Nitric oxide and hyperoxic acute lung injury

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Abstract

Hyperoxic acute lung injury (HALI) refers to the damage to the lungs secondary to exposure to elevated oxygen partial pressure. HALI has been a concern in clinical practice with the development of deep diving and the use of normobaric as well as hyperbaric oxygen in clinical practice. Although the pathogenesis of HALI has been extensively studied, the findings are still controversial. Nitric oxide (NO) is an intercellular messenger and has been considered as a signaling molecule involved in many physiological and pathological processes. Although the role of NO in the occurrence and development of pulmonary diseases including HALI has been extensively studied, the findings on the role of NO in HALI are conflicting. Moreover, inhalation of NO has been approved as a therapeutic strategy for several diseases. In this paper, we briefly summarize the role of NO in the pathogenesis of HALI and the therapeutic potential of inhaled NO in HALI.

Key words: hyperoxic acute lung injury; hyperoxia; nitric oxide; nitric oxide synthase; reactive oxygen species; reactive nitrogen species; inhaled nitric oxide; nitro-L-arginine methyl ester

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Introduction

It is well known that oxygen is indispensable for human life. In clinical practice, oxygen therapy is also one of the main supportive modalities for the diseases with presentations of hypoxemia. However, oxygen also has affinity for electrons and may cause damage to cells and tissues, especially in the presence of endogenous organometallic coordination compounds that can catalyze the incomplete reduction of oxygen (Allen et al., 2009). If the body is exposed to oxygen partial pressure (pO_2) at a level higher than normal atmosphere for enough time, the defenses may be compromised, and oxygen toxicity will occur (Allen et al., 2009; Thomson and Paton, 2014). This concern increases with the development of deep diving and the use of normobaric [pO_2 = 1 atmosphere absolute (ATA); 1 ATA = 100 kPa] as well as hyperbaric oxygen (pO_2 > 1 ATA) in clinical practice (Hu et al., 2015; Stoller, 2015). Usually, oxygen at elevated partial pressure may cause damage to the central nervous system (CNS) (Hampson and Atik, 2003), respiratory system (especially the lung) (Kallet and Matthay, 2013) and eyes (Nichols and Lambertsen, 1969). Of them, the hyperoxic acute lung injury (HALI) is more common in clinical practice.

Currently, available studies (Lv et al., 2014; Weaver and Liu, 2015) have indicated the pathogenesis of HALI is complex, involving reactive oxygen species (ROS)/reactive nitrogen species (RNS), inflammation, cell apoptosis, autophagy. Nitric oxide (NO) is an important component of RNS and plays an important role in the pathogenesis of HALI. Although the roles of NO and its synthetases in the pathogenesis of HALI have been investigated extensively, the available findings are still controversial. In addition,

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exogenous NO (inhaled NO, iNO) has been also used in the treatment of HALI in premature infants (Ballard et al., 2006b). Herein, we briefly summarize the role of NO in HALI.

Introduction of NO

NO is also known as the endothelium-derived relaxing factor and has been found as an omnipresent intercellular messenger in all vertebrates and a signaling molecule that is involved in a variety of physiological and pathological processes (Fu et al., 2014). The biological production of NO in the body is also crucial for the non-specific host defense (Culotta and Koshland, 1992; Pacher et al., 2007).

Endogenously NO is biosynthesized from L-arginine, oxygen, and NADPH in the catalysis of nitric oxide synthases (NOS) (Pacher et al., 2007; Bogdan, 2015). To date, three isoforms of NOS have been identified. Neuronal NOS (nNOS) is formed constitutively in the central and peripheral nervous systems (Li et al., 2014), and its activity is calcium dependent. The other constitutive isoform of NOS, endothelial NOS (eNOS), is also calcium dependent and is expressed constitutively by a variety of cells, including the pulmonary vascular endothelial cells (Pacher et al., 2007). The tonic production of NO by eNOS is important for the maintenance of blood flow in some organs such as the heart, lung, liver and kidneys (Culotta and Koshland, 1992). In addition, NO derived from eNOS is able to regulate the platelet and neutrophil adhesion and activation (Culotta and Koshland, 1992). The third isoform of NOS is inducible NOS (iNOS) that is calcium-independent. iNOS activity is induced by a variety of pro-inflammatory cytokines both *in vivo* and *in vitro*, including tumor necrosis factor (TNF), interferon (IFN) gamma and interleukin-1 (IL-1) (Pacher et al., 2007; Liu et al., 2014; Bogdan, 2015). iNOS expression/activity is also induced both *in vivo* and *in vitro* by administration of bacterial endotoxin (lipopolysaccharide, LPS) (Bogdan, 2015). However, the regulation of iNOS expression varies with the specific cell type or animal model studied.

All the NOS isoforms are constitutively expressed in human airways. eNOS is constitutively expressed in human bronchial epithelial cells as well as type II human alveolar epithelial cells (Shaul et al., 1994), and abundant eNOS immunoreactivity was found in endothelial cells of pulmonary blood vessels. *In situ* hybridization and immunohistochemistry show iNOS is expressed in airway epithelial cells of resected lung tissues and specimens obtained bronchoscopically (Kobzik et al., 1993; Guo et al., 1995). Although the activated macrophages can express iNOS, alveolar macrophages appear to have little or no basal iNOS expression (Guo et al., 2000; Lane et al., 2004). Immunohistochemistry for nNOS has localized it to nerves of the inhibitory nonadrenergic noncholinergic system in the airway smooth muscle (Ward et al., 1995) and the submucosa (Kobzik et al., 1993). Immunohistochemically, extraneuronal nNOS is described in the airway epithelium (Ricciardolo et al., 2001) and endothelium (Luhrs et al., 2002).

Biological activities of NO

The major signal transduction mechanism of NO has been ascribed to the production of cyclic guanosinc monophosphate (cGMP) by guanylate cyclase (Pacher et al., 2007). NO is a small hydrophobic molecule and can cross cell membranes without the help of channels or receptors. NO can diffuse into surrounding cells and then activate soluble guanylate cyclase in the target tissues leading to the production of cGMP. In turn, cGMP activates cGMP dependent kinases in the target tissues, which may modulate the intracellular calcium levels and regulate a variety of diverse activities in the target tissues.

NO is a potent oxidant or a free radical, and many of its potentially toxic effects are more likely mediated by its oxidation products rather than NO itself. NO can react with superoxide anion to form the potent oxidant peroxynitrite ($ONOO^-$). $ONOO^-$ production has been demonstrated in the lungs of rodents exposed to prolonged hyperoxia (Haddad et al., 1994).

NO is a critical mediator of vasodilation. The regulation of extracellular fluid homeostasis and the control of blood flow and blood pressure are largely dependent on the vasodilatory actions of NO (Bredt, 1999). The vasodilatatory effect of NO is also crucial for the development and maintenance of penile erection, which is the biological basis of sildenafil (Viagra), which acts to inhibit the phosphodiesterase type 5 to lower the cGMP concentration by converting it back to GMP (Burnett, 2008).

NO and other RNS can react with structural elements, components of the replication machinery, nucleic acids, metabolic enzymes, or with virulence-associated molecules of infectious pathogens, which is the basis for their direct anti-viral or anti-microbial effects (Pacher et al., 2007). In addition, NO is crucial for the T and B cell differentiation, and tumor defense (Bogdan, 2015).

NO also serves as a neurotransmitter between nerve cells. As an important nonadrenergic noncholinergic neurotransmitter, NO may also cause the relaxation of the gastrointestinal smooth muscle (Bult et al., 1990).

Under physiological conditions, endogenous NO may tonically suppress the microvascular permeability in the airway mucosa, but it is unlikely that NO is a significant endogenous regulator of basal airway tone. In contrast, NO is crucial in the regulation of airway responsiveness

(Redington, 2006). In addition, NO is also involved in the lung inflammation, but the available findings on this issue are still controversial, which may be ascribed to the use of the relative selectivity of the different NOS inhibitors (Redington, 2006).

NO AND LUNG DISEASES

iNOS has been considered as the principal NOS isoform and a therapeutic target in lung diseases, but increasing evidence suggests its role of the "constitutive" NOS isoforms in airways diseases (Barnes, 1995). Findings have shown that nNOS is involved in the development of allergen-induced hyper-responsiveness and that eNOS may regulate the microvascular permeability in inflammation, but further exploration is warranted (Redington, 2006). Studies have described the relationships between the eNOS (Lee et al., 2000; Yanamandra et al., 2005) and nNOS (Grasemann et al., 1999) gene polymorphisms and the asthma phenotype. On the other hand, nNOS derived NO was found to inhibit the proliferation of human airway smooth muscle cells *in vitro* (Patel et al., 1999; Hamad and Knox, 2001) and chronic blockade of this activity might therefore deteriorate airway dysfunction *via* facilitating the hypertrophy and hyperplasia of airway smooth muscle (Redington and Howarth, 1997). Nitrotyrosine is a so-called footprint of nitrosative stress. In the study of Haddad et al. (1994), immunohistochemistry showed nitrotyrosine staining in the lung of acute respiratory distress syndrome (ARDS) patients but not patients with other conditions. Findings from the study of Sittipunt et al. (2001) showed the concentrations of nitrite and nitrate in the bronchoalveolar lavage fluid (BALF) were increased in ARDS patients and those at risk for the development of ARDS. Similar findings were also present in the study of Zhu et al. (2001), concentrations of nitrite and nitrate and nitrated pulmonary surfactant protein in the pulmonary edema fluid were higher in ARDS patients than in those with cardiogenic pulmonary edema. In 23 subjects with asthma, immunoreactive iNOS in airway epithelial cells of bronchoscopic biopsy specimens was found in 22 patients, but only 2 of 20 healthy non-smoking controls were positive for iNOS (Hamid et al., 1993). In untreated asthma patients, Redington et al. (2001) found both iNOS mRNA and protein expressions were increased. In contrast, the iNOS mRNA and protein expression was comparable between non-asthmatic controls and asthmatic subjects receiving regular maintenance treatment with inhaled corticosteroids. In resected peripheral lung tissues of patients with severe chronic obstructive pulmonary disease (COPD), alveolar macrophages, airway smooth muscle cells, and cells in the alveolar walls identified as type 2 pneumocytes were found to have iNOS expression in immunohistochemistry (Maestrelli et al., 2003) and more iNOS-positive type 2 pneumocytes were found in a control group of smokers without airflow obstruction. eNOS expression was also reported in alveolar macrophages from COPD patients (van Straaten et al., 1998). In rats with LPS induced lung injury, Arkovitz et al. (1996) found delayed treatment with two different isoform-selective iNOS inhibitors was able to alleviate acute lung injury.

NO AND HALI

The role of NO in the pathogenesis of HALI has been extensive studied in animal studies and cell experiments, but the findings are still controversial. In these studies, most focus on the role of iNOS and thus therapy of HALI is often performed targeting iNOS.

In adult rat type II pneumocytes, van Klaveren et al. (1998) found hyperoxia exposure increased iNOS mRNA production > 5 fold. Exposure to 100% oxygen for 12 hours may increase the iNOS mRNA by 2.5 folds in the airway epithelial cells from healthy volunteers (Comhair et al., 2000). In a study of Kondrikov et al. (2014), pulmonary artery endothelial cells were exposed to hyperoxia (95% O_2) for 48 hours, and the decrease in transendothelial electrical resistance (TEER) was found in two phases. In the first phase, the TEER started to decrease at 1 hour and reached the lowest at 3 hours after exposure initiation. In the second phase, the TEER began to decrease at 24 hours after hyperoxic exposure and an irreversible decrease was observed after 48-hour exposure, resulting in disruption of monolayer barrier integrity in two phases and apoptosis in the second phase. Moreover, they also found non-selective NOS inhibitor (N[G]-nitro-L-arginine methyl ester, NAME) attenuated the endothelial barrier disruption in both phases; $ONOO^-$ scavenger uric acid failed to affect the first phase but ameliorated the second phase of endothelial barrier disruption and apoptosis.

In animal studies, the change in NO production in the lungs is conflicting. In adult rats exposed to hyperoxia (for 60 hours), the nitrotyrosine staining exhibited a 2-fold increase as compared to controls (Haddad et al., 1994). Chang et al. (2001) also found hyperoxia significantly promoted NO generation *via* up-regulating iNOS and eNOS, which was also confirmed by the study of Potter et al. (1999). These suggest that excess production in NO following hyperoxia exposure is involved in the pathogenesis of HALI. In isolated perfused adult rabbit lungs exposed to 100% oxygen, supplement with L-arginine, a substrate for formation NO *via* NOS, was found to cause significant edema, which was attenuated by the addition of L-NAME (Nozik et al., 1995). The investigators proposed that H_2O_2 interacts with NO or one of its oxidized metabolites to result in HALI (Arkovitz et al., 1997). In the study of

Arkovitz et al. (1997), hyperoxia failed to increase serum NO, but resulted in a small but significant increase in NO production in the BALF. In addition, Zhang et al. (2010) reported that osteopontin was able to protect against HALI by inhibiting NOS (iNOS and eNOS) (**Table 1**).

However, supplement with the non-selective NOS inhibitor NAME is also found to worsen the injury, results in earlier death, decreases tolerance to hyperoxia and abolishes the beneficial effects of a treatment (Pierce et al., 1995; Capellier et al., 1996; Arkovitz et al., 1997; Radomski et al., 1998; Visser et al., 2010). Studies (Sopi et al., 2007; Visser et al., 2010; Ali et al., 2012) also indicate that cGMP decreased after hyperoxia exposure. Thus, some investigators attempt to administer sildenafil to protect the lung against HALI (Ladha et al., 2005; Czovek et al., 2014). In 2-week old rat pups, the ability of endogenous NO to regulate the constriction of central airways was impaired after exposure to $\geq 95\%$ O_2 for 4–6 days (Iben et al., 2000). Contrary to the isolated perfused adult rabbit lungs, studies have shown that hyperoxia up-regulates arginase expression and activity, and supplementation of L-arginine, L-citrulline or arginase blockade restored hyperoxia-induced impairment of relaxation (Sopi et al., 2007; Vadivel et al., 2010; Ali et al., 2012; Grisafi et al., 2012). Other studies also find that some treatments or preventive measures for HALI are able to increase NO production or bioavailability. Ahmed et al. (2011) found transient over-expression of extracellular superoxide dismutase maintained the NO bioavailability, which maintained the cGMP activity and reduced nuclear factor kappa B activation under oxidative stress. Prophylactic treatment with apelin was also found to improve the alveolarization and angiogenesis, increase lung cGMP, reduce pulmonary fibrin deposition, inflammation, and improve the lung morphology, but these beneficial effects were completely abolished in the presence of L-NAME (Visser et al., 2010).

Of note, in the study of Cucchiaro et al. (1999), exposure to 85% oxygen for 24 or 72 hours failed to increase the exhaled NO, exogenous infusion of L-arginine after hyperoxia did not increase the exhaled NO, and immunohistochemistry of the lung showed no nitrotyrosine after hyperoxia exposure. Thus, they concluded that NO was not synthesized in rats exposed to hyperoxia. In the study of Que et al. (1998), male Sprague-Dawley rats were exposed to 100% oxygen for 60 hours, and results showed NOS activity was unchanged and inducible NOS was not induced, but the level of nitrogen oxides (NOx) in the lung decreased by 67%. Potter et al. (1999) found blockade of NOS reduced cGMP in the lung of hyperoxic rat pups, but failed to reverse the pathologic consequences of hyperoxic exposure in these animals.

Of three isoforms of NOS, iNOS is the most extensively studied one in HALI, but there is controversy on the role of iNOS in the pathogenesis of HALI. Bhandari et al. (2012) found NOS2$^{-/-}$ mice manifested deteriorated alveolar-capillary protein leak and premature death. In the study of Kobayashi et al. (2001), the lung injury was more severe in NOS2$^{-/-}$ mice than in wild-type mice indicating the anti-inflammatory role of iNOS in HALI. However, in the study of Hesse et al. (2004), the lung injury was more severe in these mice after hyperoxia exposure as compared to iNOS knockout mice, suggesting the pro-inflammatory role of iNOS in HALI. On the above findings, it seems that iNOS has dual roles in the pathogenesis of HALI. Chang et al. (2001) found that hyperoxia significantly promoted NO generation, suggesting that endogenous NO may mediate the hyperoxic pulmonary damage; but over-stimulation of iNOS may lead to the pathogenesis of HALI. Thus, they proposed that NO may have dual roles in pulmonary oxygen toxicity. The dual role of iNOS was also found in the acute asbestos-induced lung injury (Dorger et al., 2002) (**Table 2**).

In animal studies, most confirm that hyperoxia exposure is able to increase iNOS protein and mRNA expression (Arkovitz et al., 1997; Radomski et al., 1998; Cucchiaro et al., 1999; Potter et al., 1999; Hesse et al., 2004). Radomski et al. (1998) found the activity of Ca^{2+}-independent NOS increased by 10 folds after hyperoxia exposure and remained significantly elevated after 14 days of exposure to hyperoxia in the lung of rats. Moreover, there was a time-dependent, biphasic expression (peak at 7 days) of iNOS in the lungs of hyperoxic rats. Thus, some investigators attempt to treat HALI or prevent HALI by targeting iNOS. Yuba et al. (2007) found ONO-1714 was able to attenuate HALI *via* inhibiting iNOS.

Of note, there is also evidence showing that iNOS seems is not crucial for the pathogenesis of HALI. Although the mice with hyperoxia exposure had a decreased amount of total surfactant, there was no significant difference between wild type mice and iNOS$^{-/-}$ mice after hyperoxia exposure for 48 hours (Bailey et al., 2002). Bhandari et al. (2012) also found survival was similar in newborn NOS2$^{+/+}$ and NOS2$^{-/-}$ mice.

The change in eNOS varies between studies. Steudel et al. (1999) found the expression and activity of both eNOS and iNOS increased in the adult rat lung following hyperoxia exposure, but Arkovitz et al. (1997) found hyperoxia had differential effects on the eNOS and iNOS and hyperoxia was able to decrease eNOS activity . The reduction in eNOS expression was also confirmed by the study of Lu et al. (2015). However, the study of Grisafi et al. (2012) showed eNOS expression increased in hypoxia-treated rats and L-citrulline further increased eNOS expression in the lung, accompanied by the improvement of lung

Table 1: Studies on the role of nitric oxide (NO) in the pathogenesis of hyperoxic acute lung injury (HALI)

Study	Animal/cells	Model	Results
Haddad et al. (1994)	Adult rats	Exposure to 100% O_2 for 60 hours	The nitrotyrosine staining exhibited a 2-fold increase as compared to controls
Nozik et al. (1995)	Isolated perfused rabbit lungs	Ventilation with 95% O_2	1.0 mM L-arginine caused significant pulmonary hypertension and edema, which was attenuated by the L-N[G]-nitro-L-arginine methyl ester (NAME)
Pierce et al. (1995)	Newborn rats	exposure to > 95% O_2	L-NAME was administered to pregnant rats for the final 7 days of gestation and during lactation. The survival rate of L-NAME treated pups when placed in > 95% O_2 at birth was significantly lower than controls from day 4 to 14. Fetal pulmonary artery vasoconstriction was induced by L-NAME
Capellier et al. (1996)	Adult rats	Exposure to > 99% O_2 for 36 hours	L-NAME resulted in earlier death. Haematocrit and bronchoalveolar lavage fluid (BALF) protein were also significantly increased in animals exposed to oxygen and receiving L-NAME. The lung water content was slightly decreased by L-NAME. L-NAME failed to affect thiobarbituric acid reactive substances in plasma and lung
Arkovitz et al. (1997)	Adult rats	Exposure to 95% O_2 for 3, 4, and 5 days	Hyperoxia did not increase serum NO production, but it resulted in a small and significant increase in NO production in the BALF which was not associated with an induction of whole lung inducible nitric oxide synthases (iNOS). Hyperoxia significantly decreased endothelial constitutive nitric oxide synthase activity. Administration of nitric oxide synthases (NOS) inhibitor worsened the injury
Que et al. (1998)	Adult rats	Exposure to 100% O_2 for 60 hours	Hyperoxia significantly increased lung arginase activity and expression, but the lung nitrogen oxides decreased by 67% after hyperoxia
Radomski et al. (1998)	3-day-old rat pups	Exposure to ≥ 95% O_2 for 7 and 14 days	L-NAME in hyperoxic animals reduced lung oedema and epithelial proliferation
van Klaveren et al. (1998)	Adult rat type II pneumocytes	Exposure to 60% or 85% O_2 for 48 hours	Exposure to 60% and 85% O_2 decreased nitrite production 2.9-fold and 3.9-fold
Potter et al. (1999)	Rat pups	Exposure to > 95% O_2 from day 21 to 29	Cyclic guanosinc monophosphate (cGMP) (NO activity) levels were elevated after hyperoxia exposure, which was attenuated after NOS blockade with either aminoguanidine (AG) or N-nitro-L-arginine (L-NNA). The hyperoxia-induced histologic changes were not altered by NOS blockade with AG or L-NNA
Iben et al. (2000)	13–15-day-old rat pups	Exposure to ≥ 95% O_2 for 4–6 days	Prior blockade of NOS significantly potentiated total lung resistance (RL) response in normoxic animals. The responses of RL to vagal stimulation were increased by hyperoxia, but the NOS blockade induced potentiation of contractile responses was abolished after hyperoxic exposure. NOS blockade potentiated the response of lung elastance in 13- to 15-day-old animals with or without hyperoxic exposure
Chang et al. (2001)	3-day-old preterm rats	≥ 90% O_2 for 3 or 7 days	Hyperoxia increased NO content in BALF. L-NAME worsened HALI in preterm rats and also had a deleterious effect on the rats exposed to air
Ladha et al. (2005)	Newborn rats	Exposure to 95% O_2	Sildenafil preserved alveolar growth and lung angiogenesis, and decreased pulmonary vascular resistance, right ventricular hypertrophy and medial wall thickness
Demchenko et al. (2007)	Adult rats	Exposure to ≥ 98% for 56 hours	Oxygen at 1 atmosphere absolute increased nitrogen oxides (NOx) and 3-nitrotyrosine in BALF progressively over 56 hours of exposure.
Sopi et al. (2007)	Rat pups	Exposure to ≥ 95% O_2 for 7 days	Hyperoxic exposure significantly reduced electrical field stimulation (EFS)-induced relaxation of lung parenchymal strips at 7 and 12 days but not 21 days. NO synthase blockade diminished relaxant responses in room air but not in hyperoxic pups at 12 days. L-arginine restored the relaxation response of hyperoxic strips. cGMP also decreased in strips from hyperoxic pups but was restored by L-arginine. Hyperoxia significantly increased arginase activity of lung parenchymal strips
Vadivel et al. (2010)	Newborn rats	Exposure to 95% O_2 from birth through postnatal day (P) 14	L-citrulline prevents HALI and pulmonary hypertension in newborn rats
Visser et al. (2010)	Neonatal rats	Exposure to 100% O_2	Prophylactic treatment with apelin improved HALI and increased lung cGMP levels, which were completely absent in the presence of L-NAME
Ahmed et al. (2011)	Neonatal rabbits	Exposure to 95% O_2 for 7 days	cGMP increased significantly in human extracellular superoxide dismutase-transfected neonatal rabbit lung tissues after hyperoxia exposure for 3 and 7 days
Ali et al. (2012)	Rat pups	Exposure to ≥ 50% O_2 for 7 days	In bethanechol-preconstricted lung parenchymal strips, hyperoxia significantly reduced relaxation, which was restored by L-arginine or arginase blockade. Expression and activity of arginase in airway epithelium were increased in response to hyperoxia but reduced by arginase Rat pups blockade. EFS-induced production of NO was decreased in hyperoxia-exposed airway smooth muscle and restored by arginase blockade
Grisafi et al. (2012)	Newborn rats	Exposure to 60% O_2 for 14 days	L-citrulline was effective to improve alveolar and vascular growth in oxygen-induced pulmonary damage
Czovek et al. (2014)	28-day-old rats	Exposure to > 95% for 72 hours	Sildenafil was able to protect the lung against hyperoxia-induced bronchial hyperreactivity *via* preserving normal end-expiratory lung volume, inhibiting airway inflammation and preserving the physiological lung structure
Kondrikov et al. (2014)	Pulmonary artery endothelial cells	Exposure to 95% O_2 for 48 hours	Hyperoxia caused the disruption of transendothelial electrical resistance (TEER) in two phases and the apoptosis in the second phase; NOS inhibitor attenuated the TEER disruption in both phases; Peroxynitrite scavenger uric acid did not affect the first phase but ameliorated the second phase of TEER disruption and apoptosis

Table 2: Studies on the role of inducible nitric oxide synthases (iNOS) and endothelial nitric oxide synthases (eNOS) in the pathogenesis of hyperoxic acute lung injury (HALI)

Study	Animal/cells	Model	Results
Que et al. (1998)	Adult rats	Exposure to 100% O_2 for 60 hours	Nitric oxide synthases (NOS) activity and iNOS remained unchanged after hyperoxia exposure
Radomski et al. (1998)	3-day-old rat pups	Exposure to ≥ 95% O_2 for 7 and 14 days	Hyperoxia caused a decrease in Ca^{2+}-dependent NOS activity, which was associated with increased eNOS protein expression. Hyperoxia caused 10-fold increase in the activity of Ca^{2+}-independent NOS which remained significantly elevated after 14-day exposure
van Klaveren et al. (1998)	Adult rat type II pneumocytes	Exposure to 60% or 85% O_2 for 48 hours	Exposure to 85% O_2 increased iNOS mRNA production 5.4-fold
Cucchiaro et al. (1999)	Adult rats	Exposure to 85% O_2 for 24 and 72 hours	Hyperoxia induced iNOS expression in the lung, but exhaled nitric oxide (eNO) was not elevated by hyperoxia and exogenous L-arginine after hyperoxia did not increase eNO. Nitrotyrosine was not found in the hyperoxic group after NO was scavenged by oxygen radicals to form peroxynitrite
Potter et al. (1999)	Rat pups	Exposure to > 95% O_2 from day 21 to 29	Hyperoxia significantly up-regulated the expression of iNOS and eNOS in inflammatory cells and epithelia in the lungs of preterm rats. Over-stimulation of iNOS contributes to the pathogenesis of HALI
Steudel et al. (1999)	Adult rats	Exposure to > 87% O_2 for 28 days	NOS (NOSII and NOSIII) expression and activity significantly increased in hyperoxia, and NOS III expression increased selectively in vascular endothelial cells, while both NOS isoforms were expressed by the pulmonary alveolar macrophages
Comhair et al. (2000)	Human airway epithelial cells from healthy volunteers	Exposure to 100% O_2 for 12 hours	Hyperoxia increased NOS2 mRNA in airway epithelial cells by 2.5-fold
Chang et al. (2001)	3-day-old preterm rats	≥ 90% O_2 for 3 or 7 days	Hyperoxia increased iNOS airway and alveolar epithelial cells. iNOS expression after 7-day exposure was stronger than after 3-day exposure. Shortly after 7-day exposure, stronger immunostaining for eNOS in airway epithelial was seen. L-N[G]-nitro-L-arginine methyl ester worsened HALI in preterm rats and also had a deleterious effect on the rats exposed to air
Kobayashi et al. (2001)	Adult mice	Exposure to > 98% O_2 for 72 hours	Lung injury was more severe in iNOS-deficient mice and associated with increased polymorphonuclear leukocytes in bronchoalveolar lavage fluid (BALF). iNOS mRNA expression increased in the lungs of wild-type hyperoxic mice. Nitrotyrosine was expressed in both wild-type and iNOS-deficient mice in hyperoxia
Bailey et al. (2002)	Adult mice	Exposure to > 90% O_2 for 48 hours	Hyperoxia decreased total surfactant, but there was no significant difference between wild-type and $iNOS^{-/-}$ mice
Hesse et al. (2004)	12–16 weeks old mice	60% O_2 or > 95% O_2 for 72 hours	Hyperoxia induced a significant increase in total cell count, protein concentration, lactate dehydrogenase activity, lipid peroxidation, and tumor necrosis factor-α concentration in the BALF as well as a higher binding activity of nuclear factor kappa B and activator protein-1 as compared to iNOS knockout mice
Yuba et al. (2007)	Adult mice	Exposure to > 98% O_2 for 72 hours	ONO markedly inhibited iNOS protein expression and nitrotyrosine production in lung homogenates and attenuated lung injury
Zhang et al. (2010)	Adult mice	Exposure to > 95% O_2 for 24-72 hours	Hyperoxia exposure significantly increased mRNA and protein expressions of iNOS and eNOS in osteopontin knockout mice than their matched wild-type mice
Bhandari et al. (2012)	Adult and newborn mice	Newborn mice exposed to 100% O_2 since PN1 with alternation in hyperoxia and room air every 24 hours; adult mice exposed to 100% O_2 for 60 hours	$NOS2^{-/-}$ animals manifest exaggerated alveolar-capillary protein leak and premature death. Survival was similar in adult $NOS3^{+/+}$ and $NOS3^{-/-}$ mice and NB $NOS2^{+/+}$ and $NOS2^{-/-}$ mice, respectively
Grisafi et al. (2012)	Newborn rats	Exposure to 60% O_2 for 14 days	Hyperoxia exposure increased eNOS protein expression and L-citrulline in combination with hyperoxia further increase eNOS protein expression
Saric et al. (2014)	Female and male CBA/H mice	Exposure to 95% O_2 for 48 hours	Hyperoxia significantly up-regulated eNOS protein expression in females, but not in males. However, eNOS mRNA expression increased significantly after hyperoxia exposure in both males and females. Females showed better survival, were resistance to hyperoxia and had more efficient defense systems
Lu et al. (2015)	Neonatal rats	Exposure to 85% O_2 for 28 days	Hyperoxia exposure led to low expression of eNOS. Inhaled nitric oxide and transplanted endothelial progenitor cells increased eNOS protein expression

injury, suggesting that eNOS is protective on HALI. Saric et al. (2014) found eNOS was significantly up-regulated in hyperoxia-exposed groups of both sexes, and difference between sexes was insignificant but eNOS protein level was significantly up-regulated in hyperoxia-exposed females, while in males the increase in eNOS protein did not reach significance due to a large variation among individual mice. The eNOS expression after hyperoxic exposure was also confirmed in the study of Potter et al. (1999), but the increase in eNOS was lower than in iNOS after hyperoxia exposure. Radomski et al. (1998) found hyperoxia increased the protein expression of eNOS in the lung after hyperoxia, and the eNOS expression reduced with the prolongation of hyperoxia exposure, but hyperoxia decreased Ca^{2+}-dependent NOS activity. However, Bhandari et al. (2012) found the survival was similar in adult $NOS3^{+/+}$ and $NOS3^{-/-}$ mice.

In acute pulmonary oxygen toxicity following hyperbaric oxygen exposure, Demchenko et al. (2007) proposed that extrapulmonary, neurogenic events predominated in the pathogenesis of lung injury, and nNOS activity drove the lung injury by regulating the output of central autonomic pathways.

TREATMENT OF HALI WITH EXOGENOUS NO

Low dose iNO has been approved by the US Food and Drug Administration (FDA) for the treatment of persistent pulmonary hypertension of the newborn (Ballard et al., 2006b) and this treatment is safe without adverse short or long term sequelae. The therapeutic use of iNO has expanded to older patients with congenital heart disease and ARDS. However, whether exogenous NO is protective or harmful is still unclear when it is administered in combination with hyperoxia (Rieger-Fackeldey and Hentschel, 2008).

Effects of iNO on HALI

In vivo, Turanlahti et al. (2000) found 6-hour exposure to NO at 40 ppm alone induced free radical-mediated lung injury, but 40 ppm NO in the presence of hyperoxia significantly attenuated free radical-mediated effects in the lungs compared to hyperoxia or 40 ppm NO alone. In the study of Nelin et al. (2003), NO at 100 ppm alone led to greater salicylate hydroxylation, but 100 ppm NO resulted in less salicylate hydroxylation than either did individually when it was administered during hyperoxia exposure; the production of hydrolytic radical ($OH^{\bullet}$) and/or $ONOO^{-}$ in the lung during iNO was dependent on the ratio of NO to oxygen (10 ppm and 100 ppm NO was used in this study in combination with oxygen at different concentrations). However, in the study of Youssef et al. (1999), iNO at 50 ppm did not improve HALI. In the study of Gries et al. (2000), NO exposure for 5 days alone had no noticeable respiratory effects and could not cause pulmonary dysfunction, but short-term exposure (≤ 5 days) to NO/O_2 was able to delay the onset of respiratory distress and neither deteriorated nor alleviated lung dysfunction as compared to oxygen exposure alone. In neonatal mice exposed to > 95% oxygen, the mortality occurred earlier in pups exposed to the mixture of > 95% oxygen and NO than in those with hyperoxia exposure alone (Stenger et al., 2010). The Ekekezie's group (Ehekezie et al., 2000a) found 5-day exposure to NO (50 ppm) significantly increased lung collagen content, but this effect appeared potentially reversible; in contrast, hyperoxia exposure with or without NO resulted in pulmonary matrix degradation and increased lung collagen content. The authors proposed that NO could potentially induce pulmonary fibrosis. In Fischer 344 rats, hyperoxia failed to induce significant injury to mitochondrial DNA (mtDNA), whereas iNO in the presence of hyperoxia (> 95% O_2) caused mtDNA damage in the lung, but the lesions were rapidly repaired during recovery, and the ratio of pulmonary mtDNA to genomic DNA was the same between treatment groups (Lightfoot et al., 2004). Couroucli et al. (2006) found newborn rats exposed to iNO at 40 ppm in the presence of hyperoxia were more susceptible to lung injury than rat pups exposed to hyperoxia alone or iNO alone, but animals with 20 ppm iNO exposure in the presence of hyperoxia did not elicit lung damage. This suggests that the effects of iNO on HALI are NO dose dependent. In the study of Garat et al. (1997), results suggested that, depending on its concentration, iNO could either reduce or increase the early consequences of HALI (10 ppm iNO attenuated the increases in thiobarbituric acid reactive substances (TBARS) and wet to dry lung weight ratio [Q_W/Q_D] of the lungs, did not affect the alveolar barrier impermeability to protein, and improved alveolar liquid clearance, but 100 ppm iNO had no effect on the increased TBARS and Q_W/Q_D but elevated vascular permeability to protein). ter Horst et al. (2007) also investigated the effects of iNO at different concentrations. Results showed, in the presence of 100% oxygen exposure, continuous exposure to NO at 8.5 and 17 ppm NO reduced fibrin deposition by 1.6-fold and 4.3-fold, respectively; the survival in 17-ppm NO group was prolonged as compared to animals with oxygen exposure alone; the reduction in pro-inflammatory cytokines after 17-ppm NO-O_2-exposure was more obvious than after 8.5-ppm NO-O_2-exposure; the histology was also improved after NO-O_2-exposure. In addition, iNO at 50 ppm alone was also found to decrease intracellular oxidant production, but iNO during hyperoxia did not impact lung neutrophil accumulation, instead increased lung apoptosis and prevented the increase in SOD and catalase activity during hyperoxia, potentially increasing injury (Ekekezie

et al., 2000b; Franek et al., 2002). Moreover, NO inhalation in combination with hyperoxia was found to alter the lung function in neonates, but it increased the lung vascular protein leakage (Storme et al., 1999). In fibroblasts, iNO in hyperoxic condition induced fibroblast cell death and DNA fragmentation (Raghuram et al., 1999).

Mechanisms underlying the protective effects of iNO on HALI

Although there is controversy on the protective effects of iNO on HALI, a majority of studies confirm that iNO may exert protective effects (improvement of pulmonary angiogenesis, lung alveolarization, distal lung growth and pulmonary function) on HALI *via* different mechanisms in rodents, pigs and primate (Rieger-Fackeldey and Hentschel, 2008).

Youssef et al. (1999) found 50 ppm of iNO reduced the expression of Na, K-ATPase which constituted a part of the cellular defense mechanism against oxygen toxicity (vascular permeability). iNO may also inhibit inflammation, reduce fibrin deposition (Lightfoot et al., 2004), nitrative stress (Stenger et al., 2010) and plasminogen activator inhibitor-1 (Chen et al., 2015), decrease leukocyte trafficking (Ekekezie et al., 2001; Rose et al., 2010), suppress cell apoptosis (Howlett et al., 1999), induce marked pulmonary vasodilatation (Mourani et al., 2004), elevate angiogenesis (Lin et al., 2005), improve lung volume (Ballard et al., 2006a) and restore distal lung growth (Lin et al., 2005).

iNO in hyperoxia was also found to improve the hyperoxia-induced surfactant abnormality in primates (Ballard et al., 2006a) and preterm rabbits (Issa et al., 1999), but this was not found in human alveolar type II cells (Johnston et al., 2010). Couroucli et al. (2006) proposed that the hyperxia induced expression of CYP1A1 was protective against HALI, and the maintenance of pulmonary CYP1A1 induction by 20 ppm iNO in the presence of hyperoxia was related to the protective effects of iNO on HALI in newborn rats, but Cotton et al. (2006) found the protective effects of iNO had no relationship with CYP activity in lambs exposed to > 95% O_2. In rat lungs, Gong et al found inhaled NO alleviated hyperoxia suppressed phosphatidylcholine synthesis in rats with endotoxin-induced injury (Gong et al., 2006), but the results of Hu's study (Hu et al., 2007) showed iNO attenuated hyperoxic injury without altering phosphatidylcholine synthesis.

Different uses of iNO

In the above studies, iNO is usually administered during the hyperoxia exposure, which implies that iNO is employed for the prevention of HALI. In a study of Waldow et al. (2008), they found pre-conditioning by inhaled NO (15 ppm, 10 minutes) was able to prevent hyperoxic and ischemia/reperfusion injury in adult rat lungs. In addition, Lu et al. (2015) investigated the protective effects of inhaled NO in combination with endothelial progenitor cells transplantation on HALI, and results showed this was able to improve lung alveolar and vascular structure in neonatal rats with prolonged hyperoxia exposure.

Although a lot studies have investigated the roles of NO and NOS in the pathogenesis of HALI, the available findings are still conflicting. This may be ascribed to the differences in the animal model, hyperoxia exposure protocol, time points of sample collection, methods used for the detections and the gender and age of animals used in experiments. In addition, in respect of iNO treatment of HALI, the dose of NO varies significantly and ranges from 5 ppm to 100 ppm in animal studies although the concentration of NO used in clinical practice has been determined, which may cause the discrepancy in the findings between studies. Thus, more studies are warranted to confirm the roles of NO and different iNOS in the pathogenesis of HALI and the therapeutic effects of iNO on HALI.

Author contributions

XJS designed this paper; KL and JZ collected literatures; PXZ, CHH, and WWL wrote the paper. All the authors approved the final version of the paper for publication.

Conflicts of interest

There is no conflict of interest in this paper.

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