We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

22

Bronchopulmonary Dysplasia: The Role of Oxidative Stress

Jean-Claude Lavoie and Ibrahim Mohamed
Université de Montréal
Canada

1. Introduction

One of the critical and chronic complications of preterm birth is bronchopulmonary dysplasia (BPD). The incidence of BPD is high, ranging from 40% to 70% of infants born before 28 completed weeks' gestation (Stoll et al., 2010). The disease is characterized by impaired alveolar and vascular maturation, with long-term consequences on a number of systems including neurodevelopment. Risk factors for BPD include gestational age at birth, sex, inflammation and/or infection, oxygen supplementation, mechanical ventilation, and parenteral nutrition. Although the etiology of BPD is not well understood, risk factors are all associated with oxidative stress. A modulation of the redox environment is believed to play a major role in the pathogenesis of BPD.

This chapter will start by describing BPD, and then focus on the molecules involved in oxidative stress, the aim being that a better understanding favours more effective clinical intervention. Each of the risk factors in turn will be discussed according to the implied redox modifications occurring during BPD development.

2. Description of BPD

2.1 Historical perspective

Prior to the era of mechanical ventilation, few infants of very low birth weight (less than 1500 g) survived, and neonatal mortality for extremely low birth weight infants (less than 1000 g) exceeded 90% (Behrman et al., 1971). Most survivors required little or no oxygen supplementation initially but later deteriorated to requirements of up to 40% in order to prevent cyanosis. On radiography, findings included microcystic changes as well as varying degrees of hyperinflation and flattening of the diaphragm. Some infants recovered spontaneously over weeks to months but others died, with postmortem examination revealing hyperaeration and reduced alveolar septa. Wilson and Mikity in 1960 were the first to describe this chronic pulmonary syndrome, in a case report of five very small preterm survivors (Wilson & Mikity, 1960). At that time, assisted ventilation was not used in preterm infants. An additional 29 babies with Wilson–Mikity syndrome (WMS) were identified at the same medical institution in 1969 (Hodgman et al., 1969), and many other cases worldwide.

After the introduction of mechanical ventilation to manage respiratory distress syndrome in the mid-1960s, reports began to appear of radiographic and pathological abnormalities that

seemed to result from exposure to high concentrations of oxygen and mechanical ventilation. In 1967, Northway et al. coined the term "bronchopulmonary dysplasia" to describe findings of pulmonary complications following respiratory therapy for hyaline membrane disease (Northway et al., 1967). Northway et al. believed the critical factor to be exposure to an inspired oxygen concentration > 80% for longer than 150 hours.

The 1990s saw major changes in both obstetric and neonatal care for preterm labour, with surfactant administration and assisted ventilation. The outcome of most preterm infants improved in the first half of the decade, particularly for infants with very low birth weight, who benefitted from decreased mortality and morbidity (Horbar et al., 2002). Following these changes, classical BPD, which occurred as a result of injury to the immature lung, became less common. Chronic lung disease in preterm infants became increasingly attributable to the response of the immature lung to early air breathing rather than to damage from barotrauma or oxygen toxicity. In 1999, Jobe described the "new" BPD as occurring in immature infants who did not have extensive lung disease soon after birth (Jobe, 1999). Jobe attributed the "new" BPD to pulmonary anomalies resulting from an inhibition of alveolar and vascular development (Jobe, 1999).

2.2 Clinical definitions

With the change in clinical presentation over time, a variety of definitions of BPD have been used in the literature.

i. **Original criteria for BPD**: A U.S. National Institutes of Health (NIH) workshop held in 1979 proposed to define BPD as a "continued oxygen dependency during the first 28 days plus compatible clinical and radiographic changes" (Natl Inst Health Consens Dev Conf Summ, 1979).

ii. **Traditional definition**: Instead of the original definition, Shennan et al. (1988) suggested a more accurate predictor of BPD to be, "the requirement for additional oxygen at a corrected postnatal gestational age of 36 weeks in infants born with a birth weight of less than 1,500 g". This definition appears to also predict pulmonary outcome among infants with the "new" BPD (Davis et al., 2002).

iii. **Severity definition**: Participants at a joint U.S. National Institute of Child Health & Human Development (NICHD)-National Heart, Lung, and Blood Institute (NHLBI) workshop defined mild, moderate and severe BPD according to both 28 days' and 36 weeks' criteria (Jobe & Bancalari, 2001). Mild BPD was defined as the need for supplemental oxygen at 28 days after birth but not at 36 weeks' postmenstrual age (PMA); moderate BPD, the need for supplemental oxygen at 28 days and at a fraction of inspired oxygen (FiO_2) < 0.30 at 36 weeks' PMA; and severe BPD, the need for supplemental oxygen at 28 days and, at 36 weeks' PMA, the need for mechanical ventilation and/or FiO_2 > 0.30. In a validation study, the NICHD–NHLBI workshop definitions accurately predicted pulmonary outcomes including percent of patients needing treatment with pulmonary medications and rehospitalization for pulmonary causes (Ehrenkranz et al., 2005).

iv. **Physiological definition**: An inherent limitation of all previous definitions is that the need for oxygen is determined by individual physicians rather than on the basis of a physiologic assessment. The assumption that the criteria on which the decision to administer oxygen is uniform and applied similarly across institutions is erroneous because there is no consensus in the literature, neonatologists have widely divergent

practices regarding oxygen-saturation targets. Indeed, published literature cites acceptable saturation ranges from 84% to 98% (Garg et al., 1988; Moyer-Mileur et al., 1996; Sekar & Duke, 1991; Walsh, 2003; Zanardo et al., 1995). Accordingly, the physiological definition determined BPD at 36 weeks of correct age as follows: 1) In all infants treated with mechanical ventilation, continuous positive airway pressure, or supplemental oxygen at $FiO_2 > 0.30$, without additional testing; 2) If the $FiO_2 < 0.30$, infants are to be gradually weaned to room air, in a timed stepwise fashion; those who cannot maintain an $SaO_2 \geq 88\%$ are diagnosed with BPD, unless they pass a timed, continuously monitored oxygen reduction test. An oxygen saturation 80% to 87% for 5 minutes, or < 80% for 1 minute, indicates BPD. If all SaO_2 measurements over 15 minutes ≥ 96%, or if instead, all SaO_2 measurements in a 60-minute period > 88%, the infant is deemed not to have BPD (Walsh et al., 2003).

To evaluate the impact of the physiological definition on BPD rates, 1598 consecutively born preterm infants (birth weight 501–1249 g) in hospital at 36 weeks' PMA were prospectively assessed and assigned an outcome using both the clinical and physiological definitions of BPD. The NICHD neonatal network centers demonstrated that many babies who, according to the nursing staff, required oxygen were able to maintain an $SaO_2 > 90\%$ on room air. Though 560 (35%) had clinical BPD (oxygen use at 36 weeks), only 398 (25%) had physiological BPD (as defined above) (Walsh et al., 2004).

2.3 Structural lung changes

As described by Northway et al. (1967), the histological features of classical BPD included prominent interstitial fibrosis, alveolar overdistention alternating with regions of atelectasis, and airway abnormalities such as squamous metaplasia and excessive muscularization. On the other hand, the "new" BPD shows histological features consistent with developmental arrest and impaired alveolar development (Husain et al., 1998): alveoli are fewer in number and larger in diameter than normal; the fibrosis, squamous metaplasia and excessive airway muscularization seen in classical BPD are conspicuously absent; airway and microvascular growth are affected. A short comparative study by Bhatt et al. (2001) found decreased levels of vascular endothelial growth factor (VEGF) and angiogenic receptors Flt-1 and Tie-2 in infants who died from BPD vs. from other causes. The authors concluded that the lungs from infants with BPD showed abnormal development of alveolar microvessels (abnormal placement in the alveolar septa) and that the capillaries were frequently dilated, changes attributable to low VEGF and associated receptors (Bhatt et al., 2000, 2001). Controls were five children born at term who died at a mean of 3.4 ± 1.3 days, whereas the five BPD subjects were born at 27 ± 2 weeks' gestation, received $FiO_2 > 0.5$ during 37 ± 33 days, and died at 65 ± 34 days.

2.4 Epidemiology

BPD remains the most prevalent and one of the most serious long-term sequelae of preterm birth (Fanaroff et al., 2007). There is considerable variation in reported rates, however, depending upon the centre. Among 4213 infants born in 2003 at 24–31 weeks' gestation in 10 different European regions, the rate of BPD (oxygen requirement at 36 weeks' PMA) was anywhere from 10.5% to 21.5% (Zeitlin et al., 2008).

A 2010 NICHD Neonatal Research Network report on neonatal outcomes of extremely preterm infants assessed 9575 infants born at extremely low gestational ages (22–28 weeks)

and very low birth weights (401–1500 g) at network centers between January 1, 2003 and December 31, 2007. Including babies with mild BPD (oxygen therapy for 28 days but use of room air at 36 weeks), the incidence of BPD as determined by the severity-based definition was 68%; traditional definition, 42%; physiologic definition, 40% (Stoll et al., 2010).

2.5 Demographic factors

Factors linked to BPD include: 1) low gestational age at birth (Kraybill et al., 1989; Darlow & Horwood, 1992; Antonucci et al., 2004; Ambalavanan & Novak, 2003), 2) low birth weight (Darlow & Horwood, 1992; Hakulinenet al., 1988; Avery et al., 1987; Ambalavanan et al., 2008), 3) growth restriction (small for gestational age) (Durrmeyer X et al., 2011; Lal Mk et al., 2003; Zeitlin J et al., 2010), 4) male sex (Kraybill et al., 1989; Darlow & Horwood, 1992; Ambalavanan & Novak, 2003; Avery et al., 1987), and 5) white race (Avery et al., 1987; Palta et al., 1991). In a recent cohort, BPD affected 85% of infants born at 22 weeks' gestation vs. 23% of those born at 28 weeks' (Stoll et al., 2010). Furthermore, of the infants affected by BPD in a large American study which included over 9.5 million very low birth weight infants between 1993 and 2006, 59.3% were male while 40.7% were female (male : female ratio = 1.46 : 1) (Stroustrup & Trasande, 2010).

2.6 Impact of perinatal lung injury later in life

Preterm infants with BPD commonly develop impaired health, neurodevelopment, and quality of life later on in childhood. Often noted are: 1) increased risk of postneonatal mortality (Van Marter, 2009), 2) higher rates of rehospitalization (Jeng et al., 2008), 3) long-term pulmonary impairments (Broström et al., 2010) such as asthma (Baraldi et al., 2009) and emphysema (Wong et al., 2008), 4) failure to thrive (Theile et al., 2011), and 5) cognitive impairment (Anderson & Doyle, 2006), cerebral palsy (Koo KY et al 2010; Majnemer et al., 2000), and global neurodevelopmental deficits (Short EJ et al, 2003).

3. The preterm lung: Set-up for injury

Human lung development proceeds in five regulated stages: embryonic (3–7 weeks' gestation), pseudoglandular (7–17 weeks'), canalicular (17–27 weeks'), saccular (28–36 weeks') and alveolar and microvascular maturation (36 weeks' gestation to at least 2 years after birth). The lungs of preterm infants born at 24–28 weeks' gestation are in the late canalicular or early saccular stages and therefore cannot support efficient gas exchange. Branching and expansion of air spaces to form saccules and thinning of mesenchyme occur later in gestation, as do the formation of alveoli and the synthesis of surfactant by type II alveolar cells which only commence in late gestation. Any injury to the lung at the early stages of development can potentially alter the developmental process, leading to long-term pulmonary sequelae (Chakraborty et al., 2010).

Whereas fetal development is predicated on a hypoxic environment, at birth the oxidative load is sharply increased. At the same time, oxygen demands increase abruptly. The baby born at term easily adapts to this transition in most cases but for the preterm infant, the intra- to extra-uterine transition is not without risks. Among the reasons why the preterm infant is more likely to experience oxidative injury than more mature newborns and older children are the following: 1) intracellular defences against oxidative stress are still poorly developed; 2) the preterm infant is often, for various reasons, exposed to high concentrations of supplemental oxygen; and 3) the fetus and premature infant are also

susceptible to inflammation and infection that may lead to increased oxidative stress (Saugstad, 2010).

It may therefore be instructive to look at some of the molecules implicated in oxidative stress, while drawing parallels with the corresponding processes in BPD. This added insight will contribute to delimiting specific sources of oxidant molecules that may contribute to the development of BPD, a topic we will explore later in the chapter in relation to BPD risk factors.

4. Oxidative stress

In utero, the arterial pressure of oxygen (PaO_2) is close to 30 mm Hg. After birth, with the baby breathing in ambient air, the PaO_2 rises to 75 mm Hg. This greater oxygen load increases the concentration of dissolved oxygen available for oxidative phosphorylation in the mitochondria, organelles that release 1-3% of oxygen in the form of reactive oxygen species (ROS).

Inspired oxygen (O_2) is a diatomic molecule with two free electrons (•O-O•). This molecule has the highest half-cell reduction potential (E_{hc}) *in vivo* (E_{hc} for the $½O_2/H_2O$ couple = 0.816 V). Consequently, dissolved O_2 readily accepts an electron (•) from donors such as polyunsaturated fatty acids or ascorbic acid, generating the free radical superoxide anion (•O-O•• or $O_2•^-$). This transformation of O_2 into $O_2•^-$ is spontaneous, generating the oxidized form of vitamin C (dehydroascorbate, DHA) and/or the by-products of fatty acid oxidation (lipid peroxides, aldehydes such as malondialdehyde or 4-hydroxy-2-nonenal (HNE), or isoprostanes). The reaction may also be catalyzed by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Thus, the inspiration of diatomic oxygen leads to an increase in the cellular concentration of free radicals ($O_2•^-$) as well as free O_2, which will contribute to metabolic regulation by hydroxylation of several biologically active molecules. For instance, O_2 is essential for the degradation of hypoxia-inducible factor-1α (HIF-1α); HIF-1α activates transcription of the gene encoding VEGF, an important growth factor for angiogenesis. This process is impaired in BPD (Husain et al., 1998; Bhatt et al., 2000, 2001). Figure 1 shows a number of oxidative-reduction (redox) reactions of interest.

4.1 Superoxide anion

The dismutation of the superoxide anion ($O_2•^-$) into O_2 and H_2O_2 (2 •O-O•• + $2H^+$➔ •O-O• + H••O-O••H) may be either spontaneous or catalyzed by a superoxide dismutase (SOD). In preterm infants, the pulmonary activity of SOD is suspected to be immature. As reported by Lee Frank in several animal species (mice, hamster, rat, guinea pig), the pulmonary activity of SOD, catalase, and glutathione peroxidase are only 10-15% of that in term babies, in preterm newborns < 32 weeks of human-equivalent gestation (Frank & Sosenko, 1987a, 1987b; Frank, 1991). As a result, the levels of $O_2•^-$ may be higher in preterm than term neonates. Furthermore, the oxidant property of $O_2•^-$ is not related to the attraction of an electron from a common antioxidant such as ascorbate, but to the donation of an electron to a free transition metal such as ferric iron (Fe^{3+}) in a Haber-Weiss reaction ($O_2•^- + Fe^{3+}$ ➔ $O_2 + Fe^{2+}$). The resulting ferrous ion (Fe^{2+}) from this reaction reacts rapidly with hydrogen peroxide (H_2O_2) in a Fenton reaction to generate Fe^{3+}, OH^- and •OH. This hydroxyl radical (•OH) is among the most reactive of molecules, leading to the oxidation of proteins, lipids and DNAs. Therefore, high oxygen supplementation coupled with low SOD activity add to oxidative stress, and this may be evidenced by an increase in the by-products of lipid peroxidation (lipid peroxides, malondialdehyde, HNE, alkanes such as ethane and pentane,

and isoprostanes) and/or of protein oxidation (carbonyl compounds, o-dityrosine). Newborn infants receiving O_2 supplementation have demonstrably elevated levels of markers of oxidative stress such as exhaled ethane and pentane (Nycyk et al., 1998; Pitkanen et al., 1990), serum HNE (Ogihara et al., 1999), F_{2a}-isoprostanes in tracheal aspirate (Cotton et al., 1996) or in plasma (Ahola et al., 2004), protein-carbonyl in bronchoalveolar fluid (Gladstone & Levine et al., 1994) or o-dityrosine in urine (Kelly & Lubec, 1995; Lubec et al., 1997). It has been suggested that some of these markers may be higher in the first few days of life in preterm infants who will develop BPD as compared to those who will not (Gladstone & Levine et al., 1994; Hodgman et al., 1969). Hence, reducing the $O_2^{\bullet -}$ levels in preterm neonates has been a seductive approach to BPD prevention. Indeed, a randomized study of human recombinant SOD administered intratracheally in the first 24 hours to preterm infants at high risk (birth weight 600-1200g) has been associated with a lower incidence of respiratory illnesses such as wheezing, asthma and pulmonary infections (Davis et al., 1993; Davis et al., 2003).

4.2 Hydrogen peroxide

As noted in Figure 1, H_2O_2 is generated following high oxygen supplementation. Chemically, H_2O_2 is a relatively stable molecule that can diffuse passively through cell membranes. Its oxidation reactions occur in two ways, one by accepting an electron from ferrous iron (Fe^{2+}) to generate the free radical hydroxyl (•OH), the other by oxidizing sulfhydryl or thiol groups (R-SH) on protein. By its high affinity for thiol, H_2O_2 is considered an important player in the regulation of several metabolic pathways (Winterbourn & Hampton, 2008). Of interest to BPD, H_2O_2 can activate nuclear factor kappa B (NF-kB) (Flohé et al., 1997; Haddad, 2002; Haddad & Land, 2000; Takada et al., 2003), upregulating the transcription of genes encoding pro-inflammatory cytokines (Randell et al., 1990). H_2O_2 also contributes to the stability of HIF-1α (Bonello et al., 2007; Chen Y Shi, 2008; Haddad, 2002; López-Lázaro, 2006; Simon, 2006), a transcription factor involved in angiogenesis. It is therefore important that the intracellular level of H_2O_2 be tightly regulated.

The intracellular concentration of H_2O_2 depends on the balance between production from the dismutation of superoxide anions catalyzed by manganese superoxide dismutase (MnSOD) (Buettner et al., 2006), and detoxification by catalase and/or glutathione peroxidase. Catalase has a high catalytic activity but relative low affinity for H_2O_2 (K_m of 1.1 M) (Jones & Suggett, 1968), whereas glutathione peroxidase has a K_m close to 1 μM (Flohéa & Branda, 1969). With the exception of erythrocytes (Gaetani et al., 1996), catalase is present in peroxisomes and mitochondria. Glutathione peroxidase, however, is present in the cytosol, where it is an efficient regulator of the intracellular level of H_2O_2. Reduction of H_2O_2 by glutathione peroxidase implies a conversion of glutathione (GSH) to its disulfide form (GSSG). The cell exerts tight control over the intracellular concentrations of GSH and GSSG in order to maintain the appropriate redox environment for the various cellular processes to occur efficiently. Indeed, the redox potential is a component of the Gibbs free energy equation that predicts the feasibility of a chemical reaction. Several biochemical pathways are dependent on the intracellular redox potential, including NF-κB activation and HIF-1α levels as discussed earlier (Bonello et al., 2007; Chen & Shi, 2008; Haddad et al., 2000; Haddad & Land, 2000; Land & Wilson, 2005; López-Lázaro, 2006; Roy et al., 2008). In the presence of a large peroxide load or sustained generation of peroxides, the formation of GSSG can exceed the capacity of glutathione reductase to recycle it into GSH, and the redox potential will change to a more oxidized state.

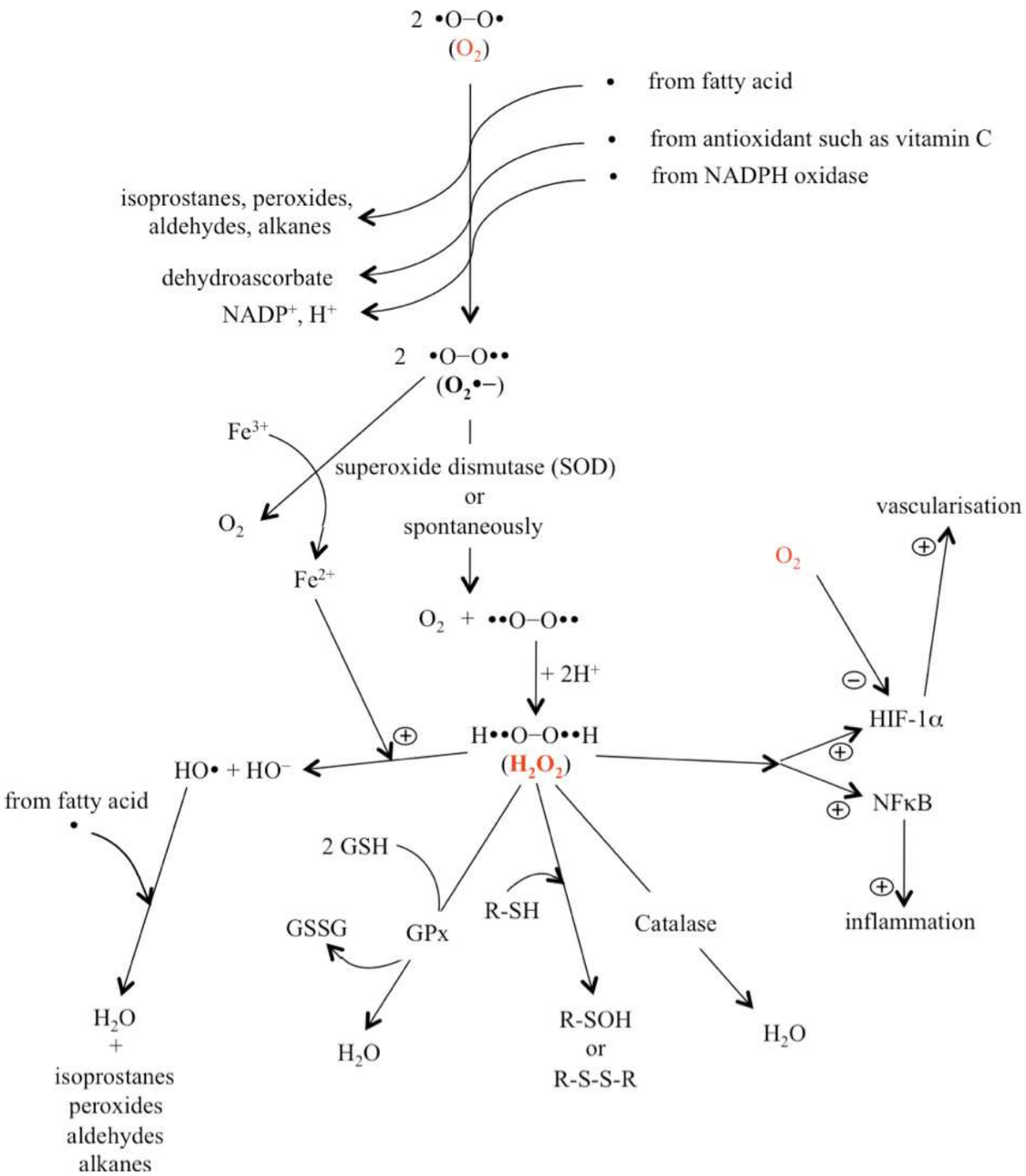


Fig. 1. Relationship between oxidant molecules and endogenous antioxidant defences.

Oxygen (O_2) supplementation as well as hydrogen peroxide (H_2O_2) from parenteral nutrition can lead to modulation of: 1) transcription factors such as hypoxia-inducible factor-1α (HIF-1 α) and nuclear factor kappa B (NF-κB), important players in the pathogenesis of BPD; 2) levels of oxidative stress markers (isoprostanes, peroxides, lipid aldehydes, alkanes); 3) activity of thiol-sensitive proteins (R-SH); and 4) redox potential of glutathione (GSH), as influenced by glutathione peroxidase (GPx) and the intracellular concentrations of reduced (GSH) and oxidized (GSSG) glutathione.

4.3 Redox potential of glutathione

The redox potential is dependent of the concentration of GSH and GSSG according to the Nernst equation: $\Delta E = \Delta E^{\circ} \cdot (RT/nF) \cdot \log ([GSH]^2/[GSSG])$ (Schafer & Buettner, 2001). In cells extracted from the endotracheal aspirate of intubated newborns, the level of glutathione increases with gestational age and female sex, being lower in preterm and male infants (Lavoie & Chessex, 1997). The sex is a significant risk factor for BPD, as BPD affects more boys than girls (Ambalavanan et al., 2008; Ambalavanan & Novak, 2003; Darlow & Horwood, 1992; Kraybill et al., 1989; Stroustrup & Trasande, 2010). The low glutathione concentration measured in preterm newborns (Lavoie & Chessex, 1997) is associated with an oxidized redox potential. Low blood level of glutathione were also reported in preterm neonates with chronic lung disease (White et al., 1994). Recently, Chessex et al. (2010) demonstrated a correlation between BPD severity in preterm infants (26 ± 1 weeks' gestation) and blood redox potential measured one week after birth: the more oxidized the redox potential, more severe the disease.

As previously reported (Schafer & Buettner, 2001), the redox potential acts as a switch for a number of metabolic pathways, inducing cellular proliferation, differentiation or death (apoptosis) (Figure 2). During organ development, cells must pass through the various cell cycle stages in order to allow for continued remodelling. This process is essential to proper lung development (Bruce et al., 1999; Luyet et al., 2000). Consequently, the redox potential must also cycle continuously (Figure 3). The proliferation phase is accompanied by a higher metabolic rate leading to increased generation of ROS. These ROS in turn favour a shift of the redox potential toward a more oxidized status, inducing the differentiation phase. Alternatively, the oxidized status may 1) induce apoptosis, which favours tissue remodelling, and 2) activate redox-sensitive factors inducing the transcription of genes that encode enzymes involved in glutathione synthesis and GSSG recycling (glutathione reductase). This last event will shift the redox potential toward a more reduced state, beginning a new cell cycle.

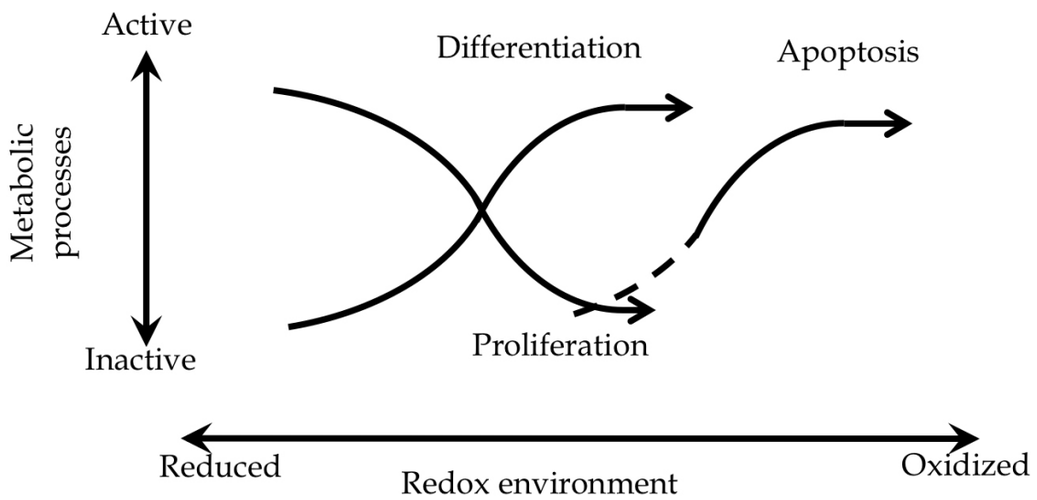


Fig. 2. The redox environment influences metabolic processes.
By modulation from a more reduced to a more oxidized state, the redox environment allows activation and inactivation of various metabolic processes controlling the cell cycle. A reduced state favours cellular proliferation whereas an oxidized state favours differentiation. A more oxidized state will also induce cell death by apoptosis.
(Adapted from Schafer FQ et al., 2001)

The link between redox potential and BPD can be explained by an exacerbated apoptosis rate caused by an abnormally elevated redox potential (Luyet et al., 2000). Lung samples from premature baboons with BPD (Das et al., 2004) showed a large number of apoptotic events. In newborn guinea pigs given parenteral nutrition for 4 days, the alveolar count was 20% lower when the nutritive solution was infused without light protection, peroxide concentration being higher in light-exposed solutions (Section 5.2 below) (Lavoie et al., 2004, 2005, 2008). On histology, 30% of alveolar cells were in an apoptotic state (Lavoie et al., 2004). During normal alveolar development, however, about 10% of cells die by apoptosis (Luyet et al., 2000), in order to thin the septa between alveoli for more efficient gas exchange (Bruce et al., 1999; Luyet et al., 2000).

Various factors may contribute to a shift in redox potential to a more oxidized state (Figure 3, dashed line). An induced or sustained oxidized status favours the apoptosis process, leading to a loss of tissue such as observed in BPD (Das et al., 2004; Lavoie et al., 2004, 2005, 2008). In preterm infants, these factors are oxygen supplementation, parenteral nutrition (containing peroxides), and inflammation.

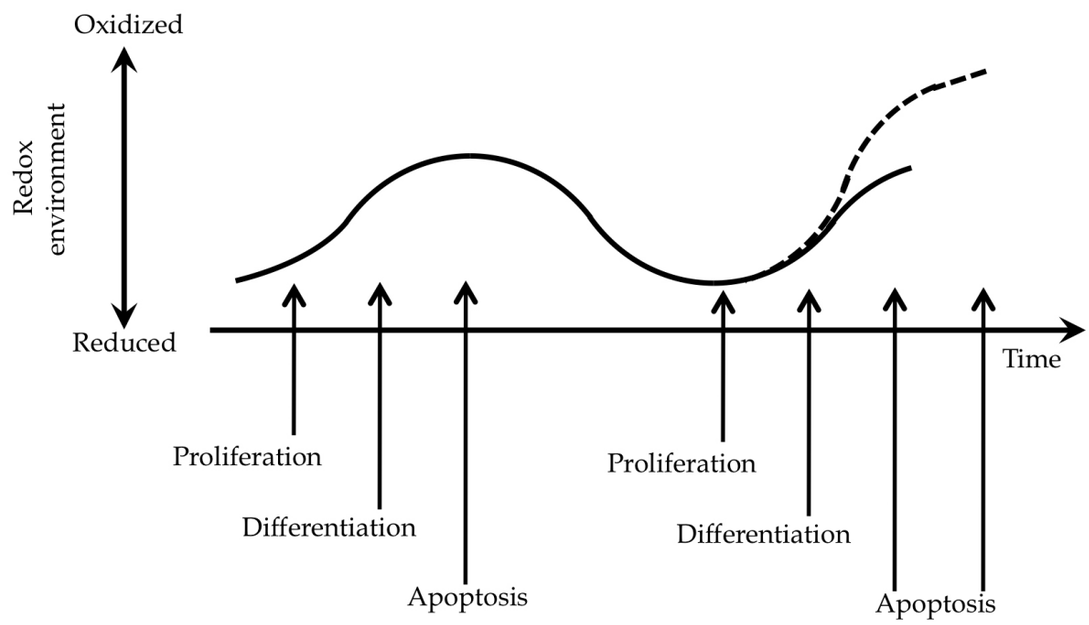


Fig. 3. The redox environment as a function of time.

A normal oscillation of the redox environment occurs over time, between a more reduced and a more oxidized state. As the environmental redox potential changes, pulmonary development is supported by cell proliferation, differentiation, and controlled apoptotic events. An excessively oxidized redox environment, such as that caused by oxidative stress, will favour an apoptotic phase, leading to loss of cells and impaired development.

5. Sources of oxidant molecules in BPD

Oxygen supplementation and parenteral nutrition are exogenous sources of oxidant molecules affecting the preterm neonate. Inflammation, however, is an endogenous source of oxidants and its role is complex. Indeed, inflammation can either be a source or consequence of oxidative stress. In this section, we will analyze each of these sources for their potential role in BPD.

5.1 Oxygen supplementation

Oxygen supplementation increases ROS generation in the lungs. For this reason, and because of the potential effect of oxidative stress on the development of BPD, it has been hypothesized that high O_2 concentration in inspired air is linked to the development of BPD in preterm neonates (Northway et al., 1967). This hypothesis is supported by animal studies. In rats, exposure to 95% O_2 during the first week of life resulted in a 13% reduction in pulmonary alveolar surface area at 40 days (Randell et al., 1990). However, the impact of oxygen has recently been questioned. Although major clinical advances such as the use of surfactant and continuous positive airway pressure (CPAP) have led to a reduction in oxygen supplementation, their impact on lessening the incidence of BPD has been only about 3% per year between 1993 and 2006, for a global reduction of 30% in 13 years (Stroustrup & Trasande, 2010). This relatively weak contribution was confirmed by studies in newborn preterm baboons, where a reduction in the fraction of inspired oxygen (FiO_2) from 80-100% to 21-50% had no significant impact on the levels of fibrosis and alveolar hypoplasia (Coalson et al., 1995, 1999). Similarly, a 2010 study of 1316 human infants born at less than 28 weeks' gestation reported a non-significant effect of ventilation strategy leading to a lower oxygen saturation (85-89% versus 91-95%) on the incidence of BPD (SUPPORT Study Group, 2010). Furthermore, The use of high-dose antioxidants scavenging free radicals (vitamins C and E) did not have any protective effect against alveolar hypoplasia (Berger et al., 1998). Free radicals were therefore not the major player in BPD.

If higher O_2 in inspired air could lead to a greater cellular concentration of H_2O_2 that is not quenched by vitamins C or E, the apparently weak effect of oxygen supplementation on BPD development must be explainable by another source of oxidant molecules masking the impact of O_2. It is noteworthy that the major risk factor for BPD is gestational age; the lower the age, the greater the incidence of BPD. Coincidentally, the more premature the infant, the greater is his dependence on parenteral nutrition. A 2011 study showed that preterm infants developing BPD received more parenteral than enteral nutrition (Wemhöner et al., 2011). In the various studies on BPD, including those in baboons, the gestation ages of the subjects were such that the infants likely required parenteral nutritive support, a major source of ROS and particularly of H_2O_2 (Laborie et al., 1998; Lavoie et al., 1997). In itself, parenteral nutrition may be sufficient to induce the development of BPD. In fact, however, it is highly probable that both parenteral nutrition and oxygen supplementation induce oxidative stress, by both increasing the intracellular concentration of H_2O_2 and modifying the redox potential of glutathione (Chessex et al., 2010).

5.2 Parenteral nutrition

Parenteral nutrition consists of the intravenous administration of a solution containing amino acids, dextrose, electrolytes, vitamins and lipids. Parenteral nutrition is essential for the nutritional support of the preterm infant, bypassing a gastrointestinal system whose

immaturity severely limits the natural feeding process. Although parenteral nutrition is sufficient to support growth in the child, the instability of the nutrients in solution favours the generation of undesirable molecules. The admixture of redox-sensitive elements such as amino acids (tryptophan, tyrosine and others), polyunsaturated fatty acids, and vitamin C, in the presence of a strong oxidizing molecule such as dissolved oxygen, will induce oxidation of the nutrients and the formation of their consequent derivatives. For instance, peroxidation of omega-6 polyunsaturated fatty acids will yield lipid hydroperoxides and HNE (Massarenti et al., 2004; Silvers et al., 2001), while vitamin C and dissolved oxygen will produce H_2O_2 (Laborie et al., 1998; Lavoie et al., 1997). As vitamin C is the most powerful antioxidant found in parenteral nutrition, the main source of peroxides in parenteral nutrition would appear to be the multivitamin preparation (Laborie et al., 1998; Lavoie et al., 1997). Furthermore, this solution contains riboflavin, a photosensitive molecule. In the presence of light, photoexcited riboflavin catalyzes a peroxide-producing reaction (Laborie et al., 1998). The simple act of adequately shielding parenteral nutrition solutions from ambient light halved the concentration of peroxides in the infused solution (Chessex et al., 2001; Laborie et al., 1998, 1999, 2000; Lavoie et al., 1997, 2007) as well as in the urine of preterm infants (Bassiouny et al., 2009; Chessex et al., 2001). Adequate photoprotection of parenteral nutrition has also been reported to reduce the incidence of chronic lung disease (Bassiouny et al., 2009) or BPD (Chessex et al., 2007) in premature infants.

As administered in neonatal units, without adequate photoprotection, parenteral nutritive solutions are contaminated with several molecules having the potential to perturb the redox status of the lung, i.e. lipid hydroperoxides (Silvers et al., 2001), HNE (personal communication of Lavoie JC, 2011), ascorbylperoxide (Lavoie et al., 2004; Maghdessian et al., 2010), and H_2O_2 (Laborie et al., 1998; Lavoie et al., 1997; Silvers et al., 2001). All these molecules are detoxified by the glutathione system. Since glutathione levels are low in preterm infants (Lavoie & Chessex, 1997), these molecules can conceivably overwhelm the glutathione system, allowing the redox potential to shift toward an oxidized state. Infusion of parenteral nutrition without light protection for 4 days in newborn guinea pigs was associated with: 1) a loss of glutathione (Lavoie et al., 2000), 2) a more oxidized glutathione redox potential (Lavoie et al., 2008), and 3) a lower alveolar count (Lavoie et al., 2004, 2005, 2008), as compared to animals infused with a fully photoprotected solution. A recent study demonstrated that the blood glutathione redox potential measured in 7-day-old preterm infants (26 ± 1 weeks' gestation) was correlated with the severity of BPD; a more oxidized status was measured in the most severe cases (Chessex et al., 2010). Therefore, current knowledge suggests that each oxidant molecule affecting the glutathione system, whether from oxygen supplementation or from parenteral nutrition, may contribute to the development of BPD.

5.3 Inflammation

The third major risk factor for BPD is inflammation, a significant source of ROS (Federico et al., 2007; Pereda et al., 2006). Several pro-inflammatory cytokines have been detected in aspirated fluids from infants with BPD, the concentration increasing as a function of assisted ventilation duration and level of oxygen supplementation (Bose et al., 2008). As previously demonstrated, exposure to high amounts of O_2 favours the production of H_2O_2, a known activator of transcription factor NF-κB (Flohé et al., 1997; Haddad, 2002; Haddad & Land, 2000; Takada et al., 2003), which in turn upregulates the expression of several pro-

inflammatory cytokine genes (Federico et al., 2007; Pereda et al., 2006). The oxygen-cytokine connection was further supported by research showing that oxygen supplementation induced an inflammatory response in preterm infants (Lavoie et al., 2010). The association between BPD and inflammation may therefore be explained by an initial oxidative stress followed by a local increase in H_2O_2 concentration. However, other researchers have argued that an inflammatory process independent of the variation in inspired oxygen concentration could also induce BPD, for example chorioamnionitis (Gien & Kinsella, 2011). Paananen R et al (2009) reported that elevated plasma concentrations of IL-6, a pro-inflammatory cytokine, and IL-10, an anti-inflammatory cytokine, on the first day of life were indicative of greater BPD risk, independently of previous exposure to chorioamnionitis (39% of the 128 preterm neonates in the cohort had had chorioamnionitis; incidence of BPD in cohort, 25%). The lack of correlation between an initial inflammatory process and BPD development was confirmed in 2010 in a study investigating the association between chorioamnionitis and BPD (Prendergast, et al., 2010). From the 71 preterm infants developing BPD, 41 had been exposed to chorioamnionitis and/or funisitis. Their results, however, showed a significant correlation between the severity of BPD and gestational age or birth weight. Thus, endogenous infection does not seem to be connected to the development of BPD while cytokines are, underlining a possible implication of oxidative stress early in life.

6. Strategies for prevention/treatment

Under the hypothesis that glutathione, by its very involvement in the cellular redox environment, could be a key player in BPD development, one strategy to prevent BPD development or reduce its severity would be to preserve or increase the intracellular concentration of glutathione. It is noteworthy that the low levels of glutathione observed in preterm infants (Lavoie & Chessex, 1997) are not due to a defective enzymatic process. Indeed, GSH synthesis is very active, even in newborns of 26 weeks' gestation (Lavoie & Chessex, 1998). The defect comes rather from the immaturity of the cellular transport system of cysteine (Lavoie et al., 2002), an amino acid whose low intracellular availability limits the synthesis of glutathione (Deneke & Fanburg, 1989). This fact may explain the failure of intravenous administration of N-acetylcysteine to prevent the development of BPD in extremely low birth weight newborns (Ahola et al., 2003).

If it is difficult to increase the intracellular concentration of glutathione, one must at least prevent its consumption by reducing oxidative stress. This can be partly achieved by monitoring blood oxygen saturation levels to prevent excessive oxygen supplementation. Prevention of inflammation will help as well. However, limiting peroxide contamination in parenteral nutrition is essential. Though photoprotection of the solution may be difficult to institute in the clinical setting, the process must be initiated in the pharmacy department at the time of compounding and continued until bedside. New nutritive strategies leading to improvements in the nutritive quality of parenteral products, reducing the oxidation of nutrients and preventing the generation of oxidant molecules, will have a positive impact on the incidence of BPD.

7. Conclusions/perspectives

Presently, no therapy exists for BPD (Gien & Kinsella, 2011) and its prevention is difficult. The etiology is multifactorial. This chapter focused on the part played by oxidative stress, in

particular the glutathione redox potential. While a number of oxidant sources can contribute to the shift in redox potential toward a more oxidized state, several BPD-related factors were found to have an impact, among them oxygen supplementation, parenteral nutrition, and inflammation. Modification of even one of these factors may decrease the incidence of BPD, but the best practice remains to administer a combination of new measures, as suggested by Geary C et al. (2008), including early use of surfactant and nasal continuous positive airway pressure for ventilatory support, as well as lowered oxygen saturation targets and better nutritive support. It is remarkable that all associations between biochemical markers and BPD have been observed with parameters measured in the first days of life (Ahola et al., 2004; Geary et al., 2008; Gladstone & Levine, 1994; Lavoie et al., 2008; Ogihara et al., 1999; Pitkanen et al., 1990; Welty, 2001). The first week of life, in both infants and animal models, seems be a critical window during which all efforts to reduce oxidative stress must be pursued.

8. Acknowledgements

The authors are grateful to Danielle Buch, medical writer/editor at the Applied Clinical Research Unit of the Sainte-Justine Research Centre, for editing of this chapter.

9. References

Ahola T, Lapatto R, Raivio KO, Selander B, Stigson L, Jonsson B, Jonsbo F, Esberg G, Stôvring S, Kjartansson S, Stiris T, Lossius K, Virkola K, Fellman V. 2003. N-acetylcysteine does not prevent bronchopulmonary dysplasia in immature infants: a randomized controlled trial. J Pediatr 143:713-719.

Ahola T, Fellman V, Kjellemer I, Raivio KO, Lapatto R. 2004. Plasma 8-Isoprostane Is Increased in Preterm Infants Who Develop Bronchopulmonary Dysplasia or Periventricular Leukomalacia. Pediatr Res 56: 88–93.

Ambalavanan N, Novak ZE. 2003. Peptide Growth Factors in Tracheal Aspirates of Mechanically Ventilated Preterm Neonates. Pediatr Res 53: 240–244.

Ambalavanan N, Van Meurs KP, Perritt R, Carlo WA, Ehrenkranz RA, Stevenson DK, Lemons JA, Poole WK, Higgins RD; NICHD Neonatal Research Network, Bethesda, MD. 2008. Predictors of death or bronchopulmonary dysplasia in preterm infants with respiratory failure. J Perinatol 28:420-426.

Anderson PJ, Doyle LW. 2006. Neurodevelopmental outcome of bronchopulmonary dysplasia. Semin Perinatol 30:227-232.

Antonucci R, Contu P, Porcella A, Atzeni C, Chiappe S. 2004. Intrauterine smoke exposure: a new risk factor for bronchopulmonary dysplasia? J Perinat Med 32:272-277.

Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, Epstein MF, Fitzhardinge PM, Hansen CB, Hansen TN, et al. 1987. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 79:26-30.

Baraldi E, Carraro S, Filippone M. 2009. Bronchopulmonary dysplasia: definitions and long-term respiratory outcome. Early Hum Dev 85:S1-S3.

Bassiouny MR, Almarsafawy H, bdel-Hady H, Nasef N, Hammad TA, Aly H. 2009. A randomized controlled trial on parenteral nutrition, oxidative stress, and chronic lung diseases in preterm infants. J Pediatr Gastroenterol Nutr 48:363-369.

Behrman RE, Babson GS, Lessel R. 1971. Fetal and neonatal mortality in white middle class infants. Mortality risks by gestational age and weight. Am J Dis Child 121:486-489.

Berger TM, Frei B, Rifai N, Avery ME, Suh J, Yoder BA, et al. 1998. Early high dose antioxidant vitamins do not prevent bronchopulmonary dysplasia in premature baboons exposed to prolonged hyperoxia: a pilot study. Pediatr Res 43:719-726.

Bhatt AJ, Pryhuber GS, Huyck H, Watkins RH, Metlay LA, Maniscalco WM. 2001. Disrupted Pulmonary Vasculature and Decreased Vascular Endothelial Growth Factor, Flt-1, and TIE-2 in Human Infants Dying with Bronchopulmonary Dysplasia. Am J respir Crit Care Med 164:1971-1980.

Bhatt AJ, Amin SB, Chess PR, Watkins RH, Maniscalco WM. 2000. Expression of Vascular Endothelial Growth Factor and Flk-1 in Developing and Glucocorticoid-Treated Mouse Lung. Pediatr Res 47 :606-613.

Bonello S, Zähringer C, BelAiba RS, Djordjevic T, Hess J, Michiels C, KietzmannT , Görlach A. 2007. Reactive Oxygen Species Activate the HIF-1α Promoter Via a Functional NFκB Site. Arterioscler Thromb Vasc Biol 27:755-761.

Bose CL, Dammann CEL, Laughon MM. 2008. Bronchopulmonary dysplasia and inflammatory biomarkers in the premature neonate. Arch Dis Child Fetal Neonatal Ed 93:F455-F461.

Broström EB, Thunqvist P, Adenfelt G, Borling E, Katz-Salamon M. 2010. Obstructive lung disease in children with mild to severe BPD. Respir Med 104:362-370.

Bruce MC, Honaker CE and Cross RJ. 1999. Lung fibroblasts undergo apoptosis following alveolarization. Am J Respir Cell Mol Biol 20:228-236.

Buettner GR, Ng CF, Wang M, Rodgers VG, Schafer FQ. 2006. A new paradigm: manganese superoxide dismutase influences the production of H2O2 in cells and thereby their biological state. Free Radic Biol Med 41:1338-1350.

Chakraborty M, McGreal EP, Kotecha S. 2010. Acute lung injury in preterm newborn infants: mechanisms and management. Paediatr Respir Rev 11:162-170.

Chen H, Shi H. 2008. A reducing environment stabilizes HIF-2α in SH-SY5Y cells under hypoxic conditions. FEBS Lett 582:3899–3902.

Chessex P, Laborie S, Lavoie JC, Rouleau T. 2001. Photoprotection of solutions of parenteral nutrition decreases the infused load as well as the urinary excretion of peroxides in premature infants. Semin Perinatol 25:55-59.

Chessex P, Harrison A, Khashu M, Lavoie JC. 2007. In preterm neonates, is the risk of developing bronchopulmonary dysplasia influenced by the failure to protect total parenteral nutrition from exposure to ambient light? J Pediatr 151:213-214.

Chessex P, Watson C, Kaczala G, Rouleau T, Lavoie ME, Friel J, Lavoie JC. 2010. Determinants of oxidant stress in extremely low birth weight premature infants. Free Radic Biol Med 49:1380-6.

Coalson JJ, Winter V, DeLemos RA. 1995. Decreased alveolarization in baboon survivors with bronchopulmonary dysplasia. Am J Respir Crit Care Med 152:640-646.

Coalson JJ, Winter VT, Siler-Khodr T, Yoder BA. 1999. Neonatal chronic lung disease in extremely immature baboons. Am J Respir Crit Care Med 160:1333-1346.

Cotton RB, Morrow JD, Hazinski TA, Roberts LJ, Law AB, Steele S. 1996. F2-isoprostanes (F2-I) in tracheobronchial aspirate fluid (TBAF) indicate association between increased Fi02 and lipid peroxidation in the lungs of premature infants. *Pediatr Res* 39: 329A.

Darlow BA, Horwood LJ. 1992. Chronic lung disease in very low birthweight infants: a prospective population-based study. J Paediatr Child Health 28:301-305.

Das KC, Ravi D, Holland W. 2004. Increased apoptosis and expression of p21 and p53 in premature infant baboon model of bronchopulmonary dysplasia. Antioxid Redox Signal 6:109-116.

Davis JM, Rosenfeld WN, Sanders RJ, et al. 1993. Prophylactic effects of recombinant human superoxide dismutase in neonatal lung injury. J Appl Physiol 74:2234–2241.

Davis PG, Thorpe K, Roberts R, Schmidt B, Doyle LW, Kirpalani H, Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators. 2002. Evaluating "old" definitions for the "new" bronchopulmonary dysplasia. J Pediatr 140:555-560.

Davis JM, Parad RB, Michele T, et al. 2003. Pulmonary outcome at one year corrected age in premature infants treated at birth with recombinant CuZn superoxide dismutase. Pediatrics 111:469–476.

Deneke SM, Fanburg BL. 1989. Regulation of cellular glutathione. Am J Physiol 257:L163-L173.

Durrmeyer X, Kayem G, Sinico M, Dassieu G, Danan C, Decobert F. 2011. Perinatal Risk Factors for Bronchopulmonary Dysplasia in Extremely Low Gestational Age Infants: A Pregnancy Disorder-Based Approach. J Pediatr Oct 31. [Epub ahead of print]

Egreteau L, Pauchard JY, Semama DS, Matis J, Liska A, Romeo B, Cneude F, Hamon I, Truffert P. 2001. Chronic oxygen dependency in infants born at less than 32 weeks' gestation: incidence and risk factors. Pediatrics 108:E26.

Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, Wrage LA, Poole K. 2005. Validation of the National Institutes of Health Consensus Definition of Bronchopulmonary Dysplasia. Pediatrics 116:1353–1360.

Fanaroff AA, Stoll BJ, Wright LL, et al; NICHD Neonatal Research Network. 2007. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 196: 147.e1-8.

Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C. 2007. Chronic inflammation and oxidative stress in human carcinogenesis. Int J Cancer 121:2381–2386.

Flohéa L, Branda I. 1969. Kinetics of glutathione peroxidase. Biochim Biophys Acta (BBA) – Enzymology 191:541-549.

Flohé L, Brigelius-Flohé R, Saliou C, Traber MG, Packer L. 1997. Redox regulation of NF-kappa B activation. Free Radic Biol Med 22:1115-1126.

Frank L, Sosenko IR. 1987a. Prenatal development of lung antioxidant enzymes in four species. J Pediatr 110:106-110.

Frank L, Sosenko IR. 1987b. Development of lung antioxidant enzyme system in late gestation: possible implications for the prematurely born infant. J Pediatr 110:9-14.

Frank L. 1991. Developmental aspects of experimental pulmonary oxygen toxicity. Free Radic Biol Med 11:463-494.

Gaetani GF, Ferraris AM, Rolfo M, Mangerini R, Arena S, Kirkman HN. 1996. Predominant role of catalase in the disposal of hydrogen peroxide within human érythrocytes. Blood 87:1595-1599.

Garg M, Kurzner SI, Bautista DB, Keens TG. 1988. Clinically unsuspected hypoxia during sleep and feeding in infants with bronchopulmonary dysplasia. Pediatrics 81:635-642.

Geary C, Caskey M, Fonseca R, Malloy M. 2008. Decreased incidence of bronchopulmonary dysplasia after early management changes, including surfactant and nasal continuous positive airway pressure treatment at delivery, lowered oxygen saturation goals, and early amino acid administration: a historical cohort study. Pediatrics 121:89-96.

Gien J, Kinsella JP. 2011. Pathogenesis and treatment of bronchopulmonary dysplasia. Current Opinion in Pediatrics 23:305–313.

Gladstone IM, Levine RL. 1994. Oxidation of proteins in neonatal lungs. Pediatrics 93:764-768.

Haddad JJ. 2002. Oxygen-sensing mechanisms and the regulation of redox-responsive transcription factors in development and pathophysiology. Respir Res 3:26.

Haddad JJE, Land SC. 2000. O2-evoked regulation of HIF-1a and NF-kB in périnatal lung epithelium requires glutathione biosynthesis. Am J Physiol Lung Cell Mol Physiol 278:L492-L503.

Haddad JJE, Olver RE, Land SC. 2000. Antioxidant/Pro-oxidant Equilibrium Regulates HIF-1α and NF-κB Redox Sensitivity. Evidence For Inhibition By Glutathione Oxidation In Alveolar Epithelial Cells J Biol Chem 275:21130-21139.

Hakulinen A, Heinonen K, Jokela V, Kiekara O. 1988. Occurrence, predictive factors and associated morbidity of bronchopulmonary dysplasia in a preterm birth cohort. J Perinat Med 16:437-446.

Hodgman JE, Mikity VG, Tatter D, Cleland RS. 1969. Chronic respiratory distress in the premature infant. Wilson-Mikity syndrome. Pediatrics 44:179-195.

Horbar JD, Badger GJ, Carpenter JH, Fanaroff AA, Kilpatrick S, LaCorte M, Phibbs R, Soll RF; Members of the Vermont Oxford Network. 2002. Trends in mortality and morbidity for very low birth weight infants, 1991-1999. Pediatrics 110:143-151.

Husain AN, Siddiqui NH, Stocker JT. 1998. Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. Hum Pathol 29:710-717.

Jeng SF, Hsu CH, Tsao PN, Chou HC, Lee WT, Kao HA, Hung HY, Chang JH, Chiu NC, Hsieh WS. 2008. Bronchopulmonary dysplasia predicts adverse developmental and clinical outcomes in very-low-birthweight infants. Dev Med Child Neurol 50:51-57.

Jobe AH. 1999. The New BPD: An Arrest of Lung Development. Pediatr Res 46:641-643.

Jobe AH, Bancalari E. 2001. Bronchopulmonary Dysplasia. Am J Respir Crit Care Med 163:1723–1729.

Jones P, Suggett A. 1968. The Catalase-Hydrogen Peroxide System. Kinetics Of Catalatic Action At High Substrate Concentrations. Biochem J 110 :617-620.

Kelly FJ, Lubec G. 1995. Hyperoxic injury of immature guinea pig lung is mediated via hydroxyl radicals. *Pediatr Res* 38: 786-791.

Kraybill EN, Runyan DK, Bose CL, Khan JH. 1989. Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams. J Pediatr 115:115-120.

Koo KY, Kim JE, Lee SM, Namgung R, Park MS, Park KI, Lee C. 2010. Effect of severe neonatal morbidities on long term outcome in extremely low birth weight infants. Korean J Pediatr 53:694-700.

Laborie S, Lavoie JC, Chessex P. 1998. Paradoxical role of ascorbic acid and riboflavin in solutions of total parenteral nutrition: implication in photoinduced peroxide generation. Pediatr Res 43:601-606.

Laborie S, Lavoie JC, Pineault M, Chessex P. 1999. Protecting solutions of parenteral nutrition from peroxidation. JPEN J Parenter Enteral Nutr 23:104-108.

Laborie S, Lavoie JC, Pineault M, Chessex P. 2000. Contribution of multivitamins, air, and light in the generation of peroxides in adult and neonatal parenteral nutrition solutions. Ann Pharmacother 34:440-445.

Lal MK, Manktelow BN, Draper ES and Field DJ. 2003. Chronic lung disease of prematurity and intrauterine growth retardation: a population-based study. Pediatrics 111:483–487.

Land SC, Wilson SM. 2005. Redox Regulation of Lung Development and Perinatal Lung Epithelial Function. Antioxidants & Redox Signaling 7:92-107.

Lavoie JC, Belanger S, Spalinger M, Chessex P. 1997. Admixture of a multivitamin preparation to parenteral nutrition: the major contributor to in vitro generation of peroxides. Pediatrics 99:E6.

Lavoie JC, Chessex P. 1997. Gender and maturation affect glutathione status in human neonatal tissues. Free Radic Biol Med 23:648-657.

Lavoie JC, Chessex P. 1998. Development of glutathione synthesis and gamma-glutamyltranspeptidase activities in tissues from newborn infants. Free Radic Biol Med 24:994-1001.

Lavoie JC, Laborie S, Rouleau T, Spalinger M, Chessex P. 2000. Peroxide-like oxidant response in lungs of newborn guinea pigs following the parenteral infusion of a multivitamin preparation. Biochem Pharmacol 60 :1297-1303.

Lavoie JC, Rouleau T, Truttmann AC, Chessex P. 2002. Postnatal gender-dependent maturation of cellular cysteine uptake. Free Radic Res 36:811-817.

Lavoie JC, Chessex P, Rouleau T, Migneault D, Comte B. 2004. Light-induced byproducts of vitamin C in multivitamin solutions. Clin Chem 50:135-140.

Lavoie JC, Rouleau T, Chessex P. 2004. Interaction between ascorbate and light-exposed riboflavin induces lung remodelling. J Pharm Exp Ther 311: 634-639.

Lavoie JC, Rouleau T, Chessex P. 2005. Effect of coadministration of parenteral multivitamins with the lipid emulsion on lung remodeling in an animal model of TPN. Pediatr Pulmonol 40:53-56.

Lavoie JC, Rouleau T, Tsopmo A, Friel J, Chessex P. 2007. Influence of lung oxidant and antioxidant status on alveolarization: role of light-exposed TPN. Free Radic Biol Med 45:572-577.

Lavoie JC, Rouleau T, Tsopmo A, Friel J, Chessex P. 2008. Influence of lung oxidant and antioxidant status on alveolarization: role of light-exposed total parenteral nutrition. Free Radic Biol Med 45:572-577.

Lavoie P, Lavoie JC, Watson C, Rouleau T, Chang BA, Chessex P. 2010. Inflammatory response in preterm infants is induced early in life by oxygen and modulated by TPN. Pediatr Res 68:248-51.

López-Lázaro M. 2006. HIF-1: hypoxia-inducible factor or dysoxia-inducible factor? FASEB J 20:828–832.

Lubec G, Widness JA, Hayde M, Menzel D, Pollack A. 1997. Hydroxyl radical generation in oxygen treated infants. Pediatrics 100: 200-204.

Luyet C, Burri PH and Schittny JC. 2000. Pre- and postnatal lung development, maturation, and plasticity. Suppression of cell proliferation and programmed cell death by

dexamethasone during postnatal lung development. Am. J Physiol Lung Cell Mol Physiol 282:L477-L483.

Maghdessian R, Cote F, Rouleau T, Ouadda AB, Levy E, Lavoie JC. 2010. Ascorbylperoxide contaminating parenteral nutrition perturbs the lipid metabolism in newborn guinea pig. J Pharmacol Exp Ther 334:278-284.

Majnemer A, Riley P, Shevell M, Birnbaum R, Greenstone H, Coates AL. 2000. Severe bronchopulmonary dysplasia increases risk for later neurological and motor sequelae in preterm survivors. Dev Med Child Neurol. 42:53-60.

Massarenti P, Biasi F, de FA, Pauletto D, Rocca G, Silli B, et al. 2004. 4-Hydroxynonenal is markedly higher in patients on a standard long-term home parenteral nutrition. Free Radic Res 38:73-80.

Moyer-Mileur LJ, Nielson DW, Pfeffer KD, Witte MK, Chapman DL. 1996. Eliminating sleep-associated hypoxemia improves growth in infants with bronchopulmonary dysplasia. Pediatrics 98:779-783.

Natl Inst Health Consens Dev Conf Summ. 1979. Antenatal diagnosis. Sponsored by the National Institute of Child Health and Human Development 2:11-15.

Northway WH Jr, Rosan RC, Porter DY. 1967. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med 276:357-368.

Nycyk JA, Drury JA, Cooke RWI. 1998. Breath pentane as a marker for lipid peroxidation and adverse outcome in preterm infants. Arch Dis Child Fetal Neonatal Ed 79: F67–F69.

Ogihara T, Hirano K, Morinobu T, Kim HS, Hiroi M, Ogihara H, Tamai H. 1999. Raised concentration of aldehyde lipid peroxidation products in premature infants with chronic lung disease. Arch Dis Child Fetal Neonatal Ed 80: F21–F25.

Paananen R, Husa AK, Vuolteenaho R, et al. 2009. Blood cytokines during the perinatal period in very preterm infants: relationship of inflammatory response and bronchopulmonary dysplasia. J Pediatr 154:39–43.

Palta M, Gabbert D, Weinstein MR, Peters ME. 1991. Multivariate assessment of traditional risk factors for chronic lung disease in very low birth weight neonates. The Newborn Lung Project. J Pediatr. 119:285-292.

Pereda J, Sabater L, Aparisi L, Escobar J, Sandoval J, Viña J, López-Rodas G, Sastre J. 2006. Interaction between cytokines and oxidative stress in acute pancreatitis. Curr Med Chem 13:2775-2787.

Pitkanen OM, Hallman M, Andersson SM. 1990. Correlation of free oxygen radical-induced lipid peroxidation with outcome in very low birthweight infants. J Pediatr 116: 760-764.

Prendergast M, May C, Broughton S, Pollina E, Milner AD, Rafferty GF, Greenough A. 2010. Chorioamnionitis, lung function and bronchopulmonary dysplasia in prematurely born infants. Arch Dis Child Fetal Neonatal Ed 96:F270-F274.

Randell SH, Mercer RR, Young SL. 1990. Neonatal hyperoxia alters the pulmonary alveolar and capillary structure of 40-day-old rats. Am J Pathol 136:1259-1266.

Roy S, Khanna S, Sen CK. 2008. Redox regulation of the VEGF signaling path and tissue vascularization: Hydrogen peroxide, the common link between physical exercise and cutaneous wound Healing. Free Radic Biol Med 44:180-192.

Saugstad OD. 2010. Oxygen and oxidative stress in bronchopulmonary dysplasia. J Perinat Med 38:571-577.

Schafer FQ, Buettner GR. 2001. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathionne couple. *Free Radic Biol Med* 30:1191–1212

Sekar KC, Duke JC. 1991. Sleep apnea and hypoxemia in recently weaned premature infants with and without bronchopulmonary dysplasia. Pediatr Pulmonol 10:112-116.

Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. 1988. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 82:527-523.

Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kercsmar C, Baley J, Singer LT. 2003. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. Pediatrics 112:e359.

Silvers KM, Darlow BA, Winterbourn CC. 2001. Lipid peroxide and hydrogen peroxide formation in parenteral nutrition solutions containing multivitamins. JPEN J Parenter Enteral Nutr 25, 14-17.

Simon MC. 2006. Mitochondrial reactive oxygen species are required for hypoxic HIF alphastabilization. Adv Exp Med Biol 588:165-170.

Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, hale EC, Newman NS, Schibler K, Carlo WA, Kennedy KA, Poindexter BB, Finer NN, Ehrenkranz RA, Duara S, Sanchez PJ, O'Shea M, Goldberg RN, Van Meurs KP, Faix RG, Phelps DL, Freantz ID, Watterberg KL, Saha S, Das A, Higgins RD, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. 2010. Neonatal Outcomes of Extremely Preterm Infants From the NICHD NeonatalResearch Network. Pediatrics 126;443-456.

Stroustrup A, Trasande L. 2010. Epidemiological Characteristics and Resource Use in Neonates With Bronchopulmonary Dysplasia: 1993 -2006. Pediatrics 126:e291–e297.

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, et al. 2010. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 362:1970-1979.

Takada Y, Mukhopadhyay A, Kundu GC, Mahabeleshwar GH, Singh S, Aggarwal BB. 2003. Hydrogen peroxide activates NF-kappa B through tyrosine phosphorylation of I kappa B alpha and serine phosphorylation of p65: evidence for the involvement of I kappa B alpha kinase and Syk protein-tyrosine kinase. J Biol Chem 278:24233-24241.

Theile AR, Radmacher PG, Anschutz TW, Davis DW, Adamkin DH. 2011. Nutritional strategies and growth in extremely low birth weight infants with bronchopulmonary dysplasia over the past 10 years. J Perinatol May 26 [Epub ahead of print].

Van Marter LJ. 2009. Epidemiology of bronchopulmonary dysplasia. Semin Fetal Neonatal Med. 14:358-366.

Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. 2003. Safety, Reliability, and Validity of a Physiologic Definition of Bronchopulmonary Dysplasia. J Perinatology 23, 451–456.

Walsh MC, Yao Q, Gettner P, Hale E, Collins M, Hensman A, Everette R, Peters N, Miller N, Muran G, Auten K, Newman N, Rowan G, Grisby C, Arnell K, Miller L, Ball B,

McDavid G; National Institute of Child Health and Human Development Neonatal Research Network, 2004. Impact of a Physiologic Definition on Bronchopulmonary Dysplasia Rates. Pediatrics 114:1305–1311.

Welty SE. 2001. Is There a Role for Antioxidant Therapy in Bronchopulmonary Dysplasia? J. Nutr 131: 947S–950S.

Wemhöner A, Ortner D, Tschirch E, Strasak A, Rüdiger M. 2011. Nutrition of preterm infants in relation to bronchopulmonary dysplasia. BMC Pulmonary Medicine 11:7.

White CW, Stabler SP, Allen RH, Moreland S, Rosenberg AA. 1994. Plasma cysteine concentrations in infants with respiratory distress. J Pediatr 125:769-777.

Wilson MG, Mikity VG. 1960. A new form of respiratory disease in premature infants. AMA J Dis Child 99:489-499.

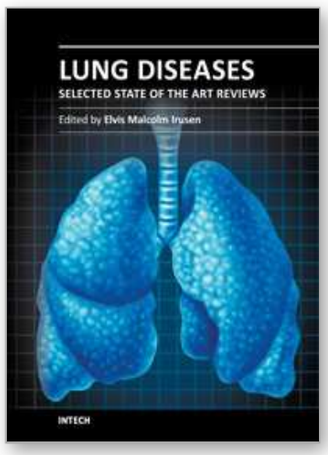
Winterbourn CC, Hampton MB. 2008. Thiol chemistry and specificity in redox signaling. Free Radic Biol Med 45:549-561.

Wong PM, Lees AN, Louw J, Lee FY, French N, Gain K, Murray CP, Wilson A, Chambers DC. 2008. Emphysema in young adult survivors of moderate-to-severe bronchopulmonary dysplasia. Eur Respir J 32:321-328.

Zanardo V, Trevisanuto D, Dani C, Bottos M, Guglielmi A, Cantarutti F. 1995. Oxygen saturation in premature neonates with bronchopulmonary dysplasia in a hammock. Biol Neonate 67:54-58.

Zeitlin J, Draper ES, Kollée L, Milligan D, Boerch K, Agostino R, Gortner L, Van Reempts P, Chabernaud JL, Gadzinowski J, Bréart G, Papiernik E; MOSAIC research group. 2008. Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: results from the MOSAIC cohort. Pediatrics 121:e936-e944.

IntechOpen



Lung Diseases - Selected State of the Art Reviews
Edited by Dr. Elvisegran Malcolm Irusen

ISBN 978-953-51-0180-2
Hard cover, 690 pages
Publisher InTech
Published online 02, March, 2012
Published in print edition March, 2012

The developments in molecular medicine are transforming respiratory medicine. Leading clinicians and scientists in the world have brought their knowledge and experience in their contributions to this book. Clinicians and researchers will learn about the most recent advances in a variety of lung diseases that will better enable them to understand respiratory disorders. This treatise presents state of the art essays on airways disease, neoplastic diseases, and pediatric respiratory conditions. Additionally, aspects of immune regulation, respiratory infections, acute lung injury/ARDS, pulmonary edema, functional evaluation in respiratory disorders, and a variety of other conditions are also discussed. The book will be invaluable to clinicians who keep up with the current concepts, improve their diagnostic skills, and understand potential new therapeutic applications in lung diseases, while scientists can contemplate a plethora of new research avenues for exploration.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Jean-Claude Lavoie and Ibrahim Mohamed (2012). Bronchopulmonary Dysplasia: The Role of Oxidative Stress, Lung Diseases - Selected State of the Art Reviews, Dr. Elvisegran Malcolm Irusen (Ed.), ISBN: 978-953-51-0180-2, InTech, Available from: http://www.intechopen.com/books/lung-diseases-selected-state-of-the-art-reviews/bronchopulmonary-dysplasia-the-role-of-oxidative-stress

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen