12 van der Velden VH, Hochhaus A, Cazzaniga G, Szczepanski T, Gabert J, van Dongen JJ. Detection of minimal residual disease in hematologic malignancies by real-time quantitative PCR: principles, approaches, and laboratory aspects. *Leukemia* 2003; **17**: 1013–34.

13 Bruggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18–20 September 2008. *Leukemia* 2010; **24**: 521–35.

Resuscitation of newborn infants: from oxygen to room air

Published Online July 20, 2010 DOI:10.1016/S0140-6736(10)60543-0

Over the past decade, there has been lively discussion about the optimum oxygen concentration for resuscitation of newborn babies.[1,2] Until recently, the routine had been to use 100% oxygen for resuscitation at birth, but was this harmful? Elemental oxygen was discovered in about 1775 and, by 1780, it was being used to resuscitate newborns. It took, however, 200 years before this unproven practice was questioned[3] and systematic experimental and clinical studies were done to assess the short-term and long-term effects of oxygen.

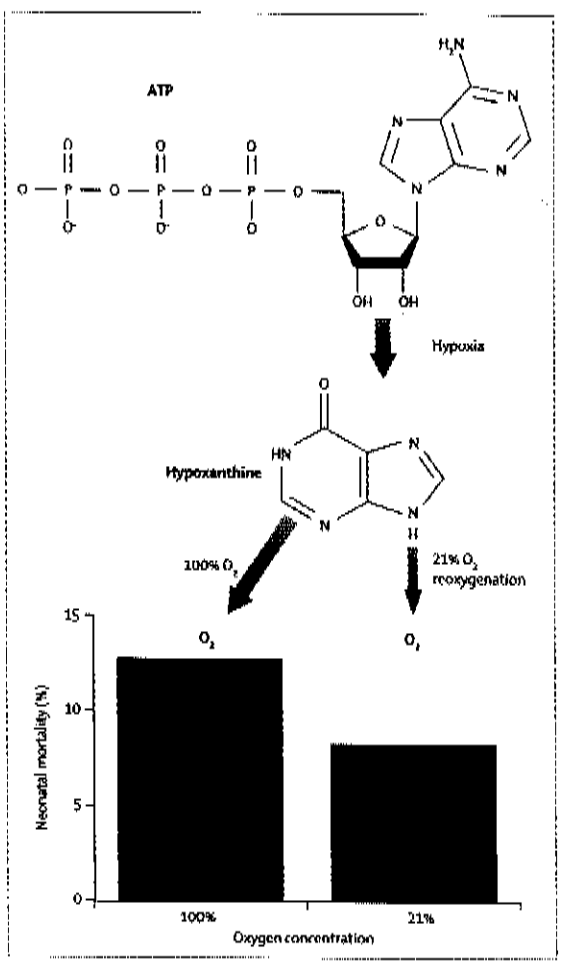

Figure: From molecular understanding to clinical practice in newborn resuscitation

ATP is degraded in hypoxia with accumulation of hypoxanthine. During reoxygenation/resuscitation, oxygen radicals are produced, more when reoxygenation occurs with 100% than with 21% oxygen. Use of 100% oxygen in newborn resuscitation translates into significantly higher neonatal mortality.[16]

A new understanding flowed from two findings: our report that the ATP-breakdown metabolite, hypoxanthine, increases in concentration after birth asphyxia[4] and knowledge that hypoxanthine is a potential generator of oxygen radicals.[5] We became concerned that the combination of high hypoxanthine levels and high oxygen concentrations, typically found in neonatal resuscitation with oxygen, might be harmful.[3]

Experimental studies showed that heart rate and metabolic changes in asphyxiated newborn piglets returned to normal just as quickly when resuscitation was with 21% as with 100% oxygen.[6] Subsequent studies showed that pure oxygen also caused direct injury to organs, such as the brain, and augmented pulmonary contractility to increase the risk of pulmonary hypertension.[7–9] In hypoxic newborn mice and piglets, oxygen exposure delays DNA repair after oxidative damage.[10,11]

Clinical studies of term or late preterm newborns needing resuscitation indicated that those resuscitated with 21% oxygen had higher Apgar scores at 5 min, higher heart rate at 90 s of age, and took their first breath 30 s earlier than those who received 100% oxygen.[12,13] Pure oxygen seems to trigger a long-term increase in oxidative stress and more injury to the myocardium and kidney.[14]

The most important finding is that use of 21% oxygen was associated with lower neonatal mortality. The clinical studies are summarised in systematic reviews and meta-analyses showing that neonatal mortality is reduced by 30% in babies resuscitated with room air.[15,16] The most recent systematic review included ten studies with 2134 infants of whom 1051 were resuscitated with 100% and 1082 with 21% oxygen.[16] Neonatal mortality was reduced from 12·8% in those treated with oxygen to 8·2% in the room-air group (relative risk 0·69, 95% CI 0·54–0·88) (figure). A separate analysis of the six strictly randomised studies, all from Europe, indicated that

neonatal mortality was reduced from 3·9% to 1·1%, an almost 70% (0·32, 0·12–0·84) relative risk reduction compared with the room-air group.

Accumulating data from small studies of preterm infants indicate that babies of less than 29 weeks' gestation should not be stabilised and resuscitated with 100% oxygen but instead 21–30% oxygen should initially be used. The oxygen supply should then be adjusted according to response, preferably by measuring oxygen saturations with a pulse oximeter.[17,18]

Two studies, from Sweden and the USA, showed an association between childhood cancer, particularly leukaemia, and exposure to oxygen at birth. Even a few minutes of oxygen supplementation seems to represent a risk, increasing the odds for cancer about threefold.[19,20] About one in seven childhood cancers could be prevented by avoiding use of pure oxygen for newborn resuscitation.[21]

Previous international guidelines uncritically recommended use of 100% oxygen for newborn resuscitation. However, in 2005, doubts about this practice were recognised.[22] In 2010, it is believed that the International Liaison Committee on Resuscitation might change the guidelines to recommend a low-oxygen approach for newborn resuscitation. Before this, in 1998, WHO recommended use of 21% oxygen for basic newborn resuscitation,[23] and from 2006 several countries, including Canada, Australia, Sweden, Finland, the UK, the Netherlands, Belgium, Spain, and Russia, followed this guidance.

Each year, 4 million newborn infants have birth asphyxia and 1 million die. A 30% reduction in mortality with 21% instead of 100% oxygen means that more than 100 000 newborn lives could be saved globally each year by switching from pure oxygen to ambient air for newborn resuscitation. The use of 100% oxygen for newborn resuscitation probably will be remembered as one of the most dangerous therapies inflicted on newborns.

Ola Didrik Saugstad
Department of Paediatric Research, Oslo University Hospital, Rikshospitalet, University of Oslo, 0027 Oslo, Norway
odsaugstad@rr-research.no

I declare that I have no conflicts of interest.

1 Tarnow-Mordi WO. Room air or oxygen for asphyxiated babies? *Lancet* 1998; **352**: 341–42.
2 Hansmann G. Neonatal resuscitation on air: it is time to turn down the oxygen tanks. *Lancet* 2004; **364**: 1293–94.
3 Saugstad OD, Aasen AO. Plasma hypoxanthine concentrations in pigs: a prognostic aid in hypoxia. *Eur Surg Res* 1980; **12**: 123–29.
4 Saugstad OD. Hypoxanthine as a measurement of hypoxia. *Pediatr Res* 1975; **9**: 158–61.
5 McCord JM, Fridovich I. The reduction of cytochrome c by milk xanthine oxidase. *J Biol Chem* 1968; **243**: 5753–60.
6 Rootwelt T, Løberg EM, Moen A, Oyasaeter S, Saugstad OD. Hypoxemia and reoxygenation with 21% or 100% oxygen in newborn pigs: changes in blood pressure, base deficit, and hypoxanthine and brain morphology. *Pediatr Res* 1992; **32**: 107–13.
7 Munkeby BH, Børke WB, Bjørnland K, et al. Resuscitation with 100% O_2 increases cerebral injury in hypoxemic piglets. *Pediatr Res* 2004; **56**: 783–90.
8 Koch JD, Miles DK, Gilley JA, Yang CP, Kernie SG. Brief exposure to hyperoxia depletes the glial progenitor pool and impairs functional recovery after hypoxic-ischemic brain injury. *J Cereb Blood Flow Metab* 2008; **28**: 1294–306.
9 Lakshminrusimha S, Russell JA, Steinhorn RH, et al. Pulmonary arterial contractility in neonatal lambs increases with 100% oxygen resuscitation. *Pediat Res* 2006; **59**: 137–41.
10 Solberg R, Andresen JH, Escrig R, Vento M, Saugstad OD. Resuscitation of hypoxic newborn piglets with oxygen induces a dose-dependent increase in markers of oxidation. *Pediatr Res* 2007; **62**: 559–63.
11 Sejersted Y, Aasland AL, Bjørås M, Eide L, Saugstad OD. Accumulation of 8-oxoguanine in liver DNA during hyperoxic resuscitation of newborn mice. *Pediatr Res* 2009; **66**: 533–83.
12 Ramji S, Ahuja S, Thirupuram S, Rootwelt T, Rooth G, Saugstad OD. Resuscitation of asphyxic newborn infants with room air or 100% oxygen. *Pediatr Res* 1993; **34**: 809–12.
13 Saugstad OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. *Pediatrics* 1998; **102**: e1.
14 Vento M, Sastre J, Asensi MA, Viña J. Room-air resuscitation causes less damage to heart and kidney than 100% oxygen. *Am J Respir Crit Care Med* 2005; **172**: 1393–98.
15 Davis PG, Tan A, O'Donnell CP, Schulze A. Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis. *Lancet* 2004; **364**: 1329–33.
16 Saugstad OD, Ramji S, Soll RF, Vento M. Resuscitation of newborn infants with 21% or 100% oxygen: an updated systematic review and meta-analysis. *Neonatology* 2008; **94**: 176–82.
17 Escrig R, Arruza L, Izquierdo I, et al. Achievement of targeted saturation values in extremely low gestational age neonates resuscitated with low or high oxygen concentrations: a prospective, randomized trial. *Pediatrics* 2008; **121**: 875–81.
18 Wang CL, Anderson C, Leone TA, Rich W, Govindaswami B, Finer NN. Resuscitation of preterm neonates by using room air or 100% oxygen. *Pediatrics* 2008; **121**: 1083–89.
19 Naumburg E, Bellocco R, Cnattingius S, Jonzon A, Ekbom A. Supplementary oxygen and risk of childhood lymphatic leukaemia. *Acta Paediatr* 2002; **91**: 1328–33.
20 Spector LG, Klebanoff MA, Feusner JH, Georgieff MK, Ross JA. Childhood cancer following neonatal oxygen supplementation. *J Pediatr* 2005; **147**: 27–31.
21 Paneth N. The evidence mounts against use of pure oxygen in newborn resuscitation. *J Pediatr* 2005; **147**: 4–6.
22 The International Liaison Committee on Resuscitation (ILCOR) Consensus on science with treatment recommendations for pediatric and neonatal patients: neonatal resuscitation. *Pediatrics* 2006; **117**: e978–88.
23 WHO. Basic newborn resuscitation; a practical guide. 1997. http://whqlibdoc.who.int/hq/1998/WHO_RHT_MSM_98.1.pdf (accessed April 9, 2010).