to Lane [7]: “Our obvious dependence on oxygen conceals the fact that individual cells within internal organs are not at all adapted to bathe in an oxygen bath. The development of multicellular organisms can even be considered an antioxidant response, which has the effect of lowering oxygen levels inside individual cells. Our elegant circulatory system, which is usually presented as a means of distributing oxygen to individual cells, can be seen equally as a means of restricting, or at least regulating, oxygen delivery to the correct amount.” Lanes goes on to calculate the partial pressure of oxygen at various stages in its journey to the cells of the body: about 160 mm Hg in air, about 100 mm Hg in the bloodstream when hemoglobin is 95% saturated, about 70 mm Hg in the

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**Mediators of radiation toxicity**

![Diagram of radiation toxicity intermediates](image)

**Mediators of oxygen toxicity**

![Diagram of oxygen toxicity intermediates](image)
arterioles, about 50 mm Hg in the capillaries, and approximately 1 to 10 mm Hg in most cells. In the final stage, oxygen is sucked into the mitochondria, in which the oxygen pressure is about 0.5 mm Hg. This amounts to less than 0.3% of atmospheric levels. “This is a surprisingly low figure, and not so far above the supposedly “anoxic” conditions of the early Earth. Might it be that mitochondria have succeeded in preserving a ghost of times past?” Lane goes on to suggest that “we should not think of haemoglobin as an oxygen transporter, but rather as a molecule that regulates oxygen storage and supply . . . it maintains intracellular oxygen at a low level, releasing its own oxygen on demand” [7].

Question addressed

As part of a general review of the scientific evidence concerning interventions related to resuscitation of infants at birth, the authors undertook a review of the published scientific evidence concerning the use of 100% oxygen or air, or comparing the effects of these gases, in resuscitation at birth. The authors’ purpose was to determine if sufficient evidence existed to alter significantly the advice given in the international guidelines for neonatal resuscitation in: “100% oxygen is recommended for assisted ventilation; however, if supplemental oxygen is unavailable, positive pressure ventilation should be initiated with room air” [8].

Evidence review

J.P.G. and S.R. independently performed literature searches to identify all peer-reviewed publications on the topic. Primary searches involved Medline, Embase, and Cochrane Reviews in addition to the studies identified when this question was examined before the issuing of the 2000 guidelines [8]. Keywords used in electronic searches were neonatal resuscitation, oxygen, and neonatal resuscitation, room air. Hand searches of bibliographies of articles identified by the primary searches also were conducted, and after an initial meeting in December 2003, any further publications identified were immediately shared. All animal and human studies, other than those published only in abstract form, were reviewed. Commentaries, editorials, and review articles were examined only to check through the bibliographies for further published data. The results of these searches can be found in the scientific worksheets of the International Liaison Committee on Resuscitation by accessing the website.

Human efficacy studies

The authors identified five studies involving human subjects apparently requiring resuscitation at birth being randomized to resuscitation with air or 100% oxygen [5,9–13]. These same studies also have been the subject of a Cochrane
Review, which has been published separately by the same authors as a meta-analysis [14,15]. One surprising finding was that the formal meta-analysis showed a statistically significant reduction in the relative risk of death at latest follow-up in favor of patients resuscitated with air (odds ratio [OR] 0.71; 95% confidence interval [CI] 0.54–0.94). No individual study reached this conclusion. Evidence from the various studies supported the contention that the onset of regular breathing was faster in the air groups. There was minimal difference in recovering Apgar scores in most studies, although one study suggested a small difference in the 5-minute Apgar score favoring the air group [5]. A significantly lower PCO$_2$ and lower PO$_2$ were found in the air group [11], but no differences were found in pH or base deficit [5,9,12]. The only follow-up study at 18 to 24 months showed no significant differences in somatic growth or neurologic handicap between infants resuscitated with air or 100% oxygen [10].

Other human studies

Numerous studies in human infants have reported physiologic, biochemical, and other changes during or after exposure to high concentrations of oxygen in the newborn period [6,11,12,16–22]. In 1988, Nijjima et al [16], using duplex Doppler ultrasound measurements, showed that exposure to hyperoxia resulted in reduced cerebral blood flow velocity in 15 of 17 preterm infants. Although a similar effect noted in 15 term infants in the same study was found by analysis of variance to be largely due to changes in PCO$_2$, there were no significant changes in PCO$_2$ or blood pressure during hyperoxia in the preterm group. Lundstrom et al [6] randomly assigned preterm infants to receive room air ($n=34$) or 80% oxygen ($n=36$) during initial stabilization in the delivery room. Global cerebral blood flow measurements were made after the infants had been settled in the neonatal unit. These investigators reported data suggesting that exposure to oxygen in the delivery room for a maximum of 10 minutes influenced subsequent global cerebral blood flow when measured at 2 hours of age in a manner suggesting that excess oxygen produced prolonged cerebral vasoconstriction.

Aizad et al [17] explored the effect of a single breath of 100% oxygen in term and preterm infants and found a significant decrease in minute volume. This decrease was more pronounced in preterm infants and in this group was primarily due to a decline in breathing frequency and tidal volume. The decrease in minute volume was less pronounced in term infants and was primarily due to a decline in tidal volume with little effect on breathing frequency. These studies were done in infants whose extrauterine existence was already established. Mortola et al [18] conducted physiologic measurements on a group of full-term infants in the first few days of life while breathing air or 100% oxygen. In contrast to Aizad’s single-breath study, they found that continued breathing of 100% oxygen resulted in an increase in tidal volume, but a decrease in breathing frequency. There also was an overall increase in oxygen consumption greater than could be accounted for by the 45% increase in respiratory work.
Vento et al [11,12] looked at the reduced-to-oxidized glutathione ratio, a biochemical marker in which a low value indicates oxidative stress, in infants randomized to resuscitation with either air or 100% oxygen at birth. They found significantly lower values in both groups at 3 days compared with non-asphyxiated controls. At 28 days, the ratio was still significantly lower in the 100% oxygen group, however, than the room air group and the control group. There was no difference between the latter two groups at this point. At 4 weeks of age, no differences were found between any of the groups with respect to clinical neurologic evaluation, cerebral ultrasound imaging, or electroencephalogram findings.

In 1995, a register-based, case-control study reported that exposure to supplementary oxygen at birth constituted an increased risk of developing leukemia [19]. In response to this finding, a case-control study was performed using the Swedish Cancer Register, known to include 97% of cancer patients, and controls selected from the Swedish Birth Registry, known to include 99% of births [20]. Resuscitation with 100% oxygen after delivery was found to be significantly associated with an increased risk of childhood lymphatic leukemia (OR 2.57; 95% CI 1.21–6.82). The oxygen-related risk increased further if manual ventilation lasted 3 minutes or more (OR 3.54; 95% CI 1.16–10.80). Children with Down syndrome were excluded. Infants with low Apgar scores at 1 and 5 minutes were associated with a nonsignificantly increased risk.

More recently, prospectively gathered cohort data on 60,000 pregnancies in the United States delivering in the period 1959–1966 (the Collaborative Perinatal Project) was analyzed. An association between exposure to 3 or more minutes of oxygen in the delivery room and cancer diagnosed before the age of 8 years was found. The hazard ratio for this group was reported as 2.87 (95% CI 1.46–5.66) [21].

Klinger et al [22] undertook a retrospective cohort study of term infants with neonatal encephalopathy thought to be secondary to intrapartum asphyxia in an attempt to determine whether episodes of hyperoxemia with or without hypocapnia during the first 2 hours of life added to the risk of brain injury. Of the 244 infants identified, the outcome was known in 218 infants, of which 127 were dead or had neurodevelopmental deficits. Multivariate analysis showed that a PaO₂ greater than 26.6 kPa (200 mm Hg) (OR 3.85; 95% CI 1.67–8.88) or a PaCO₂ less than 2.6 kPa (20 mm Hg)(OR 2.34; 95% CI 1.02–5.37) were each associated with adverse outcome, and the risk was highest if both were present (OR 4.56; 95% CI 1.4–14.9).

Animal studies

Numerous studies have been undertaken in which animals have been asphyxiated and randomized to resuscitation with either air or 100% oxygen. Unless otherwise specified, the animals used in the studies described here were piglets studied at a few days of age with a handful of animals in each arm. Many studies were unable to detect any significant difference in various important

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respects between the two groups [23–31]. A few detected a difference in favor of the use of air [32–35], and a few showed differences favoring use of oxygen [35–38]. Most of these studies have emanated from a few laboratories that have shown a continued interest in this subject.

Rootwelt et al [23–25], in a series of studies using piglets rendered hypoxic in the first few days of life by ventilation with 8% oxygen in nitrogen and resuscitated using air or 100% oxygen, were unable to detect any significant difference between the two groups in return of blood pressure, speed of correction of base deficit, brain histology, normalization of plasma hypoxanthine levels, cerebral blood flow, forebrain oxygen uptake, somatosensory evoked potentials, or blood flow to various major organs, Poulsen et al [26] also failed to detect any difference in plasma hypoxanthine or xanthine levels in a similar study. Tølløfsrud et al [27] used a similar model to which a homogenized solution of meconium was added before resuscitation with either air or 100% oxygen. No difference was found in plasma hypoxanthine levels in the two groups, and there were no differences in lung function measurements or lung histology.

Bagenholm et al [28], working with rats subjected to hypoxia and severe brain ischemia (left carotid artery ligation), found no differences in brain weight deficit between rats resuscitated in air as opposed to 100% oxygen. Medbo et al [29], using piglets rendered hypoxic but not hypercapnic or ischemic, found that pulmonary artery pressure increased just as quickly, pulmonary vascular resistance decreased just as quickly, and plasma endothelin-1 levels recovered just as quickly when resuscitation was performed with air or 100% oxygen. Feet et al [30] could not show any differences in time to electroencephalogram recovery, quality of electroencephalogram on recovery, or plasma hypoxanthine levels. Børke et al [31] could find no significant differences in levels of various indicators of myocardial damage, such as cardiac troponin, myoglobin, or creatine kinase–myocardial band, and no differences in mean arterial pressure when comparing resuscitation with 100% oxygen or air in piglets.

Goplerud et al [32] looked at Na⁺,K⁺-ATPase activity in the corpus striatum after resuscitation. (The corpus striatum is the striped mass of white and gray matter lying in front of the thalamus and consisting of the caudate and lenticular nucleus.) The membrane bound enzymes in this area are likely to be affected by significant membrane disruption and have been shown to be inhibited by lipid peroxidation; both conditions are likely to be associated with oxygen free radical–mediated events. The investigators found no inhibition of Na⁺,K⁺-ATPase activity in the group that was not asphyxiated, no inhibition in the group that was asphyxiated and resuscitated with air, 29% inhibition in the group that was asphyxiated and not resuscitated, and 16% inhibition in the group resuscitated with 100% oxygen. The study animals were rendered hypoxic, but not hypercapnic or ischemic.

Kondo et al [33] used a luciferin derivative, MCLA, which reacts specifically with superoxide radicals and singlet oxygen and is chemiluminescent. MCLA was given intravenously, and the proton count from the lung surface was measured after a brief period of asphyxia and resuscitation with either air or
100% oxygen. A control group was switched from ventilation with air to ventilation with 100% oxygen without undergoing any asphyxial insult. This control group had a relative maximum chemiluminescence of 108.4 ± 39.8 photons/min in 100% oxygen, significantly higher than the air group (59.5 ± 39 photons/min), but also significantly lower than in the group resuscitated with 100% oxygen (186.1 ± 72.5 photons/min), showing that the production of reactive oxygen species had been increased significantly by resuscitation with oxygen.

Kutzsche et al [34] studied hydrogen peroxide concentrations in neutrophils taken from the sagittal sinus after resuscitation. Neutrophil hydrogen peroxide was measured by its ability to oxygenate the nonfluorescent dihydrorhodamine (DHR123), producing the highly fluorescent rhodamine (Rho123). The investigators found that the hydrogen peroxide concentration in neutrophils of piglets resuscitated with oxygen remained high, whereas the concentration in the air group returned to normal.

Huang et al [35] could show no differences in blood flow in the corpus striatum after resuscitation with air or oxygen. They found, however, that levels of dopamine increased to similar levels in both groups during resuscitation, but decreased to 200% of control values by 2 hours in the air group at a time when they were more than 500% of control values in the oxygen group. Both groups experienced a secondary surge in dopamine levels, with the air group increasing to 750% and the oxygen group increasing to 3000% of baseline levels. Cortical oxygen pressure decreased from 36 to 7 mm Hg during asphyxia, but at 30 minutes postasphyxia this value increased to 19 mm Hg in the oxygen group and only 11 mm Hg in the air group. In both groups, cortical oxygen pressure decreased again so that there was no significant difference between groups at 2 hours.

Huang’s study and three further studies by Solás et al [36–38] seem to be the only animal studies yet published to suggest that 100% oxygen may have advantages over air in this context. In the first of the Solás studies [36], significantly higher levels of excitatory amino acids (glutamine, aspartate, taurine, and alanine), significantly lower mean arterial blood pressure, and a significantly greater degree of hypoperfusion of the cerebral cortex (with prolongation of high levels of cortical hypoxanthine) were found in piglets resuscitated from hypoxia-ischemia with air compared with piglets resuscitated with 100% oxygen. In a second study [37], in which carbon dioxide also was introduced to produce hypoxia, ischemia, and hypercapnia, significantly higher mean arterial blood pressure and better restoration of the striatal microcirculation was found in the 100% oxygen group. In this study, there were no significant differences in cortical extracellular hypoxanthine levels, however, or in levels of glutamate, taurine, or alanine in the corpus striatum.

In the third study by Solás et al [38], also using the hypoxia-ischemia-hypercapnia model, the asphyxiated piglets were resuscitated with 5 minutes of 100% oxygen followed by air, 20 minutes of 100% oxygen followed by air, or air only. In this study, there was more complete restoration of the cortical microcirculation and oxygen delivery to the cortex was more efficient in the two
groups exposed to 100% oxygen. There were no significant differences, however, in the cerebral metabolic rate for oxygen between the three groups, and there were no differences in striatal blood flow or striatal extracellular levels of glutamate, glycerol, or lactate-to-pyruvate ratio during reperfusion. The Solás studies used a hypoxia-ischemia-hypercapnia model that more resembles intrapartum asphyxia, whereas most of the other animal studies used hypoxia alone.

**Pulse oximetry studies**

Rather than attempting to decide between the false dichotomy of recommending air or 100% oxygen, some clinicians have suggested that it might be wiser to be guided by measurements from infants being resuscitated in the hope that one could avoid hypoxia and hyperoxia by varying the amount of oxygen offered. This recommendation requires clinicians to define what constitutes hypoxia and hyperoxia in the transition from intrauterine to extrauterine life of a normal newborn. The only tool currently available that is able to produce suitable data within the time constraints of a resuscitation is pulse oximetry, although the relationship between oxygen saturation and arterial oxygen pressure (PaO₂) is not linear, and, especially at the upper end of the saturation scale, the confidence intervals are wide (Fig. 2).

Matters are complicated further by whether saturation is measured preductally or postductally, and whether the saturation algorithm employed by the machine in use measures fractional or functional saturation. Fractional oxygen saturation—\([\text{HbO}_2/(\text{HbO}_2 + \text{reduced Hb} + \text{MetHb} + \text{COHb})] \times 100\)—is approximately 2% less than functional oxygen saturation—\([\text{HbO}_2/(\text{HbO}_2 + \text{reduced Hb})] \times 100\) [39].

Gerstmann et al [40] examined the relationship between oxygen saturation readings obtained from SpO₂ and simultaneously blood gas measurements.

![Fig. 2. Graphs showing the relationship between pulse oximeter measurements of oxygen saturation and arterial PO₂. In the graph on the left, the vertical line on the left side indicates the point at which clinical cyanosis usually is first appreciated, and the right hand vertical line indicates the maximum recommended arterial PO₂. The graph on the right indicates the mean and 95% confidence intervals at specific points on the curve. The vertical line on this graph indicates the maximum recommended arterial PO₂. (Adapted from Northern Neonatal Network Staff. Hey E, editor. Neonatal Formulary. 4th edition. London: Blackwell Publications Ltd; 2003. p. 187; with permission.]


of $\text{SaO}_2$ and $\text{PaO}_2$ using four different pulse oximeters (Fig. 3). From this information, the investigators were able to produce an operational performance graph of varying pulse oximeters by plotting actual $\text{SaO}_2$ against the percentage of pulse oximetry readings where the $\text{SpO}_2$ value was within the accepted tolerance of the machine (ie, when $\text{SpO}_2 = \text{SaO}_2 \pm 3$). As can be seen from the graph, machines differ as to levels of $\text{SaO}_2$ at which their performance exceeds 70% accuracy within this tolerance.

Numerous studies have attempted to measure oxygen saturation in the minutes immediately after birth in term and preterm infants using pulse oximetry [41–43]. Harris et al [41] attempted to measure postductal functional saturation in 76 infants for the first few minutes after elective cesarean section or by vertex vaginal delivery to mothers who were receiving additional oxygen via a nonrebreathing facemask. They found that saturation increased from a mean of 65% (vaginal delivery) or 47% (cesarean section) to a mean of 82% ± 2% by 7 minutes of age.

House et al [42] measured preductal saturation using Nellcor and Ohmeda pulse oximeters (and presumably using functional and fractional saturation measurements) and found mean values at 15 minutes of 90.3% (SD 6.6%) in infants weighing at least 2 kg and 88.2% (SD 10.8) in smaller infants. Toth et al [43] found that in healthy term infants it took more than 12 to 14 minutes to achieve

Fig. 3. Pulse oximeter operational performance defined as the percent of pulse oximetry readings at each $\text{SaO}_2$ value where the pulse oximeter is within the device-specified accuracy for neonates, that is, $\text{SpO}_2 = \text{SaO}_2 \pm 3$. Displayed here are the polynomial curves fitted to the operational performance data for the four models for which data are available. Operational performance is plotted against $\text{SaO}_2$. Because $\text{SaO}_2 \pm 3 = \text{SaO}_2 \pm 1$ SD, operational performance for the devices should be equal to or greater than 68% (horizontal line) across the range of $\text{SaO}_2$ values. No model shows instrument performance, which is consistent except within a narrow range. (From Gerstmann D, Berg R, Haskell R, et al. Operational evaluation of pulse oximetry in NICU patients with arterial access. J Perinatol 2003;23:382; with permission.)
a preductal functional (Nellcor) saturation of 95%, and in some cases it took 55 minutes to reach this level.

Preductal fractional oxygen saturation was measured by pulse oximetry in many infants in both groups in the study by Lundstrom et al [6]. Infants in the control group (term infants) needing no resuscitation had median (interquartile range) readings of 66% (56–75%), 80% (55–85%), and 83% (68–88%) at 3, 5, and 7 minutes. Infants in the preterm-air group had readings of 70% (65–74%), 75% (65–87%), and 80% (70–87%) at similar times, whereas infants in the preterm-oxygen group had readings of 83% (74–93%), 92% (90–97%), and 94% (90–95%).

**Interpretation of data**

*Human efficacy studies*

Interpretation of the meta-analysis is not straightforward [14]. It is important to bear in mind numerous important features of these studies. A total of only 1252 infants were involved, none of whom weighed less than 1000 g at birth, and only a few were preterm. The Ramji [5] and Saugstad [9,10] studies were only pseudorandomized in that infants were allocated to air or oxygen depending on whether they were born on an even or an odd date, and the clinicians were not blinded to the gas being used. Only the two smaller Vento [11,12] studies, involving about 150 infants, were truly randomized and blinded.

In the Ramji [5] and Saugstad [9,10] studies, the protocols allowed for administration of backup oxygen to study infants in the air group under certain conditions, but there was no option for the oxygen group to revert to air. In the Vento [11,12] studies, the option existed to change the gas supplied to either group at the clinicians’ discretion. Overall, 168 of 635 infants in the various studies who were assigned to air received 100% oxygen as backup at some point during resuscitation. This change in treatment may have increased the apparent effectiveness of air on an intention-to-treat analysis, but equally also may have masked any potential damaging effects of oxygen by confounding separation of the two groups.

The definitions of asphyxia used as entry criteria into all five human studies have been criticized for not being sufficiently stringent to exclude many minimally compromised infants. One study required only apnea or gasping at birth with a heart rate less than 80 beats/min [9]. Two studies required clinical hypotonia, apnea, or bradycardia and a blood gas indicating a $P_{O_2}$ less than 70 mm Hg, $P_{CO_2}$ greater than 60 mm Hg, and pH less than 7.15. It was not stated whether these were cord arterial, cord venous, or subsequent neonatal blood gas analyses. Apgar scores in both groups of these two studies ranged from 3 to 5 at 1 minute [5,13]. Two other studies required a heart rate of less than 100 beats/min or unresponsive to stimuli and needing assisted ventilation [11,12]. If one accepts that the incidence of severe intrapartum asphyxia in the developed world is
approximately 1 to 2 per 1000 live births, it is likely that many of the infants in these studies had only mild or moderate asphyxia (primary apnea), and their good response to resuscitation with either oxygen or air is not surprising [44]. Nevertheless, whatever the definitions for entry, 177 of the 1252 infants (14%) entered into these studies were ill enough to die within 4 weeks.

Regarding mortality, no individual study found a significant difference, and 174 of the 177 deaths occurred in developing countries, where the health and demographics of the populations served and the pattern of health care provision are very different from those in industrialized nations. No plausible mechanism for such an immediate effect on mortality has been suggested, and until such time as one is, these mortality findings will be considered by many as unbelievable, however unimpeachable the statistics. Finally, although the available follow-up data would suggest that there is no difference in longer term outcome between the two groups, information beyond 28 days of life is available only for 76% of the cohort of the one study in which this has been attempted [10].

Other human studies

The possibility that spontaneous breathing patterns are changed or that work of breathing may be increased if 100% oxygen is used in the newborn period is not worrying in the context of resuscitation at birth [17,18]. If resuscitation is truly needed, presumably spontaneous respiration at least is being assisted by positive-pressure ventilation in some form. The possibility that use of oxygen not only reduces cerebral circulation, but also does so in a manner that might persist for some time is of concern, although these findings were more pronounced in preterm infants [6,16]. Equally, the evidence that other signs suggesting oxidative stress are still detectable at 28 days is worrying, as is the apparent association between asphyxia complicated by early hyperoxia or hypocapnia and adverse outcome [11,12,22].

Epidemiologic studies reporting serious health hazards associated with common exposures are notoriously difficult to evaluate. Two such studies from different countries, the larger involving retrospective data collection, but the other prospective, have reported a significant association, however, between exposure to oxygen for 3 minutes or more in the delivery room and childhood cancer [19–21]. The authors of the smaller prospective study argued that “no change in pediatric practice should be made on the basis of these results” [21], whereas the accompanying editorial by an epidemiologist suggested that “brief neonatal exposures to pure oxygen should no longer be considered familiar, routine and ordinary” [45].

Animal studies

The transition from intrauterine to extrauterine life is a complex and crucial one involving major changes in circulation and respiration. The mammalian fetus is well adapted to cope with the potentially asphyxial journey along the birth
canal, in particular by means of considerable storage of glycogen in the heart muscle. This crucial adaptation is not maintained for long after birth. All of the animal studies can be criticized on the basis that they studied animals that already were well established in the extrauterine environment, and it is questionable whether results gained from such postnatal experiments are relevant to intrapartum asphyxia. In most studies, asphyxia was induced in a manner that ensured hypoxia and possibly a degree of ischemia, but only four studies also ensured hypercapnia [33,35,37,38].

The equally rapid decrease in pulmonary vascular resistance index and increase in plasma endothelin-1 when resuscitated with air or oxygen, in the one study in which this problem was addressed, is helpful for clinicians concerned about the effectiveness of air in cases of pulmonary hypertension, but hardly constitutes definitive reassurance [29]. The conflicting results concerning the production of excitatory amino acids and recovery of the cerebral microcirculation do not make interpretation of these data any easier [24,35–38]. In the studies in which a model of hypoxia-ischemia-hypercapnia was used [35,37,38], the significant differences in levels of excitatory amino acids, mean arterial blood pressure, and perfusion of the cerebral cortex favoring the use of 100% oxygen should caution the clinician from the abandonment of oxygen in cases of severe intrapartum asphyxia.

**Pulse oximetry**

The acceptable limits of oxygen saturation in a term infant during the first hours of life are relatively unexplored. What constitutes an acceptable range of oxygen saturation in the management of a preterm infant is currently the subject of considerable international debate [46]. The little evidence available seems to indicate that the avoidance of saturations greater than 95% in an infant 32 weeks gestation or less is desirable [47,48]. These facts, combined with the technical difficulties associated with accurate measurement of this unspecified normal range by pulse oximetry, make it impossible to recommend any specific value or range of values to be achieved within a specified time frame immediately after delivery. Differences in the optimal performance ranges of the various machines available and the nonlinear nature of the relationship between oxygen saturation and PaO₂ complicate the picture further. The relatively modest preductal pulse oximeter readings (83%, 92%, and 94% at 3, 5, and 7 minutes) in the preterm infants randomized to stabilization with oxygen in the Lundström [6] study nevertheless seem to have been sufficient to alter significantly the cerebral blood flow when measured 2 hours later.

**Gaps in the knowledge**

The number of infants that have been entered into formal studies so far is small. The data would suggest, however, that within the groups so far tested air is
likely to be as effective as 100% oxygen in terms of survival in infants with mild or moderate asphyxia. The various caveats outlined concerning the design of the various human efficacy studies, the environments in which many of them were conducted, and their small size make it difficult to accept as the true and final answer the bald result of the meta-analysis suggesting statistically improved survival in the air group. The most important information that is missing is long-term follow-up data from human studies. After all, the ultimate objective of resuscitation at birth is to allow an infant not only to survive, but also to develop entirely normally thereafter.

Also distinctly lacking are data on the changes in saturation during the first few minutes of life in infants resuscitated with air or 100% oxygen. Equally unavailable are data on infants in whom the use of 100% oxygen from the start intuitively might seem preferable. These include infants with severe intrapartum asphyxia (pH < 7.0), infants with significant meconium aspiration, infected term or preterm infants, and infants with persistent pulmonary hypertension. Other infants to consider are infants with conditions that might limit lung function, such as congenital pneumonia or pulmonary hypoplasia secondary to diaphragmatic hernia or oligohydramnios. Another group in whom data are lacking comprises infants with severe anemia secondary to fetomaternal bleeding, ruptured vasa previa, or rhesus hemolytic disease.

Potential translation of data into guidelines for clinical practice

Guidelines for resuscitation of infants at birth have been developed and refined gradually over the years, but most are based on theoretical advantages, sometimes resulting from extrapolation of research results rather than any formal studies proving their utility. Authors reviewing resuscitation guidelines have agreed that currently accepted practices should continue to be recommended until such time as they can be replaced by proven superior practices, or until they have been shown to be harmful or ineffective. One side effect of this disciplined approach is that it is easier for an accepted practice to remain, however poor the evidence in its support, than it is for a new intervention to be adopted. This is true, but a moment’s thought would reveal the difficulties that would be introduced if yet more inadequately tested interventions were added to the large number already incorporated into current practice. Whether this discipline should be applied quite so rigorously to a suggestion that would remove exposure to a drug previously thought to be powerful and innocuous, but now known to be less innocent and frequently unnecessary, is debatable.

When presented with an apneic infant at delivery, it usually is impossible to determine immediately whether the infant is in primary or secondary apnea, although this often can be resolved afterward when one knows how the infant responded to resuscitative measures. If one accepts Dawes’ [49] assertion, however, that “very few infants which are apnoeic on delivery are in secondary
apnoea,” given what is now known about the potential toxicity of oxygen, it becomes difficult to continue to insist that 100% oxygen should be recommended for assisted ventilation in all cases in which resuscitation is deemed necessary at birth.

The approach taught in the US Neonatal Resuscitation Program has been to assume that an infant apneic at birth is in secondary apnea and to respond accordingly, even though, statistically, primary apnea is more likely. Traditionally, this approach has demanded that 100% oxygen be used from the start to minimize the period of hypoxia on the assumption that a brief exposure to high concentrations of oxygen is unlikely to be harmful should the infant prove to be in primary apnea. Should this approach continue? Here the two authors cannot agree. One is in favor of continuing this approach with rapid withdrawal of oxygen when it is clear it is not needed; the other would prefer to start with air and add oxygen if it seems to be required. Both recognize that these conclusions demand a step off the firm ground of currently available evidence.

In a world context, the question does not arise. Most births occur in settings where oxygen is completely unavailable or at least an expensive luxury. What is reassuring is that research has shown that, for the term infant, unavailability of oxygen does not seem to be a disadvantage. Much evidence supports the view that where a choice exists, it is becoming progressively easier to justify using air rather than oxygen to start resuscitation, with oxygen being kept in reserve for infants in whom it becomes clear that arterial saturation remains low without it (although many clinicians still would have reservations about starting resuscitation with air in severe asphyxia). Whether this same evidence is enough to insist on costly alterations to resuscitation equipment to allow air or air/oxygen mixtures to be used in all delivery areas is considerably less clear.

There is a caveat, however. Almost all research done in the last decade has focused on term infants compromised by mild-to-moderate intrapartum asphyxia. It would be unwise to assume that what is best for such an infant also would be best for an infant compromised by severe intrapartum asphyxia or intrapartum sepsis or showing early signs of persistent pulmonary hypertension. If a term infant can suffer from being given too much oxygen as well as too little, this is almost certainly even more true of a preterm infant. To paraphrase Paracelsus, “Everything is potentially toxic. However, what determines whether it is poisonous is the dose.”

References

[29] Medbo S, Yu XQ, Asberg A, Saugstad OD. Pulmonary hemodynamics and plasma endothelin-1


