Newborn resuscitation: should we oxygenate or not?

Ola Didrik Saugstad

Department of Pediatric Research, University of Oslo, Oslo, Norway

How should we oxygenate newborn and infants suffering from hypoxia and ischemia? Is it harmful to use 100% O2? It may seem odd to question a practice that has been carried out for so long, seemingly without any adverse effects. The case is, however, that after the practice of routinely using 100% O2 for newborn resuscitation was examined, many serious potentially harmful effects have to date been described (for review, see Ref. 13).

Fabian et al. (1) add new information to the topic of how asphyxiated newborns should be reoxygenated (1). By inducing unilateral brain ischemia and hypoxia in newborn (7 day) rats, they showed that cerebral blood flow in the ischemic cortex declined following resuscitation with 100% O2 but not with ambient air. These findings in hyperoxic animals were accompanied by a reduction in perivascular production of nitric oxide (NO). Intraperitoneal injection with tetrahydrobiopterin (BH4) increased cerebral blood flow during hyperoxic resuscitation. This was followed by increased perivascular NO and reduced perivascular O2. The authors suggest that hyperoxia uncouples perivascular NO synthase (NOS), probably endothelial NOS, leading to a reduced NO and increased O2 production. An injection of apocyanin, which is an inhibitor of NADPH oxidase, also increased NO and reduced O2, indicating that an oxidative burst may be of importance in neonatal hypoxic-ischemic brain injury.

This study confirms that a hyperoxic resuscitation of newborns may reduce the restoration of cerebral blood flow and therefore may be detrimental. But it also indicates that BH4 and perhaps also apocyanin should be interesting agents to test out in similar models to prevent such potentially harmful effects.

For many reasons one should be careful drawing firm conclusions from newborn rats to newborn human infants. One major difference between birth asphyxia and the present model is that in the former the partial carbon dioxide tension of blood flow during reoxygenation differs whether it starts out with a high or as in the present study a relatively low PaCO2 (16). In resuscitated newborns, we also know that the time of reoxygenation often does not last more than a few minutes. A reoxygenation time of 2 h as in the study of Fabian et al. (1) therefore may not be relevant for newborns. On the other hand, such a long exposure to hyperoxia is not rare in the intensive care of children outside the immediate newborn period. A recent study by Koch et al. (8) showed that postischemic and posthypoxic hyperoxic exposure may have shocking effects on the brain. These authors found a dramatic augmented cerebral injury in 2-wk-old mice exposed to unilateral carotid ligation and hypoxia already after 30 min of hyperoxic reoxygenation compared with reoxygenation with ambient air.

There are now numerous experimental studies showing that hyperoxic resuscitation of newborn animals leads to inflammation and necrosis/apoptosis in the brain as well as in other organs (10, 13). Clinical studies as well show that hyperoxic compared with normoxic reoxygenation of newborn infants leads to tissue injury, for instance, in the myocardium and kidney (19). Even a brief exposure of hyperoxia after birth seems to trigger long-term elevation—at least several weeks—of oxidative stress (18). The consequence of this for growth and development is not understood. And more importantly, a recent meta-analysis including more than 2,000 newborn infants shows a 30% reduction in neonatal mortality when resuscitation was carried out with 21% instead of 100% O2 (15). This is an important finding because 5% of all newborn infants are in need of some ventilatory stimulation after birth and 1% need more extensive respiratory and ventilatory support (6). This means that in the United States 200,000 newborn infants need some kind of resuscitation every year. A reduction of mortality from 3.9% to 1.2% in these children, as found in European data (15), indicates that thousands of lives can be saved in the United States alone by avoiding the use of 100% O2 for newborn resuscitation.

This study by Fabian et al. (1), as well as the one of Koch et al. (8), strongly indicates that also in children outside the newborn period hyperoxic-reoxygenation should be avoided. However, in this age group, clinical studies are lacking and are absolutely needed.

There is in my opinion strong reasons that the results of Fabian et al. (1) have clinical relevance. Already by the mid-1990s, Lundstrøm et al. (9) showed that preterm infants exposed to a brief period of hyperoxia after birth had cerebral vasoconstriction as long as 2 h later.

The understanding that a brief exposure of hyperoxia at birth may be detrimental has slowly evolved during more than 50 years in two lines of research. In 1953, Gerschman et al. (3) formulated the hypothesis that O2 is toxic because it generates O2 free radicals. The seminal observation by McCord and Fridovich (11) 14 years later that the xanthine/xanthine oxidase system generates O2 radicals continued this line of research. The other line of evidence was accumulated in the 1960s when it was shown that purine metabolites accumulate in isolated hypoxic kidney and myocardium (5) and in the 1970s when we found that hypoxanthine, the precursor of xanthine, accumulates in the body fluids of hypoxic newborn babies (12). This is the background of so-called reoxygenation or reperfusion injury (4, 14).

One consequence of this understanding has been to reduce the O2 supplementation when hypoxic tissues or organs are reoxygenated. In the newborn this seems to be a promising strategy, and the O2 load to newborn and premature infants has been dramatically lowered the last decade or so (13). It is
surprising that this has not yet to any extent been tested out in older children or adults.

A second consequence of this line of research has been to find antioxidants that may reduce the harm inflicted by hypoxia-reoxygenation injury. So far the magic bullet has in my opinion not yet been found. One major issue is that reactive O₂ species seem to have important regulatory functions in the newborn period, so care should be exercised giving antioxidants (7). It still is not well understood as shown by Friel et al. (2) why there is increased oxidative stress the first months of life.

The study by Fabian et al. (1) opens for new therapeutic revenues, suggesting a different approach of therapy, administering BH₄. BH₄ is synthesized from GTP and is a naturally occurring essential cofactor of phenylalanine, tyrosine, and tryptophan hydroxylases and is also essential for synthesis of NO by NOS. The lack of BH₄ therefore may affect both catecholamine and NOS. BH₄ is both a growth factor and a NO by NOS. The reduction of cytochrome c by milk xanthine oxidase.

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REFERENCES