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

**Worksheet author(s)**

| Jay P. Goldsmith, M.D. | Date Submitted for review: December 7, 2009 (Revised 2/15/10) |

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### Clinical question.

**When resuscitating or stabilizing newborns at birth (P), is there an oxygen administration strategy (I) that is superior to any other in improving outcome (O)?**

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

**State if this is a proposed new topic or revision of existing worksheet:** Revision of 2005 worksheet

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### Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? **No**

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### 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

Medline, Embase, Cochrane and SciELO databases were searched without any limit of period with the following strategies:

1. MESH terms: neonatal resuscitation and oxygen/air

2. MESH term: Resuscitation LIMITED by age group (newborn).

3. MESH terms: Cardiopulmonary resuscitation with oxygen/air

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**State inclusion and exclusion criteria**

All studies included if published in full, both animal and human. 3 meta-analyses included. 3 epidemiologic studies included. Excluded commentaries, editorials

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

60
## Summary of evidence

### Evidence Supporting Clinical Question

|------------|--------------|--------------|-------------|------------|---------|------------------|-------------|---------------|----------------------|----------------|-------------|----------------|----------------------|-------------|--------------|----------------|

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A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
 Italics = Animal studies  
†† 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.* Premature infants only
### Evidence Neutral to Clinical question

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### Evidence Opposing Clinical Question

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REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

For the newly born infant in need of resuscitation at birth, the rapid establishment of pulmonary gas exchange to replace the failure of placental gas exchange prior to birth 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 which were damaged by the anaerobic process.

The difficulty encountered by the health care 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 has 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 with little evidence of its efficacy. However, an informal survey by the NRP revealed only 20% of delivery rooms in the United States could blend oxygen in the delivery room. When blended oxygen is not available in the delivery room, the provider is forced to choose between either 100% oxygen or air.

At this point in our investigations we do not know whether severely asphyxiated babies, i.e. those in secondary apnea with severe acidosis, might suffer a greater or lesser degree of neurological damage if resuscitated with judicious amounts of supplemental oxygen rather than air. However, there is now good evidence that for most term infants resuscitation with air is at least as effective as using oxygen. Moreover, there is abundant evidence in both animals and humans that exposure to a high concentration of oxygen at birth does not improve the response to resuscitation efforts and is potentially harmful at the cellular level and clinically. Two studies have shown that the high pulmonary vascular resistance seen at birth may require oxygen administration for optimal relaxation, but there is a price to pay in terms of the creation of increased reactive oxygen species producing the potential for less pulmonary artery vasorelaxation later in the neonatal course. Recently two clinical studies have indicated that the resuscitation of the premature infant with surfactant deficiency and other primary lung pathology seems to require at least some oxygen in order to reach acceptable saturations in a reasonable period of time.

It may very well be that the reversal of anaerobic metabolism is a rate limited process and that the provision of air or “some” oxygen with ventilation will be adequate, while the provision of high concentrations of oxygen will not hasten the recovery and create excess reactive oxygen species which may be harmful both in the short and long term. The problem is to determine how much oxygen is enough.

Acknowledgements: Dr. Sam Richmond
Citation List

Abstracts of and comments on papers evaluated
In alphabetical order by first author
Additions since CoSTR 2005 highlighted in yellow

Question: For neonates requiring resuscitation, does the use of room air as opposed to the use of supplemental oxygen improve outcome?


LOE: 5
Quality: Poor
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?


LOE: 5
Quality: Fair
Supportive
Comments: Despite the accumulating evidence of the potentially toxic effects of hyperoxia, these rat pups were exposed to hyperoxia for 6 days. Prolonged exposure to hyperoxia is not specifically relevant to the relatively short exposures associated with resuscitation at birth.


LOE: 5
Quality: Fair
Neutral
Comments: These animals had already established their extra-uterine existence. They 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 ischemic 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.


LOE: 2
Quality: Fair — pseudo-randomized, not blinded
Neutral
Comments: Level 3 NICU in India. Pseudo-randomized and not blinded — even dates used 100% oxygen, odd dates air. “Randomized” to receive 90 seconds of either air or 100% oxygen if more than 1000 gm and with apnea 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. 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. Similar to previous human studies and still plagued with some of
the same investigational flaws. No real diagnosis of asphyxia by cord pH; not blinded; randomization not optimal. One could conclude that air is as good as oxygen in resuscitation or that the entry criteria and outcome measures were not discriminating enough to draw any conclusions.


**LOE:** 5  
**Quality:** Fair  
**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 well as the 40% oxygen group) as compared with air. The reduction in pCO2 was unexpected and somewhat confusing, since the delay in onset of breathing with oxygen supplementation would seem to portend an increase in pCO2.

**Børkke WB, Munkeby BH, Møørkrid 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 ischemia. Length of time exposed to oxygen was reasonable. No difference found between air and 100% oxygen.


**LOE:** 5  
**Quality:** Fair  
**Neutral**  
**Comments:** Another study from the Canadian lab using the same piglet model. The piglets had already established extra-uterine existence at the time of the experiment. 100% oxygen increased TxB2 levels which has unknown clinical significance at this time.

**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(3): 457-64.**

**LOE:** 5  
**Quality:** Fair  
**Supportive**  
**Comments:** Piglets had already made extra-uterine transition. PA pressure recovered faster with oxygen, but the cardiac index deteriorated over time in this group.


**LOE:** ? — epidemiological case / control study  
**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 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:** 2
Quality: Fair
Supportive

Comments: A meta-analysis of 5 trials. This same analysis by the same authors 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. A number of other issues can and have been raised about these meta-analyses. A total of 1302 babies were included, but there is some question that some babies may have been counted twice. None of the individual papers recognized a significant difference in mortality between the two groups. The studies included very few preterm babies and almost none below 1000 grams in birth weight; 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. 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. Though 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.


LOE: 1

Quality: Fair
Supportive

Comments: The choice of an optimal saturation target is arbitrary as is the time necessary to reach it. The proportion of infants breathing air was 42% at 5 minutes and 73.7% at 10 minutes in the low oxygen group and 26% and 43.5% in the high oxygen group at 5 and 10 minutes. Starting with low oxygen reduced the oxygen load but oxygen was necessary to reach the saturation targets in all babies for several minutes and a significant number up to 30 minutes after cord clamping. Unfortunately the investigators did not use a third arm in the study starting with air. The study by Wang of similar premature infants (see below) did start with air in one arm and were not successful in reaching target saturations by 3 minutes (again an arbitrary time interval).


LOE: 5

Quality: Good animal study
Neutral

Comments: The only study to use less than 21% oxygen in resuscitation. These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic nor ischemic. No apparent advantage of 100% oxygen over air.


Richmond 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 littermates. 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-Acetylcysteine (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 littermates.

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 prolonged hyperoxia and some suggestion that this is significantly reduced if exposure is limited to oxygen levels of 40% and below. However, the exposures were much longer than would be required for standard neonatal resuscitation.


**LOE: 5**

**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.


**LOE: 5**

**Quality: Good study of the dose / effect of hyperoxia on the immature animal brain**

**Supportive**

**Comments:** Additional evidence for the careful monitoring of oxygen administration to premature infants when the white matter is most at risk..

**Comments:** These animals had already established their extra-uterine existence and were rendered hypoxic but not hypercarbic nor ischemic. 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.


**LOE: 5**
**Quality: Fair**
**Supporting**

**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 hypoxia-reoxygenation and the creation of reactive oxygen species which cause intestinal injury. 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).


**LOE: 5**
**Quality: Fair**
**Neutral**

**Comments:** The piglets had already made transition to neonatal existence. However, there was still an incremental difference in the pulmonary artery response to oxygen (either 50% or 100%) vs. air. The differences in MMP-2 activity and glutathione levels between the air and 100% oxygen levels are difficult to analyze since the early myocardial injury was similar in all groups.


**LOE: 2** (case control study although the patients were not matched)
**Quality: Poor**
**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 in 4 Swedish hospitals. Use of the umbilical artery cord blood gas would have been preferred to an Apgar score as entry criteria. Whether these babies were in primary or secondary apnea is impossible to determine. The Apgar scores are also unfortunately used as the primary outcome measure of the non-randomized intervention. The severe limitations of this study (non-randomized, subjective use of the Apgar score) two different institutions with different providers assigning a subjective score)undermines 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 difference in the death rate between the two approaches is also difficult to accept (100% oxygen group was 16/661 [2.4%] as against 9/562 [1.6%] in the 40% group [OR 1.48 95%CI 0.63 — 3.44]). Both numbers are quite low if the cohorts were truly asphyxiated.


**LOE: 5**
**Quality: Poor** in that exposure to >80% oxygen was excessively prolonged for our purposes.
**Supportive**

**Comments:** Prolonged hyperoxia for 24 hours in this rat model. Rats were 7 days old. No ischemia or acidosis. One of several experimental animal models demonstrating upregulation of ROS secondary to prolonged hyperoxia in various organ systems including the brain.

**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 ischemic 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 Solås 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.


**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.


**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 prolonged hyperoxia in the immature animal brain. In terms of our question the exposure time to high oxygen concentrations was excessively long — 12 hours. Study was also done on day 6 of life after extrauterine existence was already established


**LOE: 4**
**Quality:** Good retrospective study in humans — highly relevant

**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. However the variable of hypocapnia contaminates the findings regarding hyperoxia. No follow-up information is available for nearly 12% of the cases.


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

Comments: Another animal study (mice) indicating secondary neuronal injury after relatively brief exposure (30 minutes) to 100% oxygen. In this model, the animal brain is ischemic as well as hypoxic. However, these animals were 14 days old and had already passed the period of transition.


LOE: 5
Quality: Good animal study

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


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 ischemic. 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 Solåås studies found a lower flow in the 100% oxygen group (see below). Higher $H_2O_2$ levels in neutrophils following resuscitation with 100% oxygen suggests the possibility of hazard associated with the use of 100% oxygen.


LOE: 5
Quality: Fair

Supportive

Comments: 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 oxygen during immediate resuscitation to reduce pulmonary vascular resistance may result in ROS which have later consequences in the blunting of cellular pathways which facilitate vasorelaxation.


LOE: 5
Quality: Good

Neutral

Comments: 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 and it took 60-90 minutes for the PVR in the air group to reach the same level as the 100% oxygen and 50% oxygen 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 indicates that PVR falls slower with air but provides further suggestive evidence that use of 100% oxygen has a significant downside. However for the truly asphyxiated newborn, the most rapid and complete fall of PVR at birth would be advantageous to reestablishing aerobic metabolism.


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.

**LOE: 5**

**Quality:** Good animal study but poorly focused on our problem - Poor

**Supportive**

**Comments:** Seems to confirm Aizad”s observations in newborn infants (1984). Only tangentially relevant to resuscitation at birth.


**LOE: 2**

**Quality:** Good

**Supportive**

**Comments:** Small, well designed study but those measuring CBF were not blinded, though this is, apparently, an objective measurement beyond the influence of the investigator. Lundstrøøm”s findings of lower cerebral blood flow after 100% oxygen agree with Kutsche”s animal study; Huang”s animal study found no difference in striatal blood flow whereas the Solåås animal studies found a lower cortical flow in the air group.


**LOE: 5**

**Quality:** Good

**Supportive**

**Comments:** Finally an animal study that produces the insult in the placental respiration stage with the resuscitation in the lung respiration stage. Slightly extended exposure to oxygen (30 mins) but not excessive in the context of a difficult resuscitation. These are early events and need to be followed over a longer period to see if the potential for increased tissue damage that the authors speculate may occur.


**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.


**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”.


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.


LOE: ? epidemiological case control study
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.


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.


LOE: 5
Quality: Good animal study
Neutral
Comments: Physiological study using piglets aged 7-14 days randomized 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 hypoxaemic 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 hypoxanthine 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 ischemic. No apparent advantage of 100% oxygen over air.


LOE: 5
Quality: Good animal study
Neutral
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 – because there are conflicting findings, this reviewer classified it as neutral. Note that this study found faster return of cerebral blood flow in the oxygen group as did the Solás studies.


Comment: Another metaanalyses which supports the data of Davis and Tan. In this analysis, possible double counting of patients In the Vento studies have been accounted for.

LOE: 2
Quality: Good
Supportive


LOE: 2
Quality: Poor
Neutral

Comments: Pseudo randomized, unblinded, small pilot study. Six crossovers (from air group only). Short follow up to only 28 days. Since none of the survivors had any sequelae, the severity of the “asphyxia” must be questioned.


LOE: 2
Quality: Pseudo-randomized, non-blinded but multi-centred controlled study hence - Fair
Neutral

Comments: No true randomization — 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.


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.


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.

**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.


**LOE: 2**  
**Quality:** Pseudo-randomized, non blinded hence - Fair  
**Neutral**  
**Comments:** No true randomization — 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.


**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 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, hypercarbic and ischemic. The three studies by Solåås et al (and the study by Presti et al) are the only ones to find any disadvantage to the group randomized to resuscitation with room air and, in the Solåås studies at least, these disadvantages are reduced when the experimental animals are rendered hypercarbic as well as hypoxic and ischemic. 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, Lundstrøøm) and levels of extracellular dopamine in Huang’s study favored the 21% group; though the Presti study agrees with Solås.


Solåås 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 ischemic. The three studies by Solåås et al (and the study by Presti et al) are the only ones to find any disadvantage to the group randomized to resuscitation with room air and, in the Solåås studies at least, these disadvantages are reduced when the experimental animals are rendered hypercarbic as well as hypoxic and ischemic. 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 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 ischemic. 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 randomized 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 ischemic. 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.


**LOE:** 5  
**Quality:** Fair  
**Supportive**  
**Comments:** Another animal study indicating hyperoxia causes oxidative stress with numerous biologic markers. These animals were not in transition from placental to pulmonary respiration when asphyxiated. However, exposure to high concentration oxygen lasted 15 minutes which is comparable to the time frame of neonatal resuscitation. Oxygen 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 not asphyxiated. All pigs were killed one hour after resuscitation. The evidence that hyperoxia causes biochemical changes in neonatal animal models is overwhelming. What we don’t know is whether these changes persist and if they result in any clinical consequences either in the short or long term.


**LOE:** epidemiological case control study  
**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.


**LOE:** 5  
**Quality:** Fair  
**Opposing**  
**Comments:** The piglets had already made transition to neonatal existence. The model uses hypoxia but not ischemia. Although the GSSG:total glutathione ratios and metalloproteinase-9 levels were greater in the 100% oxygen group, the hepatic lactate levels were greater in the air group. The group wants to support the conservative use of oxygen in resuscitation, but their results in this study do not support that conclusion.

**LOE:** 5  
**Quality:** Fair  
**Neutral**  
**Comments:** Difficult paper to analyze. No real difference between reoxygenation with 21% and 100% oxygen for the parameters measured.


**LOE:** 2  
**Quality:** Fair — in view of overall quality of RCTs.  
**Supportive**  
**Comments:** The conclusions in this meta-analysis differ considerably from the conclusions of the same authors in the Lancet meta-analysis (see Davis above). A number of other issues can and have been raised about these meta-analyses. A total of 1302 babies were included, but there is some question that some babies may have been counted twice. None of the individual papers recognized a significant difference in mortality between the two groups. The studies included very few preterm babies and almost none below 1000 grams in birth weight; 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. 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. Though 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.

Temesvari P, Karg E, Bodi I, Nemeth I, Pinter S, Lazics K, Domoki F, Bari F. [Reoxigenation after neonatal asphyxia with 21% or 100% oxygen in piglets] *Orv Hetil* 2000; 141:2605-10. (Published in Hungarian)

**LOE:** 5  
**Quality:** Good animal study  
**Supportive**  
**Comments:** Original paper not examined. These animals had already established their extra-uterine existence but they do seem to have suffered hypoxia, ischemia and hypercarbia


**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.


**LOE:** 1  
**Quality:** Good human RCT  
**Supportive**  
**Comments:** True blinded randomization. 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.

**LOE: 1**
**Quality: Good**
**Neutral**

**Comments:** Finally a human study with true blinded randomization — 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 apneic, 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 randomization can perhaps be best demonstrated by the fact that 9% (95%CI 3.9-19.6%) of those randomized 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%]). Probably more important than the clinical response was the persistence of oxidative stress in the OxR group for 28 days.

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.


LOE: 1

Quality: Good

Supportive

Comments: Another study from this group in Spain, this time looking at the effects of high vs. low oxygen concentrations on preterm infants. This study shows a large difference in BPD rates for only a short period of hyperoxia. It is difficult to believe this wide disparity for such a short exposure, but the paper is consistent with other studies on the detrimental effects of oxygen.


**LOE: 1**

Quality: Good

Supportive

Comments: No differences in secondary outcomes. When the target oxygen saturations were set at greater than 70% at 3 minutes and 80% at 5 minutes, then supplemental oxygen was usually necessary. However, we do not know if those targets are appropriate.