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MINIREVIEW

Immature Lung and Acute Lung Injury

P. ZOBAN, M. ČERNÝ

Department of Neonatology, Charles University, Second Faculty of Medicine and University Hospital Motol, Prague, Czech Republic

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Summary

Acute lung injury occurs mostly in the very low birth weight and extremely low birth weight infants. The pathological process leading to acute lung injury includes immature and/or diseased lung that experienced oxidative stress, inflammation and mechanical insult with the bronchial, alveolar and capillary injuries and cell death. It may be the first step to the subsequent development of chronic lung disease of prematurity or bronchopulmonary dysplasia. The mechanisms of lung injury are extensively investigated in the experimental models and clinical studies, mostly performed on the adult patients. At present, the explanations of the mechanism(s) leading to lung tissue injury in tiny premature babies are just derived from these studies. Acute lung injury seems to be rather a syndrome than a well-defined nosological unit and is of multifactorial etiology. The purpose of this review is to discuss the main factors contributing to the development of acute lung injury in the very low or extremely low birth weight infants – lung immaturity, mechanical injury, oxidative stress and inflammation. Nevertheless, numerous other factors may influence the status of immature lung after delivery.

Key words

Acute lung injury • Immature lung • Mechanical lung injury • Oxidative stress • Inflammation

Introduction

The preterm newborn infants receiving intensive care may sustain various complications such as acute and chronic lung injury, periventricular hemorrhage, retinopathy of prematurity or necrotizing enterocolitis (Nycyk *et al.* 1998).

Acute lung injury (ALI) occurs mostly in the very low birth weight (VLBW) and extremely low birth weight infants (ELBW). It is probably an end-stage of severely immature or diseased lung which experienced oxidative stress, inflammation and mechanical insult, with the bronchial, alveolar and capillary injuries and cell death. It may be the first step to the subsequent development of the chronic lung disease of prematurity (CLDP) or bronchopulmonary dysplasia (BPD) (Jobe and Ikegami 1998, Speer 1999).

The mechanisms of lung injury are extensively investigated in the experimental models and clinical studies, mostly performed on the adult patients (Delacourt *et al.* 1996, Repine *et al.* 1997, Lang *et al.* 2000). Some of the contemporary knowledge used to

explain the mechanisms of ALI in the tiny premature babies is just derived from these studies. Acute lung injury seems to be more a syndrome with multifactorial etiology than a single distinct, well-defined nosological unit (Pittet *et al.* 1997).

Immature Lung

By being born too early, infants are delivered at a very immature stages of lung development: the late canalicular stage for infants born at 24-26 weeks (i.e. for ELBW infants), and early or mild saccular stage for those born after 26 but before 32 weeks of gestation (in part ELBW and all VLBW infants).

During the canalicular stage, development of the distal airways into primary acini occurs. The accinar structures consist of respiratory bronchioles, alveolar ducts and rudimentary alveoli. At this stage, lamellar bodies containing surfactant proteins and phospholipids in type II pneumocytes can be observed, and differentiation into type I pneumocytes occurs in conjunction with the formation of the alveolar-capillary barrier (Kotecha 2000).

During the saccular phase, further differentiation of peripheral airways and acinar tubules continues, resulting in increased gas exchange surface area. The lamellar bodies in type II cells increase, and further maturation of type I cells occurs. The capillaries accompanying acini are closely associated with type I cells reducing the distance of the future air-blood interface (Kotecha 2000).

Preterm birth occurring during the late canalicular or early saccular stage is very likely to lead to severe respiratory distress syndrome (RDS). The poorly developed peripheral airways and poor maturity of cells important for lung maturation are the major causes of poor surfactant production by type II cells and inadequate antioxidant responses to increased ambient oxygen. For example, the superoxide dismutase (SOD) activity appears in the developing lungs concomitantly with the surfactant synthesis by type II pneumocytes (Kotecha 2000). Therefore, the preterm exposure of severely immature lung to the postnatal environment may disrupt the subsequent normal development resulting in either accelerated or arrested final maturation of alveoli (Jobe and Ikegami 1998).

Both hypoxia and hyperoxia disrupt septation and reduce the ultimate gas exchange surface area (Kotecha 2000). In animal model, an increased oxygen concentration severely disrupts alveolization within the lungs *via* the formation of reactive oxygen species – ROS (Randell *et al.* 1989, Thibeault *et al.* 1990). Even after recovery from hyperoxic exposure persisting abnormalities (decreased pulmonary septation, increased terminal space diameter, and decreased surface area) are seen in the lung morphology. Based on the animal studies, the process leading to these changes may be mediated through an increase in pulmonary inflammation as pro-inflammatory cytokines were found to be significantly elevated (Warner *et al.* 1998). Additional factors including mechanical ventilation, oxygen therapy, and nosocomial infection further adversely affect the postnatal growth, structural development and function of the immature lung (Coalson 1997, Kotecha 2000).

In summary, the preterm exposure of immature lung to the postnatal environment makes it highly susceptible to injury during resuscitation or during later intensive care, employing mechanical ventilation often with high fraction of inspired oxygen (Jobe and Ikegami 1998). This is due to its incomplete anatomical differentiation, poor biochemical maturity (inadequate control of oxidative stress and inflammatory process), and functional capacity (unstable function of alveolar-capillary membrane to keep adequate blood gas exchange). These intrinsic factors promoting lung injury in ELBW/VLBW infants after delivery reflect a prematurely disrupted process of lung development.

Mechanical Lung Injury

Ventilation-induced lung injury was, for years, synonymous with clinical terms *barotrauma/volutrauma*, i.e. the leakage of air due to disruption of the airspace wall. The extra-alveolar accumulation of air causes several manifestations, the most threatening of which is the tension pneumothorax. Recently the possibility has been recognized that more subtle physiological and morphological alterations may occur during mechanical ventilation (Dreyfuss and Saumon 1998).

Alteration of lung fluid balance, an increased endothelial and epithelial permeability, and severe tissue damages have been reported following mechanical ventilation in animals (Dreyfuss and Saumon 1998). The macroscopic and even microscopic damage observed in ventilator-induced lung injury is not specific (Dreyfuss *et al.* 1985). It closely resembles that observed in other

forms of experimental ALI (Cottrel *et al.* 1967), and it does not substantially differ from the diffuse alveolar damage observed during human acute respiratory distress syndrome – ARDS (Bachofen and Weibel 1982). Thus, ventilator-induced lung injury (mechanical injury) could be indistinguishable from most of the initial acute processes that lead to respiratory failure and the need for ventilatory support (Dreyfuss and Saumon 1998).

The possibility that mechanical ventilation can actually worsen acute lung disease is now widely accepted (Parker *et al.* 1993, Griese *et al.* 1998, Moritette *et al.* 2000). Therefore, the current orientation in the clinical practice is to emphasize the potential importance of reducing mechanical insult on acutely diseased lungs by using special modes of ventilation, like high frequency oscillatory ventilation (HFOV), that limit the pressure and volume of gas delivered to the lungs (Spragg and Smith 1997, Dreyfuss and Saumon 1998, Moriette *et al.* 2000, Henderson-Smart *et al.* 2000). The modes of mechanical ventilation, most frequently used in the VLBW/ELBW infants, are shown in Table 1.

The preterm lung is much more susceptible to injury with the onset of ventilation because potential lung gas volumes are small, surfactant may be deficient, the lung matrix is not fully developed, and the air spaces contain residual fetal lung fluid (Jobe 1998, Ikegami 2000). The considerably immature lung suffers from primary deficiency of surfactant produced by type II pneumocytes, with or without its dysfunction (Taeusch 2000). Pulmonary surfactant helps to keep the lung open throughout the complete respiratory cycle (Jonson 1997, Spragg and Smith 1997). In case of surfactant deficiency, abnormally high surface tension of immature lungs leads repeatedly to the collapse of small airways and alveoli at the end of expiration. Collapsed lung zones must be re-expanded (so-called "Recorex" mechanism re-collaps/ re-expansion) during subsequent inspiration (Jonson 1997). Gross shear forces disrupt the bronchiolar epithelium and cause protein leak into the bronchiolar-alveolar space (Groneck *et al.* 1994, Taeusch 2000). This mechanism further perturbates and inactivates surfactant (Jonson 1997, Taeusch 2000). When immature lung is subjected to an improper mode of ventilation and "Recorex" mechanism persists, morphological lung damage occurs (Jonson 1997, Dreyfuss and Saumon 1998, Jobe and Ikegami 1998).

In addition, the preterm infants are often hyperventilated and low PCO_2 values after birth correlate with an increased incidence of CLDP (Ikegami *et al.* 2000). Therefore, ventilator strategies allowing for increases in PCO_2 (permissive hypercapnia) are being emphasized to ameliorate the consequences of inflammatory-mediated lung injury induced by mechanical ventilation (Mariani *et al.* 1999). However, Lang *et al.* (2000) found out that hypercapnia modifies nitric oxide-dependent pathway and increases nitric oxide (NO) production, nitric oxide synthase (NOS) activity, and cell 3-nitrotyrosine content. These results have revealed the impact of hypercapnia on tissue inflammatory reactions and potential detrimental influences to the alveolar epithelial cells (Lang *et al.* 2000). On the other hand, hypercapnia was shown to attenuate the effects of hypoxia-induced radical tissue damage (Herget *et al.* 2001). Inflation of the lung to the volumes that approach or exceed total lung capacity or inflation from lung volumes below a normal functional residual capacity results in lung injury and the appearance of pro-inflammatory cytokines (Carlton *et al.* 1997, Dreyfuss and Saumon 1998).

Recently published results of experimental and clinical studies suggest that surfactant treatment before initiation of ventilation, together with the new ventilatory strategies employed, and the appropriate tidal volume (VT) keep the lung open and minimize lung injury (Spragg and Smith 1997, Ikegami *et al.* 2000, Gerstmann *et al.* 2001). None of hitherto published clinical trials has confirmed the elective early use of HFOV as a superior method to the conventional mode of ventilation in respect of ALI prevention in the VLBW/ELBW infants.

Oxidative Stress and Inflammation

Oxidative stress and formation of reactive oxygen species

Deficiencies of the antioxidant system and increased ROS production are serious in the fetus and newborns, since their rapidly growing structures are sensitive to uncontrolled oxidative stress which produces severe tissue compromise. The fetus has a lower antioxidant capacity than babies and adults. Free radical scavenger enzyme activities and many other components of the antioxidant system are low. Therefore, the preterm newborn infants are highly susceptible to oxidative tissue damage by ROS (Bracci 1997, 1998). ROS have been implicated in the pathophysiology of acute as well as chronic lung injury (Saugstad 1990).

Table 1. Modes of mechanical ventilation used in preterm infants. The most frequently used modes of mechanical ventilation in the VLBW/ELBW infants are PTV or HFOV. The major problems related to the mechanical ventilation in the preterm neonates are "re-collapse/re-expansion mechanism", barotrauma (excessive pressure), volutrauma (excessive volume), surfactant perturbation, and adverse effect on pulmonary and cerebral circulation.

I. CONVENTIONAL MECHANICAL VENTILATION (CMV) :
The volume of gas entering the lung over time is a function of the peak inflation pressure (PIP), duration of inspiration (Ti), and respiratory system compliance (Crs) and resistance (Rrs). Most frequently used modes of CMV are:

- *Intermittent Mandatory Ventilation (IMV, IPPV) :* - a non-synchronized mode which combines a fixed amount of mechanical ventilation, predetermined by the clinician, with the patient's own spontaneous breathing.
- *Patient-Triggered Ventilation (PTV):* - a synchronized mode of CMV in which the patient is able to initiate ventilator breaths. This technology achieves a greater degree of synchrony between the infant's breathing and ventilator.

Examples: a) *Synchronized Intermittent Mandatory Ventilation* (SIMV, a single triggered breath is given in equal windows of time, with the other patient breaths in each window not assisted). b) *Assist/Control mode* (A/C, all breaths are triggered so that the patient controls the ventilator rate).

II. HIGH-FREQUENCY VENTILATION (HFV):
HFV refers to respirator rates between 150-300 breaths/min and low tidal volume. Three major types of HFV used in the neonates: HF jet ventilation (HFJT), HF oscillatory ventilation (HFOV, most frequently used), and HF flow interruptor ventilation (HFIV).

The main mechanisms of oxidative lung injury in the premature infants are lipid peroxidation (Bracci 1997) with increased production of organic hydroperoxides and malondialdehyde (Rogers *et al.* 1998), and disturbance of membrane function in the cells (Bracci 1997). Oxidative stress can act through these mechanisms causing the development of chronic lung disease of prematurity or bronchopulmonary dysplasia (Lindeman *et al.* 1989, Bracci 1997). High concentrations of inspired oxygen have been found to be associated with an increased lipid peroxidation (Bracci 1997, Repine *et al.* 1997, Nycyk *et al.* 1998). Ischemia-reperfusion and hypoxanthine-xanthine oxidase reactions have also been demonstrated to cause free radical release in the lung (Tan *et al.* 1993, Rootwelt *et al.* 1995, Zoban *et al.* 1998) (Fig. 1). Other pathways of ROS generation include metabolism of catecholamines, arachidonic acid cascade, and mitochondrial metabolism (Bracci 1997, 1998). However, the main source of free radicals in the lungs seems to be phagocyte activation (Delacourt *et al.* 1996, Pittet *et al.* 1997). The increase in phagocyte number and interleukin concentration in bronchoalvelolar fluid obtained from premature infants with chronic lung disease indicate that oxygen toxicity and inflammation are involved in the development of lung injury (Groneck *et al.* 1993, Bracci 1997). The early detection of phagocyte activation and free radical release in the respiratory tract of preterm infants suggest that oxidative damage may occur during the first hours of life (Bracci 1997).

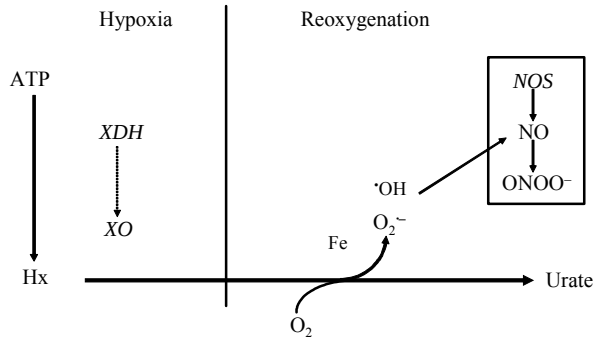

Fig. 1. *Hypoxia-reoxygenation mechanism. Hx – hypoxanthine, XDH – xanthine dehydrogenase, XO – xanthine oxidase, NOS – nitric oxide synthase, NO – nitric oxide, $ONOO^-$ – peroxynitrite radical.*

Great advances in our understanding of toxic oxygen species and free radicals were made namely during the two last decades of the 20th century. Oxygen toxicity may have fundamental consequences in the case of excess of reactive oxygen species (ROS) with respect to the detoxification capacity of the immature organism

(Delacourt *et al.* 1996, Bracci 1998, Zoban *et al.* 1998). The balance between ROS production and the antioxidant system is affected by many factors, since ROS are normally released in the human organism (Saugstad 1990, Zoban and Tomášová 1994). The main reactive oxygen metabolites are shown in Table 2. Superoxide anion formation from oxygen is the first step of the metabolic pathways producing ROS. O_2^- is generated primarily by mitochondrial metabolism, molybdenum hydroxylase (xanthine, sulfite, and aldehyde oxidases) reactions, arachidonic acid metabolism, and NADPH oxidase-dependent processes in phagocytic cells (Delacourt *et al.* 1996, Repine *et al.* 1997, Fellman and Raivio 1997). Reaction of O_2^- and H_2O_2 in the presence of transition metal (usually ferrous iron Fe^{2+}, so-called Haber-Weiss or Fenton reactions), produces ·OH. When catalyzed by neutrophil myeloperoxidase (MPO), H_2O_2 and chloride form hypochlorous acid (HOCl). H_2O_2 gains significance as a central precursor to both ·OH and HOCl (Fig. 2) (Repine *et al.* 1997). Increased H_2O_2 levels in exhaled gas and in urine were found in the patients with acute lung injury, including preterm infants (Pittet *et al.* 1997, Nycyk *et al.* 1998).

Table 2. Main reactive metabolites of oxygen

Superoxide radical	[O_2^-]
Hydrogen peroxide	[H_2O_2]
Hydroxyl radical	[·OH]
Singlet oxygen	[$^1O_2$]
Lipid peroxide	[LOOH]
Lipid peroxyl	[LOO^-]
Phenoxyl radical	[C_6H_5O·]
Nitric oxide	[NO]
Nitric oxide radical	[NO·]

Many of proinflammatory cytokines (TNF-α, IL-1, IL-6) can increase the expression of inducible nitric oxide synthase (iNOS) in a variety of cell types (Vyas *et al.* 1999). NO is formed by the iNOS from L-arginine and it has a short half-life of less than 1 sec in blood. The oxidation reactions of NO are complex and involve nitrogen in many different oxidation states (Vyas *et al.* 1999, Finner 1997). NO combines extremely rapidly with O_2^- to produce peroxynitrite. This reaction occurs preferentially to that of superoxide inactivation by superoxide dismutase (SOD) (Hallman 1997). Peroxynitrite, an unstable product, rapidly nitrates tyrosine residues to form nitrotyrosine (Saugstad 1996). Nitrotyrosine has been used as a marker of the presence of peroxynitrite in many inflammatory disorders including chronic lung disease of the newborn infants (Halmann 1997, Vyas *et al.* 1999). Plasma 3-nitrotyrosine content is increased during the first month of life in preterm infants who subsequently develop broncho-pulmonary dysplasia (Banks *et al.* 1998). It is recognized, that oxygen-rich environment inside the lung may predispose NO toward toxicity (Finner 1997, Moya *et al.* 2001). Hyperoxia, to which preterm newborn infants who progress to chronic lung disease are exposed, can increase the production of nitrate and nitrite in the lungs of animals (Arkowitz *et al.* 1997).

Reduced iron acts as a prooxidant and iron-induced formation of ROS, namely ·OH release (Bracci 1998), may play an important role in the pathogenesis of "oxygen radical disease of prematurity" including lung tissue injury (Lindeman *et al.* 1992). Silvers *et al.* (1998) reported that the frequent blood transfusions over the first week of life in very premature infants are associated with an increased risk of developing chronic lung injury. Hirano *et al.* (2001) found that plasma non-transferrin bound iron was significantly increased in preterm infants after blood transfusion and existed partly in the ferrous form, because of the low ferroxidase activity and the reduction of ferric iron by ascorbic acid. This finding was specific to preterm infants and was not observed in full-term infants after blood transfusion.

The pulmonary enzymatic and non-enzymatic antioxidant systems are on the other side of the oxidative balance. As mentioned above, the very premature infants have low antioxidant capacity. The major enzymatic antioxidants are SOD, which degrades O_2^-, and catalase and the glutathione (GSH) redox system, which inactivates H_2O_2 and hydroxyperoxides (Fig. 2).

Three forms of SOD participate in preventing of oxidative stress: Mn SOD located in mitochondria, Cu-Zn SOD in the cytoplasm, and extracellular SOD, which is in the lines of blood vessels. Extracellular SOD may modulate reactions of NO in the circulation by preventing reactions between O_2^- and NO·. Secretion of active enzyme into the extracellular compartment increases with age (Nozik-Grayck *et al.* 2000). The recombinant Cu-Zn SOD was successfully used in very preterm infants on ventilator to prevent neonatal lung injury induced by ROS (Rosenfeld *et al.* 1996), but this method needs further clinical evaluations. Another important element is glutathione (GSH), which is a water-soluble, low-

molecular-weight tripeptide (γ-glutamyl-cysteinyl glycine), that is present in high concentrations in each cell (Zoban *et al.* 2002). GSH forms the disulphide non-radical product, i.e. oxidized glutathione (GSSH). In contrast, GSSH is either exported from the cell or converted to GSH by a reductase reaction that obtains electrons from NADPH (Fig. 2).

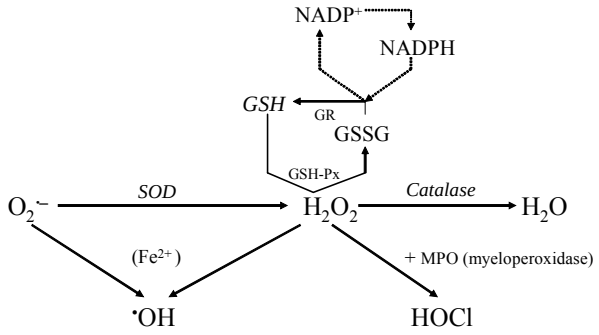

Fig. 2. *Reactive oxygen species and antioxidants. GSH – reduced glutathione, GSSG – oxidized glutathione, GR – glutathione reductase, GSH-Px – glutathione peroxidase, MPO – myeloperoxidase, HOCl – hypochlorous acid.*

The non-enzymatic system is represented mainly by vitamin E, β-carotene, vitamin C, uric acid, flavonoids, and bilirubin (Lindeman *et al.* 1992, Repine *et al.* 1997, Zoban *et al.* 1998). Vitamin E, a major antioxidant factor, is known to be low in the plasma of the prematurely born infants (Fritsma 1983, Zoban and Tomášová 1994, Bracci 1998). The role of vitamin A is discussed as additive to the vitamin E and other non-enzymatic antioxidants. Preterm infants have low vitamin A status at birth and this is associated with increased risk of developing chronic lung disease (Darlow and Graham 2000). It seems that vitamin A is necessary for normal lung growth and the ongoing integrity of epithelial cells in the respiratory tract and that its supplementation has an antioxidant effect (Schwarz *et al.* 1997, Darlow and Graham 2000). Plasma uric acid may play an important role in attenuating the oxidant-mediated tissue damage caused by xanthine oxidase released into the circulation during ischemia-reperfusion (Tan *et al.* 1993). The role of bilirubin, as the component of the body´s natural defense against the toxic oxygen radicals, remains unclear. *In vitro* bilirubin acts as the potent scavenger, but the results obtained from *in vivo* studies remain controversial (McDonagh 1990, Belanger *et al.* 1997). Other substances taking part in the defense against ROS are ceruloplasmin (ferroxidase) and transferrin that oxidize and bind iron, and thus synergistically prevent ·OH production. Nevertheless, the neonates have low ceruloplasmin and transferrin concentrations (Lindeman *et al.* 1992).

Inflammation and its contribution to acute lung injury

Intense alveolar inflammation with accumulation of complement fragments, cytokines, and oxidants in the air spaces may cause rapid stimulation and degranulation of neutrophils as they migrate into air spaces, resulting in relatively rapid loss of function. Neutrophils can cause damage to the lung at least by two potential mechanisms: the release of proteases and the production of ROS (Pittet *et al.* 1997, Repine *et al.* 1997).

The major protease released by neutrophils in ALI is the elastase stored in the primary granules of these cells. High concentrations of functional neutrophil elastase have been measured in bronchoalveolar lavage fluid of patients with ALI, and correlated with the severity of lung injury (Pittet *et al.* 1997, Tomášová *et al.* 1998). The elastase appears to be inactivated by complex formation with α1-antitrypsin and α2-macroglobulin (Griese *et al.* 1998). Free neutrophil elastase can damage air spaces by degrading elastin, and variety of extracellular membrane proteins, proteoglycans, and glycoproteins. Elastase can also stimulate inflammation by increasing interleukin-8 synthesis, impair healing by inactivating cytokines and growth factors, and produce surfactant abnormalities by cleaving surfactant apoproteins. Additionally, elastase can activate or inactivate various other serpins, inhibitors of neutrophil collagenase, and secretory leukoprotease proteinase inhibitor (SLPI), an inhibitor of neutrophil elastase, and in that way further modulate inflammation (Griese *et al.* 1998).

Matrix metalloproteinases (MMPs) are a family of endoproteinases that act in the degradation of extracellular matrix and basement membranes (Cederqvist *et al.* 2001). MMPs are secreted in latent proenzyme form and activated in the extracellular space and on the cell surface by oxidants and serine proteinases and by autocatalytic cleavage. The major local inhibitors of MMPs are tissue inhibitors of metalloproteinases (TIMPs) (Cederqvist *et al.* 2001, Sweet *et al.* 2001). MMP-1 and MMP-8 (neutrophil-derived collagenase or collagenase-2) degrades preferentially interstitial collagen type I. MMP-2 and MMP-9, also called type IV collagenases or gelatinases A and B, degrade basement membrane structures (Cederqvist *et al.* 2001). MMP-9 is

released by activated neutrophils. Elevated MMP-9 levels have recently been reported in bronchoalveolar lavage fluid from patients with acute respiratory distress syndrome. In rat model of acute hyperoxic lung injury, increased MMP-2 and MMP-9 expression was observed in lung interstitium and alveolar epithelium, suggesting that these enzymes may contribute to the pathogenesis of lung damage (Cederqvist *et al.* 2001, Sweet *et al.* 2001).

Cytokines are a diverse group of many different biologically active proteins, many of which are thought to contribute to the pathogenesis of ALI by increasing the production of substances that promote local or systemic inflammatory processes. Among them, the most important and most studied in respect to the development of ALI are the early response cytokines, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), and the potent neutrophil activating cytokine, interleukin-8 (Pittet *et al.* 1997). Inflammatory processes are further facilitated by platelet activating factor (PAF) and metabolites of arachidonic acid. PAF is a potent phospholipid mediator, which increases cell adhesion and activates endothelial cells by direct effect or through formation of toxic ROS and arachidonic acid metabolites. PAF also interacts with cytokines resulting in an amplification of the inflammatory response (Pittet *et al.* 1997). Leukotrienes are 5-lipooxygenase products of arachidonic acid that are formed when arachidonic acid is released from the plasma membrane by phospholipase A2. One of the most potent leukotrienes, leukotriene B_4 may promote the influx of neutrophils into the air spaces, and sulfidopeptide leukotrienes may be important mediators of hypoxemia, permeability edema, and reduced pulmonary compliance observed in the patients with ALI syndrome (Henderson 1994).

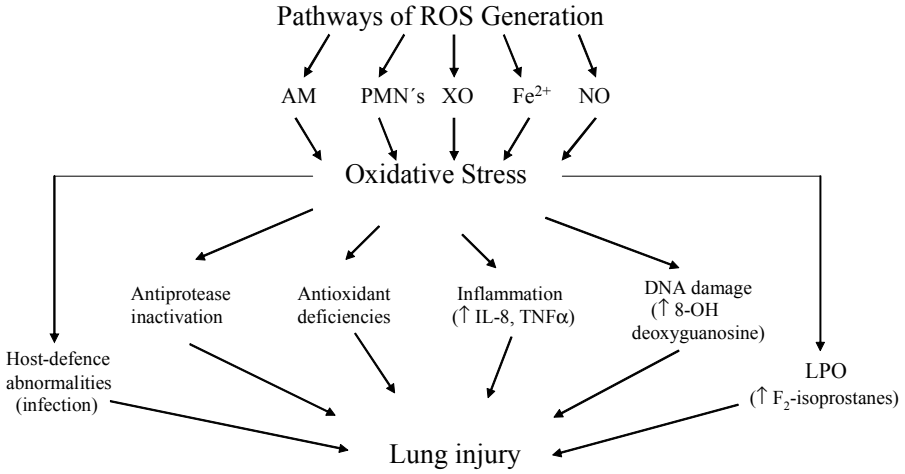

Fig. 3. *Oxidative stress and lung injury. AM – alveolar macrophages, PNM´s – polymorphonuclear leukocytes, XO – xanthine oxidase, LPO – lipid peroxidation.*

Thus, it is the inflammation accompanied with toxic effect of ROS, which closes the vicious circle in the pathogenesis of acute lung injury in the VLBW/ELBW infants treated with mechanical ventilation (Fig. 3).

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Reprint requests

Petr Zoban, MD, Department of Neonatology, Second Faculty of Medicine, Charles University, University Hospital Motol, V úvalu 84, 150 06 Prague 5, Czech Republic, e-mail: petr.zoban@lfmotol.cuni.cz