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COMMENT

Neonatal chest compressions: time to act

Ola D. Saugstad[1,2]

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In 1992, American Heart Association (AHA) published new guidelines for newborn resuscitation and underlined that early administration of 100% oxygen is important: "If respiratory efforts are absent or inadequate so that assisted ventilation is required, 100% oxygen should be delivered by positive-pressure ventilation using a face mask or endotracheal tube", and further: "The hazards of administering too much oxygen during the brief period required for a resuscitation should not be a concern.[1] Today, we know there are several reasons to be concerned about excess oxygen administration during neonatal resuscitation. During the past 10–20 years, there has been a dramatic shift regarding applying supplemental oxygen for newborn resuscitation. This was first manifested by the World Health Organization's guidelines for newborn resuscitation in 1998, which suggested to resuscitate with air instead of 100% O_2,[2] and subsequently by the International Liaison Committee on Resuscitation's guidelines in 2010 recommending "it is best to start with air in term or near-term infants in need of positive pressure ventilation in the delivery room".[3] This paradigmatic change was initiated by two clinical studies in 1993 and 1998 testing out air versus 100% oxygen for newborn resuscitation[4,5] and two meta-analyses in 2004 and 2005 summarizing the data.[6,7]

Figure 1 summarizes present recommendations regarding oxygen therapy in newly born infants. For term or near-term infants, initial FiO_2 is 0.21. For preterm infants, start with 0.21 from term to 32 weeks and 0.3 for <32 weeks gestational age. Titrate FiO_2 to target a SpO_2 of 80–85% at 5 min. During chest compressions (CCs), FiO_2 is 1.0. After return of spontaneous circulation, wean to FiO_2 of 0.21 (somewhat higher FiO_2 may be needed in preterm and term infants with lung disease). Titrate according to pre-ductal SpO_2.

The two studies from the 1990s were also important demonstrating that newborn resuscitation could be evidence based, which initiated a series of experimental and clinical studies in this field. However, one important component of the newborn resuscitation algorithm, CCs, was not studied and recommendations have hardly been changed for ≥30 years.[1,8]

One reason for such a static attitude might be that CCs are carried out so rarely it is difficult to perform randomized trials with sufficient power. Therefore, different FiO_2s and compression-to-ventilation (C/V) ratios as well have mostly been tested out in animal studies.[9–15] One recent study also tested out continuous CCs with asynchronous ventilation in an asphyxiated newborn lamb model. A higher carotid blood flow and cerebral oxygen delivery compared to C/V 3:1 was found.[16] Due to lack of human data, the present Neonatal Resuscitation Program (NRP) therefore still recommends using 100% O_2 during CCs with a C/V ratio of 3:1. However, according to NRP FiO_2 should be adjusted based on SpO_2 after return of spontaneous circulation (ROSC). The supplemental oxygen concentration may be decreased based on pulse oximetry to target a predefined physiological level to reduce the risks associated with hyperoxia. Weaning and titrating FiO_2 immediately after ROSC to maintain preductal saturations in the 85–95% range is recommended.[17] However, Badurdeen et al. demonstrated in near-term asphyxiated lambs that 100% O_2 during CCs until ROSC with subsequent weaning to SpO_2 of 88–95% is characterized by excess cerebral oxygenation.[18]

There are two fundamental unanswered questions regarding oxygenation and CCs:

1. Which FiO_2 should be applied during CCs?
2. Should FiO_2 be weaned rapidly or gradually when ROSC is achieved?

Regarding the first question, Solevåg et al. studied CCs with either 21 or 100% O_2 in a newborn piglet model.[12] No significant differences in time to ROSC, the number of epinephrine doses, carotid artery blood flow, SpO_2, or PaO_2 during CCs were found. There was a higher PaO_2 immediately post-ROSC in the 100% O_2 group. Further, CCs with 100% O_2 did not enhance oxygen delivery to the brain or time to ROSC but increased PaO_2 levels post-ROSC.

Rawat et al. randomized asphyctic newborn lambs with cardiac arrest to receive 21 or 100% O_2 during CCs.[13] The authors demonstrated that carotid blood flow, systemic PaO_2, and oxygen delivery to the brain are very low during CCs for cardiac arrest, irrespective of 21 or 100% O_2 use during resuscitation.

In fact, a meta-analysis summarizing data from animal studies demonstrated equal outcome whether using 21 or 100% O_2 during the compressions.[15]

The second question, how to wean from 100% O_2 as soon as successful CCs establishes ROSC, is therefore important and highly relevant. Should FiO_2 be reduced to 21% abruptly or slowly guided by SpO_2?

Sankaran et al. publish in this issue of *Pediatric Research* important data contributing to answer this question.[19] These authors investigated near-term lambs asphyxiated by umbilical cord occlusion to cardiac arrest and resuscitated per NRP. Following ROSC (defined as sustained heart rate >100 bpm and systolic blood pressure > 40 mmHg), lambs were randomized to gradual FiO_2 decrease versus abrupt wean to 21% O_2 followed by FiO_2 titration to achieve NRP SpO_2 targets of 85–95%. Three minutes after ROSC, PaO_2 was 229 ± 32 mmHg in the gradual wean group compared to 57 ± 13 following abrupt wean to 21% O_2 ($p < 0.001$). PaO_2 remained high in the gradual wean group at

[1]Department of Pediatric Research, University of Oslo, Oslo, Norway and [2]Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
Correspondence: Ola D. Saugstad (o.d.saugstad@medisin.uio.no)

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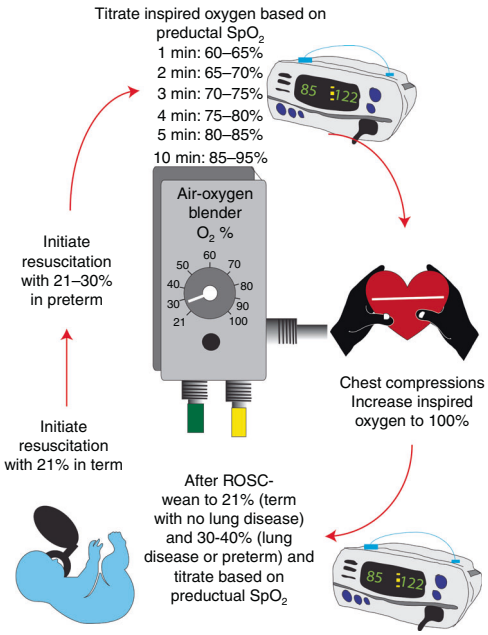

Fig. 1 Oxygen Therapy in the Delivery Room. Present recommendations for oxygen therapy of the newly born infant.

10 min after ROSC (110 ± 10 versus 67 ± 12 in the abrupt wean group, despite similar FiO_2 (~0.3) in both the groups.

Cerebral O_2 delivery (C-DO_2) was low compared to baseline despite 100% inspired O_2 in both the groups. C-DO_2 was higher and above physiological range following ROSC with gradual wean and remained persistently higher until 15 min after ROSC compared to abrupt weaning to 21% O_2. In contrast, C-DO_2 was more stable and within physiological range with abrupt weaning to 21% O_2.

Further, Sankaran et al. measured lower blood oxidized/reduced glutathione ratio (suggesting less oxidative stress) when weaning was abrupt. The authors concluded that weaning FiO_2 abruptly to 0.21 with adjustment based on SpO_2 prevents surge in PaO_2 and C-DO_2 and minimizes oxidative stress compared to gradual weaning from 100% O_2 following ROSC. These data convincingly demonstrate a potential benefit by rapid weaning when ROSC is established.[19]

Badurdeen et al. recently presented data from a similar model of near-term newborn lambs. Cardiac arrest was induced by cord clamping.[20] Also, 100% O_2 during CCs followed by a slow wean to reach a pre-specified SpO_2 target resulted in gray matter hyperoxia and mitochondrial dysfunction. On the other hand, rapid weaning from 100 to 21% O_2 reduced hyperoxia and mitochondrial dysfunction. Rapidly weaning oxygen to 21% O_2 following ROSC significantly improved cerebral mitochondrial bioenergetics in a region-specific manner. When PaO_2 during CC seemed to be low both when 100% or 21% O_2 were applied. These authors concluded that rapid weaning represents a simple approach to limit hyperoxia-mediated injury in newborn asphyxia.[20]

It is by now established that positive pressure ventilation with 100% O_2 in the newly born infant has a number of detrimental effects. It leads to brain inflammation and injury, increased pulmonary reactivity, and hence risk of pulmonary hypertension, kidney, and myocardial damage and is associated with childhood malignancies.[21–25] PaO_2 and brain tissue oxygenation are raised to toxic levels and consequently so is also the production of free radicals.[26] Reoxygenation with 100% O_2 during resuscitation impairs Krebs cycle function, probably reflecting mitochondrial dysfunction.[27] In newborn mice, hyperoxic resuscitation/ventilation leads to downregulation of DNA replication, inflammatory genes and DNA repair genes in the brain.[22,28] Oxidative phosphorylation seems also to be affected. In fact, genes in all five complexes of oxidative phosphorylation are downregulated by hyperoxic reoxygenation.[28] Thus there are reasons to assume that ATP production is hampered. This probably explains, at least in part, the higher mortality in newborns resuscitated with 100% compared to 21% O_2. However, we do not know whether resuscitation with for instance 40% O_2 is detrimental as well.

In the lungs, hyperoxic reoxygenation downregulates DNA polymerase and double-strand break repair and DNA repair. By contrast, mammalian target of rapamycin (mTOR) signaling pathway is upregulated by hyperoxic resuscitation.[29] The mTOR signaling pathway plays a crucial role in the regulation of cell proliferation, survival, and energy metabolism in response to stress. These mechanisms probably are of importance during CCs as well.

Bandurdeen et al. demonstrated that PaO_2 is not higher during the compressions with 100 versus 21% O_2.[20] Therefore, focus on the weaning phase might be more important than the compression phase. Abrupt weaning to 21% oxygen following ROSC in term infants without lung disease and possibly 30–40% oxygen in preterm infants and infants with lung disease needs to be studied.

Sankaran et al. have shown in the present article of *Pediatric Research* that this might be of clinical relevance.[19] We therefore need, as suggested by these authors, clinical studies. However, a challenge regarding research involving CCs is that this is a rare event. Less than 1 per 1000 live births would need this therapy. Collaboration in multicenter studies are therefore needed to collect new information leading to more optimal CC routines and improved outcome of newborn infants.

In conclusion, today we know why AHA in 1992 was wrong in their statements on applying 100% O_2 during newborn resuscitation.[1] We know that even a brief exposure of hyperoxia in the delivery room might be detrimental. However, we do not know whether or not this is the case also regarding CCs. Therefore, multicenter studies should be organized. This represents an obstacle and therefore a challenge to initiate and carry out such research. However, Sankaran et al. have shown we cannot wait.[19] It is time to act now.

AUTHOR CONTRIBUTIONS

ODS has alone contributed to conception and design, acquisition of data, or analysis and interpretation of data; drafted the article critically for important intellectual content; and finally approved the version to be published.

ADDITIONAL INFORMATION

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