# WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

**Worksheet author(s)**

| Sam Richmond | Date Submitted for review: 6th February 2010 |

## Clinical question.

**NRP-013B**

When starting resuscitation of neonates at birth (P), is room air (I) superior to supplemental oxygen (C) in improving outcome (O)?

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Intervention/therapy

**State if this is a proposed new topic or revision of existing worksheet:** Revision

## Search strategy (including electronic databases searched).

- AHA Endnote, Cochrane database for systematic reviews, Medline, Embase, Pubmed; hand searches of journals, review articles and books
- Key words: Neonatal resuscitation / resuscitation at birth, air; oxygen
- Searches for papers by specific authors of previous papers of interest
- Forward searches using Scopus and Google Scholar

### State inclusion and exclusion criteria

- All English language studies included, if published in full.

### Number of articles/sources meeting criteria for further review:

- 12 papers describing randomized human interventions, 1 meta-analysis (published as Cochrane review and in the Lancet), 4 case-control human studies, 4 other studies in humans and 44 animals studies.
## Summary of evidence

### Evidence Supporting Clinical Question

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### Level of evidence

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint
- **Italics** = Animal studies
- ***** = overlapping patients

† Each of these two papers is a meta-analysis of the same data by the same authors — one in Lancet and one in Cochrane Database.
# Evidence Neutral to Clinical question

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| Ramji 1993 C    | Saugstad 2003 D      |                      |                      | Mortola 1992, 11     |                      |
|                 |                      |                      |                      | Cheung, 2006, 636    |                      |

**Level of evidence**

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**Italics** = Animal studies

# Evidence Opposing Clinical Question

| Good            |                      |                      |                      |                      |                      |
|-----------------|----------------------|----------------------|----------------------|                      |                      |
|                 |                      |                      |                      | Solås 2001, 340      |                      |
|                 |                      |                      |                      | Solås 2004, 105      |                      |
|                 |                      |                      |                      | Solås 2004, 125      |                      |
|                 |                      |                      |                      | Presti 2006, 55      |                      |

| Fair            |                      |                      |                      | Escrig* 2008, 875 CE | Wang* 2008, 1083 E  |
|-----------------|----------------------|----------------------|----------------------|                      |                      |

| Poor            |                      |                      |                      |                      |                      |

**Level of evidence**

- **A** = Return of spontaneous circulation
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- **D** = Intact neurological survival
- **E** = Other endpoint

**Italics** = Animal studies

*Very preterm infants only (Escrig <29 weeks, Wang <32 weeks)
REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

An infant in need of resuscitation at birth has usually reached this stage because placental mechanisms of gas exchange have been interrupted. Following birth the placenta is no longer available and thus the logical intervention is to establish adequate pulmonary gas exchange by inflating the lungs. The effectiveness of this approach is well established. In the past we have extended this logic by administering 100% oxygen in an attempt to limit the effects of cerebral hypoxia. However, in the last 30 years the ‘oxygen paradox’ - the fact that cell and tissue injury is increased if hypoxic tissue is then exposed to high concentrations of oxygen - has been recognized, 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 the light of this knowledge it has become increasingly difficult to sustain the idea that exposure to high concentrations of oxygen, however brief, is without risk.

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 in 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. If energy failure continues for long enough depolarisation occurs, quickly followed by cell death. However, sub-lethal hypoxic ischemia 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 down regulation of future gene expression. Furthermore, there is now considerable evidence from animal and human studies that hyperoxia alone is damaging to the brain and other organs at the cellular level and that the immature brain during the brain growth spurt (mid-pregnancy to 3 years) is at considerably greater risk. This includes deleterious effects on glial progenitor cells and myelination.

Detailed interpretation of much of the animal work is difficult because exposure of the oxygen group to 100% oxygen has been for a pre-determined time that virtually ensures hyperoxia and not limited to that required for rapid achievement of normoxia. We know that hyperoxia is damaging.

Randomised studies in asphyxiated newborn babies strongly suggest that air is certainly as effective as 100% oxygen, if not more effective, at least in the short term. However, it is the long term neurological outcome that is of most interest and information on this aspect is inadequate. Assuming that the reversion to aerobic metabolism from anaerobic is not a rate limited process, then it is theoretically possible that babies who have experienced a single sudden episode of severe asphyxia just before delivery may benefit from brief exposure to high pulmonary oxygen concentrations, if hyperoxia can be avoided.

Other issues include concerns that pulmonary vascular resistance may take longer to ‘resolve’ if air is used rather than oxygen for lung inflation at birth. However, though two studies have shown that it may be reduced a little further and a little faster by use of oxygen than air, there is a price to pay in terms of the creation of increased reactive oxygen species reducing the potential for pulmonary artery vaso-relaxation later in the neonatal course. As to the stabilization of preterm infants, there seems to be a need for at least some additional oxygen if the goal is to reach arbitrarily-defined acceptable saturations in an arbitrarily-defined reasonable period of time.

When faced with a baby apparently needing resuscitation at birth the resuscitator now needs to bear in mind the toxic effects of both hypoxia and hyperoxia. This problem is exacerbated because the resuscitator does not know the severity or duration of the hypoxic-ischaemic events prior to birth.

REVIEWER’S CONFLICTS OF INTEREST:

UK NHS Consultant neonatologist. Co-chair of the Neonatal section of ILCOR – unpaid. Chair of the Newborn Life Support subcommittee of the Resuscitation Council (UK) and member of the Executive committee – both unpaid. No other conflicts.

Acknowledgements: Dr Jay Goldsmith
Question: When starting resuscitation of neonates at birth (P), is room air (I) superior to supplemental oxygen (C) in improving outcome (O)?

Aizad, 1984, p1531

LOE: 5
Quality: Poor in terms of focus on our question
Supportive
Comments: Reduced tidal volume in response to inhalation of oxygen. These were infants whose extra-uterine existence was already established. Does this matter in the context of resuscitation at birth?

Appleby, 2001, p502

LOE: 5
Quality: Fair in terms of focus on our question
Supportive
Comments: Further evidence of the potentially toxic effects of hyperoxia in general. Immature rats were used but the exposure time was measured in days rather than minutes. Not specifically relevant to resuscitation at birth.

Bagenholm, 1996, p1228

LOE: 5
Quality: Fair
Neutral
Comments: These animals had already established their extra-uterine existence. The left common carotid artery was ligated and cut (a procedure which does not normally produce either brain damage or functional impairment in rodents), and they were then subjected to hypoxia - thus rendering the left cerebral hemisphere potentially ischaemic as well. Length of oxygen exposure was reasonably appropriate. There appeared to be no cerebral protective effect of resuscitation with air or oxygen when estimated by comparing weights of the left and right cerebral hemispheres 14 days after the insult. I am uncertain as to how sensitive weighing of cerebral hemispheres is in detecting brain damage.

Bajaj, 2005, p206

LOE: 2
Quality: Poor – pseudo-randomised, not blinded
Neutral
Comments: Level 3 NICU in India. Pseudo-randomised and not blinded – even dates used 100% oxygen, odd dates air. 'Randomised' to receive 90 seconds of either air or 100% oxygen if more than 1000 gm and with apnoea or gasping respiration or heart rate less than 100 per minute after initial steps of resuscitation if they required IPPV. Switch to oxygen possible if centrally cyanosed at 90 seconds – designated as a failure of resuscitation. 236 babies – exclusions 10 less than 1000 gm, 17 congenital malformations and 5 refused consent. There were a total of 204 babies, 107 in the air group and 97 in the oxygen group. HIE or death occurred in 41.1% of the air group and 43.3 of the oxygen group – odds ratio in the group assigned to air 0.92 CI 0.52 to 1.60. HIE in the two groups was also similar 33.6% in the air group vs 34% in the oxygen group – 6.4%, 24.3% and 2.8% were stage 1, 2 or 3 HIE in the air group and 9.3%, 19.6% and 5.1% in the oxygen group. Resuscitation failure was 4
individuals in each group and there were 17 deaths before discharge in each group (15.9 vs 17.5% ns) though ‘asphyxia related mortality’ is described as being 8 (7.5%) vs 9 (9.3%) in air vs oxygen - ns. Yet another quasi-randomised air vs 100% oxygen study in humans showing that, using short term outcome measures, air is just as effective as 100% oxygen for resuscitation at birth.

Bookatz, 2007, p698


**LOE: 5**

**Quality: Fair** in terms of focus on our question

**Supportive**

**Comments:** Confirmation in an animal study of the delayed onset of breathing noted in human studies in response to resuscitation at birth with 100% oxygen as compared with air.

Børke, 2004, p F156

**Børke WB, Munkeby BH, Mørkrid L, Thaulow E, Saugstad OD. Resuscitation with 100% O2 does not protect the myocardium in hypoxic newborn piglets. Arch Dis Child Fetal Neonatal Ed 2004; 89: F156-F160.**

**LOE: 5**

**Quality: Fair**

**Neutral**

**Comments:** These animals had already established their extra-uterine existence and were rendered hypoxic and hypercarbic with resultant ischaemia. Length of time exposed to oxygen was reasonable. No difference found between air and 100% oxygen.

Børke, 2004, p459


**LOE: 5**

**Quality: Fair**

**Supportive**

**Comments:** These animals had already established their extra-uterine existence and were rendered hypoxic and hypercarbic with resultant ischaemia. Length of time exposed to oxygen was reasonable. Increased MMP activity appears to be associated with a greater degree of oxidant damage in reperfusion injury and the use of air for resuscitation resulted in lower MMP levels than the use of 100% oxygen. The observation of a protective effect to left ventricular function of hypercarbia may explain a similar protective effect in relation to improvement of cerebral perfusion noted in the latter two Solås studies (2004a and b).

Campbell, 1966, p153

**Campbell AGM, Cross KW, Dawes GS, Hyman AI. A comparison of air and O2 in hyperbaric chamber or by positive pressure ventilation, in the resuscitation of newborn rabbits. J Pediatr 1966: 68; 153-63.**

**LOE: 5**

**Quality: Good** animal study

**Neutral**

**Comments:** Perhaps the earliest randomised study of air vs oxygen in resuscitation of asphyxiated immature mammals. These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic nor ischaemic. Resuscitation by IPPV with air would appear to have been as effective as with 100% oxygen.

Cheung, 2006, p636


**LOE: 5**

**Quality: Poor** for our purposes – too small to show difference in effect

**Neutral**
Comments: These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic nor ischaemic. The study suggested that there might be a difference in the extent to which platelets were activated following resuscitation with 100% oxygen as opposed to air but the study was too small to comment on this.

Cheung, 2008, p457
Cheung PY, Johnson ST, Obaid L, Chan GS, Bigam DL. The systemic, pulmonary and regional hemodynamic recovery of asphyxiated newborn piglets resuscitated with 18%, 21% and 100% oxygen. Resuscitation 2008; 76: 457-64.

My notes: When resuscitated with 21% or 100% oxygen there was a rapid drop in Pulmonary Artery Pressure / Mean Arterial Pressure ratio to levels no different from sham operated animals within 10 minutes of resuscitation but the ratio remained significantly higher in the 18% group.

LOE: 5
Quality: Good animal study
Neutral
Comments: These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic nor ischaemic (though there was a fall in cardiac index to 40% during hypoxia). They also had the arterial duct ligated before inducing hypoxia. Exposure time to 100% oxygen was moderately prolonged (1 hour) in the context of resuscitation. Of the choices available it would appear that 100% oxygen was too much, 18% too little and 21% just right - reminds me of Goldilocks and the three bears.

Cnattingius, 1995, p908

LOE: 3
Quality: Fair in terms of focus on our problem
Supportive
Comments: It is difficult to know how much credence to give this study. Association does not confirm causation. However, use of 100% oxygen for resuscitation at birth can easily be avoided.

Davis, 2004, p1329
Davis PG, Tan A, O'Donnell CPF, Schulze A. Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis. Lancet 2004; 364: 1329-33

LOE: 1
Quality: Fair – in view of overall quality of RCTs
Supportive
Comments: Meta-analysis. This same analysis has been published as a Cochrane Review (see Tan A et al listed below). The conclusion, namely that one can reasonably start resuscitation with air in term and near term infants, is stated more strongly here than in the Cochrane Review. It is difficult to explain and equally difficult to ignore the difference in mortality (in favour of air) shown by this meta-analysis.

Escrig, 2008, p875

LOE: 1
Quality: Fair – in view of small size and short term follow up.
Opposing
Comments: Small but properly randomized study – only 42 patients all of whom were less than 29 weeks gestation [High oxygen (start at 90%) 23, low oxygen (start at 30%) 19]. Both the target oxygen saturations and the target times to reach them were arbitrary, though not unreasonable. Targets would have been well overshot with 100% oxygen and yet needed a bit more than 21% to be achieved. Babies whose ‘resuscitation’ was commenced with 30% oxygen were more likely to be ventilated in air at 10 and 20 minutes of age than babies whose ‘resuscitation’ commenced with 90% oxygen.
Feet, 1998, p1208

**LOE: 5**
**Quality: Good** animal study
**Neutral**
**Comments:** One of only two studies of the use of less than 21% oxygen in resuscitation. These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic nor ischaemic. No apparent advantage of 100% oxygen or hypoxemic resuscitation over air.

Felderhoff-Meuser, 2004, p273

**My summary:**
Wistar rat pups aged 0-14 days or 7 day old mice were placed together with their mothers into a chamber and exposed to 40%, 60% or 80% oxygen/air environment for 2-72 hours. Mothers were switched every 24 hours to prevent adult respiratory lung disease. Littermates kept in room air served as controls. Animals were sacrificed at 2, 6, 12, 24 48, 72 h following oxygen exposure. Each experimental group consisted of 6-10 pups. Exposure to 80% oxygen over 12 h was performed with sysRas-transgenic mice. The sysRas-transgenic mice were first generated on a B6 background and were then crossed back to NMRI background 30 times, as previously described. Genotype of mice was determined by PCR as previously described. To determine blood oxygen content during hyperoxia, infant pups were placed into the hyperoxia chamber for 10 min, were then taken out and anaesthetized with ether, placed back into the hyperoxia chamber for 3 min, and subsequently a left cardiac puncture was performed subcutaneously using a 32 gauge hypodermic needle. One hundred microliters of arterial blood was obtained and immediately subjected to analysis of pH, \( \text{paO}_2 \) (partial pressure of oxygen in mm Hg), \( \text{paCO}_2 \), and bicarbonate.

**80% oxygen:** Hyperoxia (80% oxygen for 24 hours) increased numerical densities of degenerating cells in various brain regions in comparison to unexposed littersmates. Brain regions affected were the caudate nucleus, nucleus accumbens, layers II and IV of the frontal, parietal, cingulated and retrosplenial cortices, as well as white matter tracts within the forebrain. After 2 hours exposure to 80% \( \text{O}_2 \) significant apoptotic cell death occurred at 24 h. Following 6 or 12 h exposure the amount of apoptotic cell death detected at 24 h increased significantly. After longer exposure (48 and 72 h) the amount of cell death detected in the brains upon the end of exposure decreased, most likely because in the meantime apoptotic cells had been eliminated and were no more amenable to detection by histological techniques. Exposure to N-Acteylcysteine (precursor of the antioxidant glutathione) before and after 80% oxygen reduced extent of brain damage in 7 day rats.

**40% and 60% oxygen:** Analysis of brains at 24 hours after beginning of hyperoxia revealed that the pups exposed to 40% oxygen had apoptotic scores similar to those littermates exposed to normoxia. Exposure to 60% oxygen resulted in significant increase of apoptotic cell death in the brain compared to normoxic littersmates. Apparently this degree of oxygen sensitivity is confined to immature rodents – ‘in the first two weeks of life, a period characterized by rapid growth, which in humans expands from the sixth month of pregnancy to the third year of life’. Hyperoxia (80%) triggered reduction in mRNA levels for brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3 (NT-3) and neurotrophin 4 (NT-4) in all brain regions examined. The knock-on effect of this fall in neurotrophins was a decrease in levels of active phosphorylated isoforms of serine-threonin kinase Akt and extracellular signal-regulated protein kinase ERK1/2 – which mediates intracellular signalling following activation of receptor tyrosin kinases by growth factors. ERK1/2 is part of the MAPK (mitogen-activated protein kinase) pathway the expression of which is significantly elevated in synRas-transgenic mice. These mice were found to be less sensitive to hyperoxia-induced apoptosis of the brain but not different in respect of physiological apoptosis suggesting that the Ras-MAPK pathway is at least partially involved in producing hyperoxic apoptotic brain damage.

**LOE: 5**
**Quality: Good** study of the dose / effect of hyperoxia on immature animal brains
**Supportive**
**Comments:** Good evidence of widespread brain damage from hyperoxia and some suggestion that this is significantly reduced if exposure is limited to oxygen levels of 40% and below. Excessive time of exposure to oxygen in relation to our question.

Fugelseth, 2005, p F229
Quality: Good animal study
Neutral

Comments: The animals used in this study had already established their extra-uterine existence. Hypoxic injury to the heart is not apparently modified by resuscitation with 100% oxygen rather than air.

Gerstner, 2008, p1236

LOE: 5
Quality: Good study of the dose / effect of hyperoxia on immature animal brain
Supportive
Comments: Good evidence of widespread brain damage to the developing brain from prolonged hyperoxia. Excessive exposure to oxygen for our purposes.

Goplerud, 1995, p161

LOE: 5
Quality: Poor in that 100% oxygen exposure was too prolonged for our purposes.
Supportive
Comments: These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic nor ischaemic. Exposure to 100% oxygen was 2 hours which is somewhat excessive. No apparent advantage of 100% oxygen over air and some suggestion of increased oxygen stress.

Haase, 2004, p364

LOE: 5
Quality: Fair
Supportive
Comments: One of a number of papers from this Canadian laboratory looking at the effects of reperfusion injury on abdominal and other organs. The premise is that NEC involves hypoxiareoxygenation and the creation of reactive oxygen species which cause intestinal injury. Once again it should be remembered that these animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic nor ischaemic. A small number of piglets tested, but the results are intriguing and add another area of concern for hyperoxia (and performed in a different laboratory than the few which have had a major interest in this area). Impressive photographs of the histology of the small intestine in the four groups showing very convincing injury in the 100% oxygen group.

Haase, 2005, p383
Haase E, Bigam DL, Nakonechny QB, Rayner D, Korbutt G, Cheung PY. Cardiac function, myocardial glutathione, and matrix metalloproteinase-2 levels in hypoxic newborn pigs reoxygenated by 21%, 50% or 100% oxygen. Shock 2005; 23: 383-9.

LOE: 5
Quality: Poor in that 100% oxygen exposure was slightly too prolonged (1 h) for our purposes.
Supportive
Comments: These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic nor ischaemic. Exposure to 100% oxygen was 60 minutes which is a bit too long. No apparent advantage of 100% oxygen over air and some suggestion of increased oxygen stress.

Hellström-Westas, 2006, p e1798
**LOE: 3**  
**Quality: Fair**  
**Supportive**  
**Comments:** Population study auditing the results of two approaches to resuscitation of babies at birth with respect to oxygen use – viz. initial use of 100% vs initial use of 40% oxygen. There are a number of concerns about the Apgar score and some have called for it to be abandoned. However, here it is used as the primary outcome measure of the non-randomised intervention. Despite the limitations of this study it does reasonably support the contention that, in the short term, those babies resuscitated using 40% oxygen recover more quickly than those resuscitated with 100% oxygen. Whether the use of 40% oxygen changes the long term neurological outcome is not addressed. The death rate in the 100% oxygen group is 16/661 (2.4%) as against 9/562 (1.6%) in the 40% group (OR 1.48 95%CI 0.63 – 3.44).

Hoehn, 2003, p179


**LOE: 5**  
**Quality: Poor** in that exposure to >80% oxygen was excessively prolonged for our purposes.  
**Supportive**  
**Comments:** Here is yet further animal evidence confirming widespread apoptotic brain damage after significant hyperoxia in rats. However, long exposure times of many hours were used.

Huang, 1995, p292


**LOE: 5**  
**Quality: Poor** in that exposure to 100% oxygen was excessively prolonged for our purposes.  
**Supportive**  
**Comments:** These animals had already established their extra-uterine existence. Levels of extracellular dopamine (which has been shown experimentally to be a mediator of ischaemic cell injury) remained higher for longer in the 100% oxygen group. This group was exposed to 100% oxygen for 2 hours – an unnecessarily long time in the context of resuscitation. In this study no difference was found in striatal blood flow (using a laser Doppler microprobe) during resuscitation using air as opposed to oxygen. [Differences in cortical blood flow measured in the Solás studies using a similar measuring technique (see below) seemed to offer an advantage to the 100% oxygen group]. Possibility of hazard associated with the use of 100% oxygen.

Hutchison, 1987, p317


**LOE: 5**  
**Quality: Good animal study but of marginal relevance to our question – hence - Poor**  
**Supportive**  
**Comments:** This study suggests a slower response to resuscitation following induction of hypopnoea when 100% oxygen is used rather than air. The exposure time to 100% oxygen is very realistic – viz 2 minutes. These animals had already established their extra-uterine existence.

Kaindl, 2006, p1097


**LOE: 5**  
**Quality: Good animal study but excessive oxygen exposure for our purposes hence - Poor**  
**Supportive**
**Comments:** Yet further animal evidence of brain damage secondary to hyperoxia in the immature animal brain. In terms of our question the exposure time to high oxygen concentrations was excessively long – 12 hours.

Klinger, 2005, pF49


**LOE:** 4  
**Quality:** Good  
**Supportive:**

**Comments:** Long-term follow-up information is the least available information in the literature on this topic and yet is probably the most important in deciding whether or not to change the guidelines. This is one of only two papers giving follow-up information, the other being Saugstad 2003 which showed no difference (but missed 34% of survivors). This is the only human follow-up paper to suggest a long-term disadvantage to excess use of oxygen. No follow-up information is available for nearly 12% of the cases.

Koch, 2008, p1294


**LOE:** 5  
**Quality:** Fair  
**Supportive:**

**Comments:** Good animal study using post-transition mice asphyxiated at 14 days of age. Exposure to 100% oxygen was varied by group using 15, 30, 60 120 and 240 min exposure times with detrimental effect being demonstrated after 30 minutes or greater exposure. The demonstration of the detrimental effect of hyperoxia after hypoxic-ischaemic brain injury on neuroglial progenitors and the subsequent effect on myelination is particularly relevant. Very important study confirming and extending our knowledge of the damaging short and long term neurological effects of hyperoxia following birth asphyxia.

Kondo, 2000, p524


**LOE:** 5  
**Quality:** Good  
**Supportive:**

**Comments:** This study demonstrates the significantly greater presence of reactive oxygen species following resuscitation with 100% oxygen after an asphyxial episode as compared with similar resuscitation with air. Exposure to 100% oxygen lasted around 10 minutes

Kutzsche, 2001, p834


**LOE:** 5  
**Quality:** Good – reasonable oxygen exposure time  
**Supportive:**

**Comments:** These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic nor ischaemic. Oxygen exposure time was 30 minutes. No differences between groups were found in regional cortical blood perfusion during the two hours following resuscitation as measured by laser Doppler flow —the Huang study found no difference in striatal blood flow whereas the Solås studies found a lower flow in the 100% oxygen group (see below). Higher H$_2$O$_2$ levels in neutrophils following resuscitation with 100% oxygen suggests the possibility of hazard associated with the use of 100% oxygen.

Lakshminrusimha, 2006, p137

The investigators speculate that changes in endogenous NO, cGMP and PDE5 affect pulmonary vascular tone. PDE5 down regulates endogenous NO signaling through inactivation of cGMP which is a critical mediator in smooth muscle cells leading to vasorelaxation. Therefore, the potential advantage of using high concentration oxygen during immediate resuscitation to reduce pulmonary vascular resistance may result in better pulmonary perfusion but may have later consequences in the blunting of cellular pathways which facilitate vasorelaxation and respond to nitric oxide.

Lakshminrusimha, 2007, p313

Rate of fall of PVR in the air group was slower – in the air group only 70% of the pure oxygen fall was achieved by 2 minutes – but PVR had reached the same level by 60-90 minutes in all groups. The ability of the lung vasculature to respond with vasodilatation to a later inhalation of NO or to an infusion of acetylcholine was decreased in the group exposed to 100% oxygen and this group also had significant rebound after cessation of NO or acetylcholine compared with the other groups. The authors speculate that this might be caused by higher levels of reactive oxygen species (ROS) induced by inhalation of 100% oxygen (ROS react with arachidonic acid to produce isoprostanes which induce vascular constriction, Superoxide anions react with NO to produce peroxynitrite – a vasoconstrictor...). This study provides further evidence that use of 100% oxygen has a significant downside. Problems: small numbers, different species, duct tied before birth.

Lofaso, 2007, p18

My summary:
This study looked at the effect of repeated hyperoxia on breathing control in newborn mice. A total of 97 Swiss mouse pups were assigned to O₂ or air on post-natal day 0, 1 or 2. Each pup in the O₂ group was subjected to four hyperoxic tests (100% O₂ for 3 min followed by 12 min normoxia), whereas pups in the air group were maintained in normoxia. Breathing variables were measured using flow-through barometric plethysmography. O₂ significantly decreased minute ventilation as seen in a decrease in respiratory rate. This decrease became significantly larger with repeated exposure and ranged 17-26% for all ages combined.

Lundstrøm, 1995, p F81

Markus, 2007, p71
Quality: Excellent animal study
Supportive
Comments: Finally an animal study of oxygen at resuscitation that produces the insult in the placental respiration stage with resuscitation in the lung respiration stage.

Medbo, 1998, p843

LOE: 5
Quality: Fair study
Neutral
Comments: These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic. Though hypoxia undoubtedly causes increased pulmonary vascular resistance this resistance falls just as quickly when resuscitation is attempted with air as with 100% oxygen. No apparent advantage to using oxygen.

Mickel, 1987, p426

LOE: 5
Quality: Good study – somewhat excessive oxygen exposure hence POOR
Neutral
Comment: These were mature animals. This is one of the earliest studies to draw attention to the 'oxygen paradox'.

Mortola, 1992, p11

LOE: 5
Quality: Limited relevance to our question - POOR
Neutral
Comments: Human study showing increased work of breathing when in high concentration oxygen but also increased oxygen consumption – more than can be accounted for by increased work.

Munkeby, 2004, p783

LOE: 5
Quality: Good
Supportive
Comments: Post-transition animals rendered hypoxic and hypercarbic (at least some) but not ischaemic. Evidence suggests increased damage to brain cells within the group resuscitated in 100% oxygen and that the increased damage involved reactive oxygen species.

Munkeby, 2005, p542

LOE: 5
Quality: Good
Supportive
Comments: These animals had already made the transition to pulmonary respiration. They were subjected to hypoxia and hypercarbia but only limited ischaemia.
Naumburg, 2002, p1328

LOE: 3
Quality: Good
Supportive
Comments: Exclusions – birth records not retrieved in 35 cases and 47 controls, Trisomy 21 (11 cases), unable to match (34 cases, 27 controls), ‘left-over’ controls 5. Further studies needed. It is difficult to know how much credence to give this study. Association does not necessarily imply causation. However, use of 100% oxygen for resuscitation at birth can easily be avoided.

Niijima, 1988, p1126

LOE: 4
Quality: Poor – not really focused on our problem
Supportive
Comments: Reduction in cerebral blood flow velocity with increased PaO₂. In this study the suggestion was made that this might have implications for the development of retinopathy of prematurity. Equally there may be effects on other areas of the brain.

Poulsen, 1993, p1058
Poulsen JP, Øyasæter S, Saugstad OD. Hypoxanthine, xanthine, and uric acid in newborn pigs during hypoxemia followed by resuscitation with room air or 100% oxygen. Crit Care Med. 1993 Jul; 21(7): 1058-65.

LOE: 5
Quality: Good animal study
Neutral
Comments: Physiological study using piglets aged 7-14 days randomised to resuscitation with 21% (10) or 100% oxygen (10) following hypoxemia induced by sedation and ventilation with 8% oxygen in nitrogen for 2 hours. Choice of re-oxygenation gas was made before induction of hypoxemia. Seven piglets suffered cardiac arrest before the end of the hypoxemic period (4 would have been resuscitated with air and 3 with oxygen) and could not be resuscitated. No differences were found between the groups in respect of hypoxantheine levels following re-oxygenation with air or 100% oxygen. These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic nor ischaemic. No apparent advantage of 100% oxygen over air.

Presti, 2006, p55

LOE: 5
Quality: Good animal study
Supportive / Opposing
Comments: This study could be said to be either opposing or supportive. A greater proportion of the Re-O₂ mice died (16/34 46.7% vs 11/38 29% - Chi² p=0.27) but when surviving mice were tested as adults, as a group, the Re-O₂ mice 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-O₂ 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. Difficult to classify this animal study – on balance probably supportive. Note that this study found faster return of cerebral blood flow in the oxygen group as did the Solås studies.

Ramji, 1993, p809
LOE: 2
Quality: Pseudo randomized, unblinded – small pilot study hence Poor
Neutral
Comments: Small pilot study, no true randomisation, no blinding of operators, six crossovers (from air group only – I wonder how many would have crossed over from oxygen to air had it been a properly blinded study).

Ramji, 2003, p510

LOE: 2
Quality: Pseudo-randomised, non-blinded but multi-centred controlled study hence - Fair
Neutral
Comments: No true randomisation – oxygen used on odd dates and air on even dates. Two exclusions both for congenital malformations (Tracheo-oesophageal fistula, Diaphragmatic hernia). 89/210 switched from air to oxygen at 90 seconds because of insufficient response – though 89/221 oxygen infants also had insufficient response at 90 seconds.

Rootwelt, 1992, p107

LOE: 5
Quality: Good
Neutral
Comments: These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic. Reasonably appropriate length of exposure to oxygen. No apparent advantage of resuscitation with 100% oxygen as opposed to air in terms of the extent of brain damage noted at 4 days in the cerebral cortex, cerebellum and hippocampus.

Rootwelt, 1993, p1054

LOE: 5
Quality: Good animal study
Neutral
Comments: These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic. Cerebral blood flow was determined using radioactive microspheres, forebrain oxygen uptake by blood gas analysis from abdominal aorta and sagittal sinus, and somatosensory evoked potentials from epidural screws. No apparent advantage of 100% oxygen over air.

Rootwelt, 1996, p227

LOE: 5
Quality: Good animal study
Neutral
Comments: These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic. No apparent advantage of 100% oxygen over air.

Saugstad, 1998, p1

LOE: 2
Quality: Pseudo-randomised, non blinded hence - Fair
Neutral

Comments: No true randomisation – oxygen used on odd dates and air on even dates. Significant exclusions – all 94 babies from one of the 11 centres were excluded because of violation of entry criteria in 86. 73/284 switched from air to oxygen after 90 seconds because of insufficient response – though 88/295 oxygen infants also had ‘insufficient response’ at 90 seconds.

Saugstad, 2003, p296

LOE: 2
Quality: As a follow up study this is poor – too many missing - Poor

Neutral

Comments: A large proportion of the children (34%) were not followed up.

Solås, 2001, p340
Solås AB, Kutsche S, Vinje M, Saugstad OD. Cerebral hypoxemia-ischemia and reoxygenation with 21% or 100% oxygen in newborn piglets: effects on extracellular levels of excitatory amino acids and microcirculation Pediatr Crit Care Med 2001; 2:340-345

LOE: 5
Quality: Good animal study

Opposing

Comments: These animals had already established their extra-uterine existence. In this study the animal subjects were rendered hypoxic and ischaemic but not hypercarbic. The three studies by Solås et al (and the study by Presti et al) are the only ones to find any disadvantage to the group randomised to resuscitation with room air and, in the Solås studies at least, these disadvantages are reduced when the experimental animals are rendered hypercarbic as well as hypoxic and ischaemic. The disadvantage relates to a less complete restoration of cerebral cortical micro-circulation in the 21% group and both a higher peak level and a slower return to normal levels of extracellular glutamate in the 2001 study. However, a number of other studies of cerebral blood flow have found no difference or the reverse (see Huang, Kutsche, Poulsen, Lundstrøm) and levels of extracellular dopamine in Huang’s study favoured the 21% group; though the Presti study agrees with Solås.

Solås, 2004, p105
Solås 2004a

LOE: 5
Quality: Good animal study

Opposing

Comments: These animals had already established their extra-uterine existence. In this study the animals were rendered hypoxic, hypercarbic and ischaemic. The three studies by Solås et al (and the study by Presti et al) are the only ones to find any disadvantage to the group randomised to resuscitation with room air and, in the Solås studies at least, these disadvantages are reduced when the experimental animals are rendered hypercarbic as well as hypoxic and ischaemic. The disadvantage relates to a less complete restoration of cerebral cortical micro-circulation in the 21% group and both a higher peak level and a slower return to normal levels of extracellular glutamate in the 2001 study. However, a number of other studies of cerebral blood flow have found no difference or the reverse (see Huang, Kutsche, Poulsen, Lundstrøm) though the Presti study agrees with Solås.

Solås, 2004, p125
Solås 2004b

LOE: 5
Quality: Good animal study

Opposing

Comments: These animals had already established their extra-uterine existence. In this study the animals were rendered hypoxic, hypercarbic and ischaemic. The three studies by Solås et al (and the study by Presti et al) are the only ones to find
any disadvantage to the group randomised to resuscitation with room air and, in the Solås studies at least, these disadvantages
are reduced when the experimental animals are rendered hypercarbic as well as hypoxic and ischaemic. The disadvantage
relates to a less complete restoration of cerebral cortical micro-circulation in the 21% group and both a higher peak level and a
slower return to normal levels of extracellular glutamate in the 2001 study. However, a number of other studies of cerebral
blood flow have found no difference or the reverse (see Huang, Kutsche, Poulsen, Lundstrøm) though the Presti study agrees
with Solås.

Solberg, 2007, p559


LOE: 5
Quality: Good animal study
Supportive

Comments: These animals had already established their extra-uterine existence and were not in transition from placental to
pulmonary respiration when asphyxiated. However, exposure to high concentration oxygen lasted 15 minutes which is very
reasonable in the context of resuscitation. Concentrations used were 100% (n=6), 60% (n=8), 40% (n=9) or air (n=8) and there
was also a control group of 7 pigs which were surgically prepared and ventilated but non-asphyxiated. All pigs were killed one
hour after resuscitation.

Spector, 2005, p27

Spector LG, Klebanoff MA, Feusner JH, Georgieff MK, Ross JA. Childhood cancer following neonatal oxygen

LOE: 3
Quality: Good – prospective data collection – data examined with pre-stated objective to investigate oxygen exposure at birth
with later development of childhood cancer.
Supportive

Comments: A very large prospective cohort study producing results consistent with the Swedish observations – Cnattingius et
al and Naumburg et al. There is now preliminary work that hyperoxia in the newborn period increases oxidative DNA damage in
hematopoietic stem cells which may be the cellular reason for this finding.

Stevens, 2007, p657

Stevens JP, Haase E, Churchill T, Bigam DL, Cheung PY. Resuscitation with 21% or 100% oxygen is equally effective

LOE: 5
Quality: Fair
Neutral

Comments: These piglets had already made transition to neonatal existence. The model uses hypoxia without
ischaemia or hypercarbia. The pH levels reached are considerably less deranged than in most term asphyxiated infants.
Despite a similar methodology to Stevens 2008 there appears to have been no difference in persistence of lactate levels
on recovery in the 21% vs 100% group. No real difference between reoxygenation with 21% and 100% oxygen for the
parameters measured.

Stevens, 2008, p385

metalloproteinase-9 activity in the liver after hypoxia and reoxygenation with 21% or 100% oxygen in newborn piglets.

LOE: 5
Quality: Fair
Neutral

Comments: The piglets had already made transition to neonatal existence. The model uses hypoxia without hypercarbia
or ischaemia. Although the GSSG:total glutathione ratios and metalloproteinase-9 levels were greater in the 100%
oxyn group, the air group did not recover to pre-intervention pH levels and had significantly higher lactate levels
suggesting slower repayment of oxygen debt in this group. This study suggests that, as far as the liver is concerned,
more rapid achievement of oxygen debt is achieved with use of 100%oxygen but at a price paid in increased oxygen
stress.
Tan, 2004,
Tan A, Schulze A, O'Donnell CPF, Davis PG. Air versus oxygen for resuscitation of infants at birth (Cochrane Review).

**LOE: 2**
**Quality: Fair** – in view of overall quality of RCTs.
**Supportive**
**Comments:** It is difficult to explain and equally difficult to ignore the difference in mortality (in favour of air) in this meta-analysis. This meta-analysis has also been published as Davis PG et al in the Lancet in 2004 – see listing above.

Temesvári, 2001, p812

**LOE: 5**
**Quality: Good animal study**
**Supportive**
**Comments:** These animals had already established their extra-uterine existence but they do seem to have suffered hypoxia, ischaemia and hypercarbia

Tølløfsrud, 2001, p423

**LOE: 5**
**Quality: Good animal study**
**Neutral**
**Comments:** These animals had already established their extra-uterine existence. No difference found between air and 100% oxygen.

Tyree, 2006, p423

**LOE: 5**
**Quality: Good animal study**
**Supportive**
**Comments:** These animals had already established their extra-uterine existence. Increased cell death in the brain stem was found in the 100% oxygen group consistent with other studies.

Vento, 2001,p642

**LOE: 1**
**Quality: Good human RCT**
**Supportive**
**Comments:** True blinded randomisation. No apparent advantages to the use of 100% oxygen when assessed at birth and on neurological examination, EEG and cerebral ultrasound at 28 days of age. There were biochemical indications of prolonged oxidative stress in the 100% oxygen group.

Vento, 2003, p240
Quality: Good
Neutral

Comments: True blinded randomisation – gas chosen by sealed envelope allocation but choice of gas controlled by nursing staff out of sight of resuscitators. The gas mixture could be changed at the request of the resuscitators. Entry if hypotonic and apnoeic, unresponsive to external stimuli, pale, bradycardic (< 80 bpm) and acidotic (pH <7.05) at birth. 45 exclusions - failure to reach biochemical entry requirements (10), insufficient blood for analysis (14), switched from room air to 100% oxygen (7) or from 100% oxygen to room air (5), or not blindly resuscitated (9). The effectiveness of randomisation can perhaps be best demonstrated by the fact that 9% (95%CI 3.9-19.6%) of those randomised to oxygen were switched to air for presumed lack of clinical effectiveness; not significantly different, statistically, to the proportion switched from air to oxygen (17.6% [95%CI 9.6-30.3%]).

Vento, 2005, 1393-8

Vento M, Sastre J, Asensi MA, Viña J. Room-air resuscitation causes less damage to heart and kidney than 100% oxygen. Am J Resp Crit Care Med 2005; 172: 1393-8

LOE: 1
Quality: Good
Supportive

Comments: Appropriately randomized and blinded study in babies. Greater biochemical measures of oxygen stress in the oxygen group as compared with the air group. No long term outcome data.

Vento, 2009, e439-49


LOE: 1
Quality: Good
Supportive

Comments: Appropriately randomized (unblinded) study on preterm human infants at birth. Significant differences in biochemical measures of oxidative stress noted. Higher incidence of BPD (supplemental oxygen requirement at 36 wks) in high oxygen group.

Wang, 2008, 1083-9


LOE: 2
Quality: Poor
Opposing

Comments: Though this is a reasonable randomized intervention the oxygenation targets are invented and not necessarily appropriate.