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Review

# Ventilation strategies for preventing oxidative stress-induced injury in preterm infants with respiratory disease: an update

Salvatore Aversa [1], Lucia Marseglia [2,*], Sara Manti [2], Gabriella D'Angelo [2], Caterina Cuppari [2], Antonio David [3], Gaetano Chirico [4], Eloisa Gitto [2]

[1] Neonatal Intensive Care Unit, Children Hospital, Spedali Civili of Brescia, Brescia, Italy, PhD course in Intensive Care, University of Messina, Messina, Italy
[2] Department of Pediatrics, University of Messina, Messina, Italy
[3] Department of Neurosciences, Psychiatric and Anesthesiological Sciences, University of Messina, Messina, Italy
[4] Neonatal Intensive Care Unit, Children Hospital, Spedali Civili of Brescia, Brescia, Italy

**EDUCATIONAL AIMS**

- Oxidative insult could be an extremely important component of the injury process of BPD.
- End-inspiratory alveolar over-stretching and/or repeated alveolar collapse and re-expansion can cause lung ventilation induced injury.
- Using lung protective strategies need to reach compromises between the satisfaction of gas exchange and potential volutrauma, barotrauma, hyperoxia.

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SUMMARY

Reactive oxygen and nitrogen species are produced by several inflammatory and structural cells of the airways. The lungs of preterm newborns are susceptible to oxidative injury induced by both reactive oxygen and nitrogen species. Increased oxidative stress and imbalance in antioxidant enzymes may play a role in the pathogenesis of inflammatory pulmonary diseases. Preterm infants are frequently exposed to high oxygen concentrations, infections or inflammation; they have reduced antioxidant defense and high free iron levels which enhance toxic radical generation. Multiple ventilation strategies have been studied to reduce injury and improve outcomes in preterm infants. Using lung protective strategies, there is the need to reach a compromise between satisfaction of gas exchange and potential toxicities related to over-distension, derecruitment of lung units and high oxygen concentrations.

In this review, the authors summarize scientific evidence concerning oxidative stress as it relates to resuscitation in the delivery room and to the strategies of ventilation.



* Corresponding author. Neonatal Intensive Care Unit, Department of Pediatrics, University of Messina, Via Consolare Valeria, 1, 98125 Messina, Italy. Tel.: +390902213100; fax: +390902213876.
*E-mail address:* lmarseglia@unime.it (L. Marseglia).

*Abbreviations:* $SaO_2$, arterial oxygen saturation; A/C, assisted/controlled; BPD, bronchopulmonary dysplasia; CAT, catalase; CTGF, connective tissue growth factor; CPAP, continuous positive airway pressure; CMV, conventional mechanical ventilation; CYR61, cysteine rich-61; DNA, deoxyribonucleic acid; EGR1, early growth response 1; ELBW, extremely low-birth-weight; $FiO_2$, fraction of inspired oxygen; GA, gestational age; VG, volume guarantee; HFOV, high frequency oscillatory ventilation; $H^2O_2$, hydrogen peroxide; IVH, intraventricular hemorrhage; NIPPV, nasal intermittent positive pressure ventilation; NO, nitric oxide; NOS, nitric oxide synthase; $NO_2$, nitrogen dioxide; $paCO_2$, partial pressure of carbon dioxide; $PO_2$, partial pressure of oxygen; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; PPHN, persistent pulmonary hypertension of the newborn; PUPLs, polyunsaturated phospholipids; PEEP, positive end-expiratory pressure; PLV, Pressure-limited ventilation; PSV, pressure support ventilation; RNS, reactive nitrogen species; ROS, reactive oxygen species; ROP, retinopathy of prematurity; SOD, superoxide dismutase; SP, surfactant protein; SLI, sustained lung inflation; SIMV, synchronized intermittent mandatory ventilation; VT, Tidal volume; VTV, volume-targeted ventilation.

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## INTRODUCTION

Oxygen- and nitrogen-derived metabolites, collectively termed reactive oxygen (ROS) and reactive nitrogen species (RNS), are continuously generated in aerobic organisms. In living organisms, they are usually controlled by a complex system of antioxidant defenses, which ensure protection against oxidative stress-induced molecular damage [1]. There is a critical balance between free radical generation and antioxidants, and when it changes, ROS/RNS can damage molecules and cellular components, and become mediators of cell and tissue damage. Free radical reactions lead to the oxidation of proteins, lipids and polysaccharides, and to deoxyribonucleic acid (DNA) injury [2]. Oxidative stress plays a key role in the pathogenesis of several conditions of the preterm newborn, including bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), and patent ductus arteriosus (PDA) [2,3]. During the 1980s, Saugstad et al. coined the phrase "oxygen radical diseases of neonatology". Their idea implies that oxidative/nitrosative stress affects a variety of organs and tissues, often simultaneously, and causes different clinical signs according to the organ most affected [4]. Preterm infants are particularly susceptible to oxidative stress; they are often exposed to increased ROS production, resulting from high oxygen concentrations, mechanical ventilation, inflammatory and infective complications [5–8]. Neonates typically present lower levels of plasma antioxidants (melatonin, b-carotene, vitamin E, etc.), lower concentrations of plasma metal binding proteins (ceruloplasmin and transferrin), reduced activity of erythrocyte superoxide dismutase, higher plasma levels of non-transferrin-bound iron, and higher erythrocyte free iron compared with adults [9]. Furthermore, the transition from fetal to neonatal life at birth leads to elevated production of ROS and RNS. During delivery, the fetus is transferred from an intrauterine hypoxic environment to an extrauterine normoxic environment with a four- to five-fold higher oxygen tension ($PO_2$) [10]. In addition, labour and child-birth may induce periods of both hypoxia and oxidative stress for the newborn, and antioxidant capacities of preterm infants are inadequate to avoid oxidative damage. Increasing evidence suggests that an oxidative insult could be an extremely important component of the injury process of BPD, which has been hypothesized to begin as acute inflammatory changes secondary to toxic free oxygen radicals which then evolve into chronic lung disease. Oxidative stress causes injury of the respiratory epithelium, inflammation and surfactant inactivation with a consequent increase of requirement for mechanical ventilation [11–13].

## OXYGEN

Oxygen is the most frequently used essential drug in neonatal intensive care. However, there is evidence that the supplementation of high concentrations of oxygen at resuscitation might be harmful for newborns, and that short exposures to elevated fraction of inspired oxygen ($FiO_2$) can lead to oxidant stress and may adversely affect neonatal outcomes. Preterm infants can be subject to significant injury to the developing lung, which may undergo an influx of inflammatory cells, increased pulmonary permeability and endothelial and epithelial cell death [14–19]. Thus, considering that oxygen will continue to be used for the care of sick neonates, it is necessary to understand the safe dose to supplement at any age and the windows of developmental sensitivity [20].

Two animal models of hypoxia-ischemia and persistent bradycardia found that those resuscitated with room air rather than 100% oxygen developed untoward biochemical changes in the brain [21,22].

In 2008, a meta-analysis of ten clinical trials comparing the efficacy of 21% and 100% oxygen in the resuscitation of newborn infants, including up to 2,133 neonates, indicated a significant reduction in the risk of neonatal mortality and severe hypoxic ischemic encephalopathy in newborns resuscitated with 21% $O_2$ [23].

To provide adequate oxygenation during initial transition, by using a targeted oxygen saturation protocol in the delivery room, pulse oximeters, blenders, and a source of compressed air are essential. Hospitals must invest more to ensure this standard of care, but it is certainly not possible in low resource situations. However, for facilities delivering very low-birth weight preterm infants, the ability to titrate oxygen use to need is now mandatory. As the average duration of delivery room care is 20 minutes, these tools are also critical for avoiding hyperoxia after initial transition (Figure 1).

Several trials have demonstrated that administration of $FiO_2$ of 1.0 is rarely needed for term or preterm infants. Current evidence on babies born at term shows that newborns should be initially resuscitated with air rather than 100% oxygen [24]. There is insufficient evidence on babies born at 32 to 37 weeks' gestation to define the appropriate oxygen administration strategy [24]. The optimal $FiO_2$ for starting preterm infant resuscitation remains unknown. Both hyperoxemia and hypoxemia should be avoided in the absence of information on the initial $FiO_2$ [24]. Data from a recent meta-analysis suggest that it is reasonable to initiate resuscitation of preterm infant <32 weeks' gestation with a low initial $FiO_2$ approach, with 21– 30% oxygen, until more data from larger studies are available [25].

Studies in neonatal medicine showed that the use of pure oxygen during resuscitation may cause oxidative stress [26,27], damage the myocardium and kidney [24,28], and/or negatively influence survival [23,29–31]. Two recent prospective randomized clinical trials were performed to evaluate the effectiveness of variable oxygen concentrations during newborn resuscitation of preterm infants [32,33]. These trials demonstrated that successful resuscitation of preterm infants can be achieved by using a low initial $FiO_2$ of 0.30 as the initial gas admixture. The average oxygen concentration used to achieve target oxygen saturations within the first 5 to 10 minutes of life and avoid bradycardia was 30% to 40% in both studies. In addition, the use of a low $FiO_2$ allows an achievement of a target saturation of 85% at 10 minutes after cord clamping with lower oxygen load [33]. Furthermore, Vento et al. [16] reported that resuscitation of preterm infants of gestational age (GA) < 28 weeks with an initial $FiO_2$ of 0.30 (n=37) resulted in decreased oxidative stress markers and a decreased risk of BPD compared to infants with an initial $FiO_2$ of 0.90 (n = 41).

Rook et al. [34] reported that $FiO_2$ of 0.30 or 0.65 were equivalent for initial respiratory support of preterm infants of about 1 kilogram. With the use of pulse oximeters to adjust oxygen need, both groups achieved comparable saturations, with about 40% oxygen, by 5 minutes of age. There were no differences in oxidant stress markers or clinical outcomes. Based on these data, authors advise starting resuscitation of preterm infants of GA <32 weeks with an initial $FiO_2$ of 30% and adjust individual needs based on the approach proposed by Dawson et al. [35]. Preductal oxygen saturation targets progressively increase over the first 10 min of life, beginning at 60% and progressively increasing to 90% by 10 min of life.

Moreover, we know that infants exposed to lower concentrations of oxygen (targeting oxygen saturations of 85-89%) in the first weeks of life are at increased risk of death, cerebral palsy, patent ductus arteriosus, pulmonary vascular resistance and apnea, whilst infants maintained in higher concentrations of oxygen (targeting oxygen saturations of 90-95%) have been reported to have greater incidence of morbidity including ROP and BPD [36,37]. In