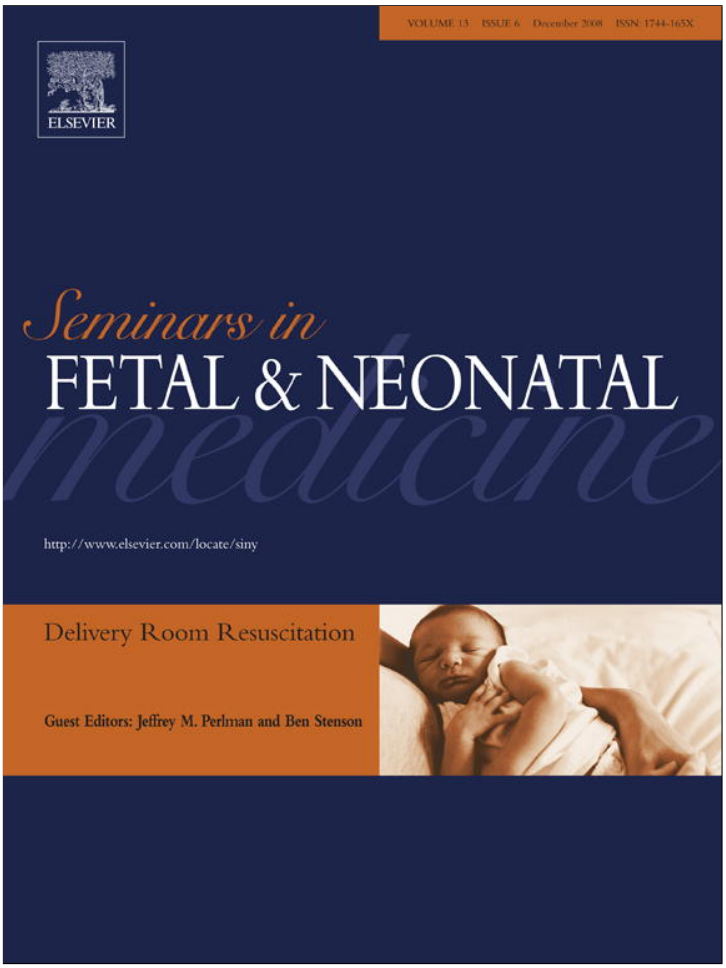

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Refining the role of oxygen administration during delivery room resuscitation: What are the future goals?

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Summary Oxygen was discovered more than 200 years ago and was thought to be both essential and beneficial for all animal life. Although it is now over 100 years since oxygen was first shown to damage biological tissues exposed to high concentrations, and more than 50 years since it was implicated in the aetiology of retinopathy of prematurity, the use of 100% oxygen was still recommended for the resuscitation of all babies at birth as recently as 2000. However, the 2005 International Liaison Committee on Resuscitation (ILCOR) recommendations allow for the initiation of resuscitation with concentrations of oxygen between 21 and 100%. There are strong arguments in favour of a radical curtailment of the use of oxygen in resuscitation at birth, and for devoting resources to defining the margins of safety for its use in the neonatal period in general.

> Our water that wets not our hands, without which no mortal can live, and without which nothing grows or is generated in the world.
>
> Sendivogius (1556–1636) describing 'aerial nitre'

Although Joseph Priestley is usually credited with the discovery of oxygen in 1774, a Polish alchemist by the name of Michal Sedziwój (Sendivogius) was well aware of it as early as 1604.[1] Unlike Priestley, Sendivogius appears to have acknowledged its full significance. He was perhaps the first person to appreciate that air was not a single entity but that it was a mixture containing 'aerial nitre' (oxygen) as an essential ingredient: ''Man was created of the Earth, and lives by vertue of the Aire; for there is in the Aire a secret food of life…whose invisible congealed spirit is better than the whole earth''.[1]

Sendivogius recognized not only that 'aerial nitre', produced by the heating of saltpetre (also known as nitre, potassium nitrate or KNO_3), made all animal life possible, but also that it seemed to circulate through all life; apparently condensing out of the air and growing as living white crystals on farmyard soil and in this solid form giving life to plants – it is an extremely effective fertilizer. Saltpetre can also be extracted from manure heaps liberally irrigated with human urine while protected from rain. The fact that saltpetre was also used in medicines, freezing mixtures, for making gunpowder, as a preservative for meat (in this context now known as E252) and in the production of 'aqua regia' (which could be used to dissolve gold) persuaded Sendivogius that he had discovered the ''universal spirit

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that pervaded all matter'' — and to some extent he had. However, it was Priestley who, in 1775, first raised concern as to the safety of this gas when he wrote:[2]

> Though pure dephlogisticated air [Priestley's term for oxygen] might be very useful as a medicine, it might not be so proper for us in the usual healthy state of the body for, as a candle burns out much faster in dephlogisticated air than in common air, so we might, as may be said, *live out too fast* [Priestley's emphasis] and the animal powers be too soon exhausted in this pure kind of air. A moralist, at least, may say, that the air which nature has provided for us is as good as we deserve.

Paediatricians were alerted to the potential toxicity of oxygen for the first time in the late 1940s with the recognition of retrolental fibroplasia, now called retinopathy of prematurity (ROP). From the early 1950s, attempts were made to control the use of oxygen in the management of preterm infants. Initially, physicians merely limited the exposure of infants to concentrations below 40% in an attempt to reduce ROP. However, in the USA this policy was later found to be associated with an increase in mortality and in the prevalence of cerebral palsy. Subsequently, attempts were made to avoid hyperoxia by means of feedback from continuous intra-arterial or transcutaneous electrode measurement of PaO_2, although this is now more commonly done by regulating oxygen saturation measured by pulse oximetry.[3] Throughout this period, the standard teaching has been that 100% oxygen is recommended for the resuscitation of babies in difficulty at birth on the assumption that it is more effective than air in reversing the consequences of anaerobic metabolism and acidosis and on the presumption that the brief exposure to a high concentration carries no long-term consequences.[4]

Over the last 30 years, the 'oxygen paradox' — the fact that cell and tissue injury is increased if hypoxic tissue is exposed to high concentrations of oxygen — has been recognized;[5] the role of free radicals, antioxidants and their link with apoptosis and reperfusion injury has been explored; and the idea of oxidative stress established. In light of these discoveries, it has become increasingly difficult to sustain the idea that exposure to high concentrations of oxygen, however brief, is without risk.[6]

Cellular metabolism is normally aerobic but, in the face of the inadequate delivery of oxygen (because of poor cardiac output, decreased oxygen-carrying capacity or lack of adequate inspired oxygen), cells switch to anaerobic metabolism, during which energy production still occurs but metabolism is incomplete and lactic acid is produced. If this is sufficiently short-lived, and the 'oxygen debt' is rapidly repaid, no harm may be done. Depolarization occurs if energy failure continues for long enough, followed fairly quickly by cell death. However, sublethal hypoxic ischaemia will often set in motion a series of toxic reactions that result in the later death of mildly affected and many initially unaffected cells, and the downregulation of future gene expression.

In the context of a hypoxic ischaemic threat at birth, the rapid establishment of pulmonary gas exchange to replace the failure of placental gas exchange is the key to success. In the past it has seemed reasonable that, following a period of potentially damaging asphyxia, the delivery of a high concentration of oxygen to the tissues at risk might help to reduce the number of cells affected by the anaerobic process.

The difficulty encountered by the healthcare provider is to decide when the effects of excess oxygen administration in a situation of acute asphyxia are overtaken by the concern of continuing anaerobic metabolism. This problem is exacerbated in postpartum resuscitation because the resuscitator does not know how severe and prolonged the anaerobic metabolism has been in the newly born infant prior to birth. Recent concerns over the potential toxic effects of high concentrations of oxygen, and the balancing concerns over the effects of prolonged anaerobic metabolism, have led to the administration of blended oxygen (when such blending is available) at concentrations between 21 and 100% as a common practice during delivery room resuscitation, although there is little evidence of its efficacy. However, when blended oxygen is not available in the delivery room, the provider is often forced to choose to use either 100% oxygen or air.

Three questions that have significant clinical implications emerge. First, is there any evidence that high-concentration oxygen is more effective than air in resuscitation at birth? Second, is there any evidence that exposure to high-concentration oxygen at birth might be harmful? Third, as high pulmonary vascular resistance is physiological *in utero* and might persist in asphyxiated infants after birth, is high-concentration oxygen necessary to produce sufficient pulmonary vasodilatation at birth to facilitate adequate pulmonary blood flow and allow resuscitation?

Is there any evidence that high-concentration oxygen is more effective than air in resuscitation at birth?

Although there is much anecdotal evidence that babies were resuscitated effectively using positive pressure ventilation with air in the nineteenth century and earlier,[7] the use of 100% oxygen took root during the twentieth century. Indeed, at one point following an observational study — and before the full elucidation of the physiology of birth asphyxia in mammals — 100% oxygen under higher-than-atmospheric pressure was strongly advised.[8] It was the publication of this study which stimulated two physiologists, Cross and Dawes, to conduct a randomized controlled animal study that not only showed that hyperbaric oxygen was completely ineffective when compared with positive pressure ventilation but also demonstrated that positive pressure ventilation with air was just as effective as with 100% oxygen in the resuscitation of asphyxiated newborn rabbits.[9–11] The message that positive pressure ventilation was effective spread rapidly but that of the equal effectiveness of air and 100% oxygen was largely ignored.

During the 1960s and 1970s, the complex biochemistry of oxygen, the damaging effect of reactive oxygen metabolites, the existence of a complex web of antioxidant enzymes and their importance began to be elucidated.[12]

In the last 15 years, researchers have begun to raise concern that even brief exposure to high concentrations of oxygen might be dangerous and a number of randomized or

pseudo-randomized studies of the effectiveness of resuscitation of asphyxiated newborn babies with air or 100% oxygen were performed.[13–18] In each of these studies it is clear that, in the short-term, air is at least as effective as oxygen.

A number of experiments have looked for possible advantages in using oxygen as opposed to air for the resuscitation of immature animals subjected to hypoxia, sometimes combined with hypercarbia, ischaemia or both.[19–27] In virtually all these studies there was no apparent advantage to the use of oxygen; the only exceptions are three studies by Solås.[25–27] In the initial study, which used a hypoxic ischaemic piglet preparation, higher levels of brain excitatory amino acids (suggesting a greater degree of cell damage), lower mean arterial pressure and reduced perfusion of the cerebral cortex were found in the group resuscitated with air when compared to the group resuscitated with 100% oxygen for 30 min. The other two studies by Solås, in which animals were rendered hypoxic, ischaemic and hypercapnic before resuscitation with: (1) air or 100% oxygen for 30 min;[26] (2) with 21% oxygen for 30 min, 100% for 5 min then air for 25 min; or (3) with 100% oxygen for 30 min,[27] the levels of excitatory amino acids in the brain were no different in the air or 100% oxygen groups but the restoration of the microcirculation was more complete and the blood pressure improvement greater in the oxygen group(s) than with air. Of the sixteen animal studies reviewed for the International Liaison Committee on Resuscitation (ILCOR) 2005 Consensus on Science and Treatment, these three studies by Solås were the only ones to show any advantage of the use of increased concentrations of oxygen.[28]

An interesting animal study by Presti et al suggests a complex effect when resuscitating young mice with 100% oxygen rather than with air.[29] Seven- and 8-day-old mice were subjected to permanent ligation of the right common carotid artery, a procedure that does not normally produce either brain damage or functional impairment in rodents, followed by a 20-min period breathing 8% oxygen in nitrogen. They were thus rendered hypoxic, with half the brain relatively ischaemic, but they were not hypercarbic. Immediately after the hypoxic insult they were placed either in 100% oxygen (Re-O_2) or in air (Re-Air) for 30 min. A greater proportion of the Re-O_2 mice died [16/34 (46.7%) vs. 11/38 (29%) chi^2; $p = 0.27$]. However, when surviving mice were tested as adults, the mice in the Re-O_2 group had a significantly better neurological outcome than the Re-Air group. Whether this difference can be ascribed to a beneficial effect of oxygen or to improved survival of more severely damaged animals in the Re-Air group is difficult to discern. Overall in the Re-O_2 group there were 13 survivors without porencephaly (38%), 5 with porencephaly (15%) and 16 deaths (47%) from a total of 34 mice. Corresponding figures for the Re-Air group were 17 survivors without porencephaly (45%), 10 with porencephaly (26%) and 11 deaths (29%) from 38 mice.

Animal studies have shown that oxygen can be protective against ischaemic cerebral injury, but only if given at greater than atmospheric pressure and only if given at the time of the ischaemic insult. In an adult rat model of temporary (1 h) unilateral middle cerebral artery occlusion, Yang et al found that 100% oxygen at 2.8 atmospheres (atm), administered during the period of ischaemia, resulted in less oedema and less neuronal shrinkage than in control rats not so exposed.[30] Hou et al looked further at the same model, comparing hyperbaric 100% oxygen at 2 atm for 60 min, normobaric 100% oxygen, and air. They also found that hyperbaric oxygen delivered during the period of ischaemia significantly reduced the size of the subsequent infarct when compared with the effect of normobaric 100% oxygen or air. There was also no apparent difference in the size of infarct between those animals exposed to normobaric 100% oxygen or to air during the period of asphyxia. Neither hyperbaric oxygen (2 atm) nor normobaric oxygen had any greater protective effect than air if given during the period of reperfusion.[31]

What evidence is there that exposure to high-concentration oxygen might be harmful?

Convulsions caused by exposure to oxygen at increased barometric pressure were first described by Paul Bert in 1878.[32] This was a problem for deep-sea divers, who avoided diving too deep when breathing 100% oxygen. With the help of J.B.S. Haldane, the British Navy began to use nitrogen/oxygen mixtures during the Second World War. This enabled Royal Navy commandos protecting the British naval base at Gibraltar to lure their oxygen-using opponents to such depths that the enemy succumbed to oxygen-induced convulsions. The danger of breathing high concentrations of oxygen at normal pressures has also been known for more than a century. In 1899, James Lorrain Smith described the serious and sometimes fatal lung inflammation induced in animals by breathing oxygen in concentrations greater than 75% at atmospheric pressure.[33]

A single breath of 100% oxygen in infants in the first week of life has been shown to result in a decrease in minute volume, more so in preterm than in term infants.[34] A similar effect was noted when newborn mice were placed in 100% oxygen for 3 min followed by air for 12 min. The mice exposed to oxygen had reduced minute ventilation, which increased in severity with repeated exposure.[35] Preterm lambs rendered hypopnoeic with a standard stimulus recovered more slowly in 100% oxygen than in air.[36] Similarly, in 8- to 10-day-old rats rendered hypoxic by breathing 5% oxygen and then resuscitated with air, 40% or 100% oxygen, the group given 100% oxygen was significantly slower to start breathing than the other groups. Both the groups offered additional oxygen were subsequently found to be hyperoxic and, curiously, also hypocarbic.[37] Similar delays in time to first cry were noted in the oxygen group of some of the human studies.[13,14]

When groups of term and preterm rat pups were placed in more than 95% oxygen or in air for 6 days, the groups placed in oxygen showed histological evidence of alveolar haemorrhage, immune-cell infiltration, oedema and collapse. In the hyperoxia groups, T_1- and T_2-weighted MRI images revealed greater pulmonary signal intensities compared with the air group.[38]

More recently, similar animal experiments have shown that hyperoxia also causes histological changes of brain injury. Hoehn et al showed that when 7-day-old rats were exposed to more than 80% oxygen for 24 h, immunohistochemical staining revealed evidence of apoptotic cell death in the retrosplenial cortex, hippocampus, frontal cortex

and thalamus; there were no such changes in the brains of control animals.[39]

Felderhoff-Mueser et al explored this further by exposing rat pups aged 14 days old or less, and 7-day-old synRas-transgenic or wild-type mice to 40%, 60% or 80% oxygen/air for 2—72 h; animals were killed 2, 6, 12, 24, 48 and 72 h after the period of oxygen exposure. An exposure to 80% oxygen of 2 h produced significant cell death at 24 h, such cell death being significantly greater if the oxygen exposure was prolonged to 6 or 12 h. The amount and distribution of damage was age dependent. In the youngest animals (day 0), the areas most affected were the thalamic nuclei, caudate nucleus, putamen, hypothalamus and white matter tracts. The most severe effect on cortical areas was seen in animals aged 7 days and the greatest overall vulnerability was seen at 3 and 7 days. In 14-day-old rats, damage was much less, although some degenerating cells were seen in the dentate gyrus after exposure to 80% oxygen for 24 h.

In these experiments, significantly less brain damage was seen in 7-day-old rats treated with *N*-acetylcysteine (a precursor of the antioxidant glutathione) before and after 12 h exposure to 80% oxygen than in controls, suggesting that the effect was mediated by hyperoxia-induced stress. Rats exposed to 40% oxygen had apoptotic scores similar to air breathing littermates, whereas those exposed to 60% had a significantly greater score.[40]

Data from synRas-transgenic mice in this study showed that hyperoxia leads to changes in gene expression and reduced phosphorylation of neurotropins. The sysRas-transgenic mice, which overexpress activated Ras, had significantly less apoptotic brain damage than the wild-type mice, but still more than controls. These experiments suggest that hyperoxia causes apoptotic brain damage in developing brains by interfering with the production of the neurotropins necessary for the continued function, and thus survival, of developing neurons.

Similar studies have looked at changes in the brain proteome in rodents induced by oxidative stress during the period of rapid brain growth.[41] These results suggest that exposing infant rodents to hyperoxia not only causes an increased rate of apoptosis in their brains but also elicits long-term alterations in cell growth and differentiation, synaptic function, neuronal migration and axonal arborization.

The period of vulnerability to these effects in rats appears to be limited to the first 2 weeks of life, which coincides with the brain growth-spurt of this species. Hyperoxia does not induce these changes in mature or adolescent rodents. In humans, the comparable period of brain growth would be from the third trimester of pregnancy to several years after birth.

Even short-term exposure to high oxygen concentrations might have a significant effect. Lundstrøm et al randomly assigned 70 preterm infants to receive either air or 80% oxygen during stabilization in the delivery room.[42] Global cerebral blood flow was decreased following oxygen exposure and this could still be detected some 2 h after birth, although without any apparent short-term effect. Niijima et al also measured cerebral blood flow velocity in preterm and term infants and also found a decrease following exposure to oxygen.[43] Interestingly, in the term infants in this study, who were not mechanically ventilated (unlike most of the preterm infants), there was a simultaneous fall in pCO_2, which analysis of variance suggested had the major effect on blood flow velocity. A similar unexplained hypocarbic effect of breathing high-concentration oxygen was noted in rats by Bookatz et al.[37] A brief exposure to high oxygen concentration at birth of 3 min or longer has also been associated with increased risk of childhood cancer, primarily acute lymphatic leukaemia, in two epidemiological studies.[44—46]

A number of experiments in young animals have confirmed that exposure to oxygen during resuscitation from hypoxia leaves evidence of significant oxygen stress that is not apparent in the controls resuscitated with air.[47—50] Vento et al have demonstrated the same in randomized human studies with measurable effects lasting at least 28 days.[16,17]

Is high-concentration oxygen necessary to reduce pulmonary vascular resistance at birth?

The composition of gas inhaled has an effect on the pulmonary vascular resistance. Oxygen is a well-recognized pulmonary vasodilator and one concern of those resuscitating babies at birth is that the use of air might result in high pulmonary vascular resistance, which could impede resuscitation or lead to persistent pulmonary hypertension of the newborn (PPHN). Two studies have addressed this concern. Medbo et al.[51] looked at newborn piglets and found that pulmonary vascular resistance rose significantly with induced hypoxia but fell as quickly when resuscitation was carried out with air as with 100% oxygen. The study by Lakshminrusimha et al.[52] looked at full-term lambs delivered abdominally and then ventilated with 21%, 40% or 100% oxygen for 30 min. Using the decrease in pulmonary vascular resistance (PVR) in response to 100% oxygen as indicative of a 100% fall, then by 2 min of age PVR in the air group had achieved 72% of this reduction. In the group ventilated with 50% oxygen, PVR fell to 80% of this level. By 30 min, the PVR of the 100% and 50% oxygen groups was identical at around 0.2, whereas that of the air group was 0.4—or 80% of the pure oxygen fall. By 60—90 min of age, the decrease in PVR in the air group had reached the same level as in the other two groups.

However, when these lambs were then ventilated with 10% oxygen, or given a thromboxane analogue to cause a rise in PVR, the response in all groups was similar but the subsequent vasodilatation response to nitric oxide (NO) or acetylcholine was reduced in the groups previously ventilated with additional oxygen. Furthermore, rebound pulmonary hypertension to a level higher than that at the start of NO/acetylcholine followed withdrawal of NO/acetylcholine, but only in the group resuscitated with 100% oxygen. A number of mechanisms are proposed to explain this phenomenon. One of these is that reactive oxygen species produced by exposure to 100% oxygen can react with arachidonic acid, leading to the production of isoprotanes, which are potent constrictors of pulmonary arteries. Similarly, superoxide reacts avidly with NO to produce peroxynitrite, which is a potent oxidant causing vasoconstriction, lipid peroxidation and damage to surfactant proteins. The authors of this study conclude that ventilation with air at birth results in a significant reduction in pulmonary vascular resistance, although the initial magnitude and rapidity of the reduction in PVR was greatest with 100% oxygen.

However, the use of 100% oxygen impairs the effect of any subsequent use of NO or acetylcholine to treat PPHN, whereas resuscitation with air or 40% oxygen does not.

What do we still need to know?

Of those babies actually requiring resuscitation at birth, the vast majority will respond immediately to lung inflation.[53] A small minority of newborns will not respond directly to lung inflation but virtually all of these will then respond quickly if lung inflation is followed by a brief period of chest compressions.[54] Of the tiny remainder, some will finally respond to intravenous drugs or possibly volume; many of those who respond only to extensive resuscitation efforts will not survive the neonatal period.

Does the use of 100% oxygen for resuscitation at birth have the potential to increase the proportion of survivors or to reduce the severity of brain damage in survivors? Such data as we have from the small number of babies (1538) entered into pseudo-randomized or truly randomized studies would suggest that 100% oxygen does not increase the proportion of survivors. Indeed, the Cochrane review of the human studies (at that time comprising 1302 babies) suggested that mortality was significantly higher in the 100% oxygen group.[55] This analysis needs to be interpreted with some caution because much of the supposed randomized control trial data was gathered in trials that were only pseudo-randomized and not blinded. Most of the overall effect on mortality was due to the large influence of one study[14] on the meta-analysis. In addition, there was significant cross-over from the air to the oxygen groups (and interestingly from the oxygen to the air groups when properly blinded), which, on an intention-to-treat analysis, either exaggerates the efficacy of air or reduces the chance of picking up the adverse effects of oxygen, depending on one's point of view.

A number of other issues can and have been raised about these studies. First, they include very few preterm babies and almost none below 1000 g in birth weight. Second, the entry criteria were such as to allow the potential inclusion of a significant number of babies who were probably not seriously asphyxiated and merely received resuscitation rather than truly required it to ensure survival. Third, the vast majority of deaths (174 of 177) occurred in under-resourced countries where the adequacy of resuscitation can be questioned. Details of the cause of death in these studies are lacking and no plausible mechanism involving hyperoxia in the cause of death has been proposed. Although short-term outcomes are of some interest, the real test is whether the long-term outcome is different between groups and this information is not available.

Objections could also be raised as to the relevance of some of the animal studies. Although these studies all involved immature mammals, virtually all had made the transition from placental to pulmonary respiration some hours or days before testing. However, the concerns raised by the studies by Felderhoff-Mueser[40] and Kaindl et al.[41] cannot be brushed aside on this basis. Similarly, much of the animal data depends on the exposure of animals to many hours of hyperoxia, rather than the few minutes that would normally be necessary for resuscitation. However, Vento et al found evidence of oxidative stress at 28 days in humans apparently requiring resuscitation who were randomized to oxygen rather than air and who received 100% oxygen merely for the period of resuscitation.[16]

In animal studies, the tendency is to randomize the gas to which the asphyxiated animal is exposed. As mentioned above, this usually means exposing a group to additional oxygen for an arbitrary time thought to mimic that needed for resuscitation. This almost always results in hyperoxia in the 'oxygen' group and we already know that hyperoxia is potentially damaging (depending on its severity and duration and the susceptibility of the victim). Presumably, the use of air for resuscitation following hypoxia limits the speed with which normoxia can be achieved. The question at issue is really whether more rapid achievement of normoxia, resulting from the use of judicious amounts of additional oxygen that avoid hyperoxia, will reduce the extent of brain damage. If a means could be derived whereby exposure in the oxygen group could be constrained by feedback on the oxygenation status of the subject, and if hyperoxia could thus be avoided, we might then be closer to answering this important question.

Those practitioners concerned about pulmonary vascular resistance should be reasonably reassured by the studies of Medbo et al.[51] and Lakshminrusimha et al.[52] The latter study not only confirms effectiveness of air in significantly reducing pulmonary vascular resistance but shows that the use of the apparently more rapidly effective 100% oxygen has a downside in this context. There remains the nagging concern that early use of high oxygen concentrations might result in more rapid repayment of the oxygen debt in some areas of the brain suffering from hypoxia, and that this might improve the long-term neurological outcome. The study by Hou et al.[31] implies that whereas hyperbaric oxygen given during the period of hypoxia might be useful, the use of either hyperbaric or normobaric 100% oxygen confers no advantage if supplied after the insult has occurred. Moreover, the use of 100% oxygen in immature animals brings us back to the concerns raised by the Felderhoff-Mueser study.[40] Additionally, in most animal studies, asphyxia was induced in a manner that produced hypoxia and possibly a degree of ischaemia, but only a few also ensured hypercapnia. In the Solås studies where a model of hypoxia—ischaemia—hypercapnia was used,[26,27] the results favouring oxygen should perhaps engender a pause for thought in cases of severe intrapartum asphyxia; even accepting that the results of these two studies suggested less of an advantage to the use of oxygen than the first study which did not include hypercapnia.[25]

As to whether to use additional oxygen at the resuscitation of babies at birth, the burden of proof of this question would now seem to have transferred from those wishing to use air (or at least a low concentration of additional oxygen) to those intending to use high concentrations of oxygen. We await future studies in the hope that they might discover whether there is an optimal concentration of oxygen at resuscitation, when to use this and how best to adjust its use to the oxygen status of the baby. While arguments rage concerning brief exposure to this powerful drug at birth, we should clearly not be ignoring what is perhaps the more important question of how safely to regulate more extended oxygen exposure in neonatal care in general.

Practice points

- Studies using short-term outcome measures, including neonatal survival, have demonstrated that air is as effective as 100% oxygen in resuscitation of babies at birth.
- Exposing newborn mammals, even those born at term, to high concentrations of oxygen places them at risk of hyperoxia, which can be damaging to the developing brain.
- Animal studies indicate that use of air for resuscitation of asphyxiated term infants is almost as effective as 100% oxygen at reducing pulmonary vascular resistance (PVR) and may prevent rebound increases in PVR.
- Whether asphyxiated babies might suffer a greater or a lesser degree of lasting neurological deficit if resuscitated with higher concentrations of oxygen rather than air remains unknown.
- At delivery, the processes of stabilizing significantly preterm infants and of resuscitating asphyxiated term infants have certain similarities but are not the same.

Research agenda

- Future randomized controlled human studies of resuscitation gases should consider:
  - adequate randomization and blinding
  - long-term neurological outcome in survivors
  - the effects of varying concentrations of oxygen between 21 and 100%, combined with measures to avoid hyperoxia, on all aspects of resuscitation.
- Future animal studies, if intending to influence resuscitation practices at birth, should include work on mammals in transition from placental to pulmonary respiration with the insult applied in the placental stage. Ideally, the insult should replicate obstetric complications in producing fetal hypoxia, ischaemia and hypercarbia.
- Devising experiments that allow the oxygen group to avoid hyperoxia and yet to be exposed to sufficient additional oxygen to rapidly re-establish normoxia, and comparing this to rapid resuscitation using air alone, might be a fruitful strategy.

Conflict of interest

Neither of the authors has any conflict of interest.

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