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Place of Iron Chelators Like Desferrioxamine and Deferasirox in Management of Hyperoxia-induced Lung Injury; A Systematic Review

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Abstract: Supraphysiological concentrations of oxygen (hyperoxia) is necessary for treatment or prevention of hypoxemic condition, but hyperoxia through activation of oxidative stress pathways and generation of reactive oxygen species directly or indirectly result in lung injury and dysfunction. Many mediators are involved in the pathways to hyperoxic cell death seeming that transition metal ions especially iron promote the generation of the very reactive free radicals which are damaging to cells. Thus concerning the role of iron, a systematic review was conducted by reviewing all papers found from searching keywords of iron, lung injury, oxidative stress or hyperoxia in bibliography databases. Due to different pathways involved in hyperoxia-induced lung injury, several classes of drugs have been tested for example antioxidants, dexamethasone, pentoxifylline, erythropoietin, lisofylline, sildenafile, N-acetyl cysteine, or prostaglandine but some of them were not only successful but caused significant adverse effects. Findings indicate that metal ions especially iron through catalyzing of most reactive free radicals has a key role in oxidative stress process and hyperoxic condition and thus limitation of iron for prevention of hyperoxia-induced injury seems reasonable. Iron chelation has been recently used for conditions without iron overload such as neurodegenerative, infectious, reperfusion injury, cardioprotection. There are some evidences about positive effects of desferrioxamine alone or in combination when tested in animal models of lung injury or in human but they are not convincing. Further studies are necessary to clarify the importance of intervention with desferrioxamine or new long acting oral agent deferasirox and their risk/benefit in hyperoxia-induced lung injury.

Key words: Systematic review, iron chelator, hyperoxia-induced lung injury, oxidative stress, desferrioxamine, deferasirox

INTRODUCTION

High concentration of oxygen is essential for patients with hypoxic respiratory failure in intensive care unit, but prolonged exposure to oxygen cause tissue damage and lead to acute and chronic lung injury. Hyperoxia through direct oxygen toxicity and accumulation of inflammatory mediators within the lungs result in a process that initiate by damaging to pulmonary epithelium and endothelium and finally lead to pulmonary interstitial fibrosis (Ansari *et al*., 2008; Vazin *et al*., 2005a, b). Proliferation of type II alveolar epithelial cells, destruction of type I alveolar epithelial cell and pulmonary vascular remodeling are examples of changes in hyperoxic condition. No level of oxygen is safe indefinitely; studies of normal individuals exposed experimentally to 100% oxygen at normal pressure have shown evidence of tracheobronchitis and changes in vital capacity, diffusing capacity and lung permeability (Beckett and Wang, 1988; Davis *et al*., 1983). Inadvertent exposure of patients with normal lungs to prolonged hyperoxia resulted in clinical findings compatible with oxygen toxicity mainly through oxidative stress. Addition of hyperoxia to mechanical ventilation especially with high tidal volume augmented lung injury (Quinn *et al*., 2002). Different underlying mechanisms are involved in this process whereas oxidative stress is the major one that damage major macromolecules within cells resulting in cell apoptosis or death (Abdollahi *et al*., 2004). Concerning the importance of oxygen therapy, different drug classes have been tested for treatment or prevention of hyperoxia-induced lung injury specially by authors' team (Kajbaf *et al*., 2007; Mahmoodpoor *et al*., 2010; Mojtahedzadeh *et al*., 2008; Najafi *et al*., 2009; Salari *et al*., 2005a, b; Soltan-Sharifi *et al*., 2007; Vazin *et al*., 2005a, b).

Neutrophils and macrophages are two major sources of reactive oxygen and nitrogen species (ROS and RNS) in the lung. Two major enzyme systems NADPH oxidase (Babior *et al*., 2002; Chung-Wai *et al*., 2003) and nitric oxide synthases (Bogdan, 2001) are responsible for

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production of ROS or RNS especially superoxide anion, hydrogen peroxide and hydroxyl radical (Abdollahi *et al*., 2000a, b). Iron as a metal has especial role in production of hydroxyl radical, which can be explained in terms of following reactions (Lloyd *et al*., 1997):

$$Fe^{3+}+O_2^{-} \longrightarrow Fe^{2+}+O_2$$

$$Fe^{2+}+H_2O_2 \longrightarrow Fe^{3+}+OH^{0}+OH^{-} \text{ (Fention reaction)}$$

$$\text{Net: } O_2+H_2O_2 \xrightarrow{Fe} O_2+OH^{0}+OH^{-} \text{ (Haber-Weiss reaction)}$$

The overall reaction is called Haber-weiss reaction (Lloyd *et al*., 1997). Hydroxyl radical react at diffusion-limited rates with various biomolecules including lipids, proteins, DNA (Nelson and McCord, 1998) and lead to cell injury (Rezaie *at al*., 2007). So chelation of iron could be a critical event in preventing iron-mediated oxidative stress.

MATERIALS AND METHODS

In order to provide enough data about the subject, we did systematic search utilizing Pubmed, Scopus, Google scholar and Embase databases. The initial search terms were iron, lung injury, oxidative stress or hyperoxia to provide data about the role of iron in hyperoxia-induced lung injury. Then search was continued with hyperoxia, lung injury and treatment as keywords without narrowing or limiting search elements to find the most relevant literatures about the subject. References from each article were also evaluated for relevancy of inclusion in the study. All papers were reviewed to omit irrelevant or duplicate papers. Then their data were extracted into tables and summarized.

RESULTS

As summarized in Table 1, different drug classes have been used for treatment of hyperoxia-induced lung injury. Almost all of the studies were done in animal models, because of the limitation to simulate same clinical condition of high concentrations of oxygen (>95%) for long duration and problems for sampling and analyzing of lung tissue or even bronchoalveolar lavage fluid in human (Cross *et al*., 1994; Van der Vliet *et al*., 1999). Furthermore, due to different pathways involved in

Table 1: Animal studies considering hyperoxia-induced lung injury treatment

Study	Model	Drug	Dose/Duration	Conclusion
Lee *et al.* (2007)	Newborn rat pups	Recombinant human erythropoietin (rhEPO)	3 U g^{-1} i.p. at 4th,5th,6th postnatal day	Attenuation of lung injury by down modulating inflammatory responses
Ozer *et al.* (2005)	Neonatal rats	Recombinant human erythropoietin (rhEPO)	400 U kg^{-1} i.p. for 10 days	Low dose rhEPO improved lung morphology and cause less fibrosis
Ter Horst *et al.* (2004)	Preterm rat pups	Pentoxifylline	75 mg kg^{-1} twice daily s.c. for 10 days	Attenuation of alveolar fibrin deposition and increase of survival by reducing capillary-alveolar leakage
Naureckas *et al.* (1994)	Rats	Pentoxifylline	20 mg kg^{-1} twice daily i.p. 48h before exposure to 120 h	No effect on mortality or lung injury
Li *et al.* (2007)	Neonatal rats	Captopril	30 mg/kg/day between 7th and 21 day of hyperoxia	Alleviation of lung injury and fibrosis by captopril
George *et al.* (1999)	BALB/C mice	Lisofylline	100 mg kg^{-1} every 8h i.p. before exposure to hyperoxia for 72 h	Alleviation of lung injury by inhibition of proinflammatory cytokines
Pan *et al.* (2009)	Neonatal rats	Melatonin	4 mg kg^{-1} i.p. for 14 days	Improvement of oxidant/antioxidant imbalance in lung injury
Li *et al.* (2008)	Premature rats	Retinoic acid (RA)	Retinoic acid 500 mcg/kg/day i.p. for 14 days	Protective effect on lung injury by modulation of MAPKs pathway
Zimova-Herknerova *et al.* (2008)	Newborn BALB/c mice	Retinoic acid (RA)	Retinoic acid 500 mcg/kg/day i.p. for 7 days	Reduction of growth retardation and VEGF-A mRNA expression
Rehan *et al.* (2006)	Rat pups	Rosiglitazone	3 mg kg^{-1} i.p. for 24 h	Prevention of morphologic, molecular and immunohistochemical changes in lung injury
Du *et al.* (2006)	Neonatal rats	Inhaled Nitric oxide (NO)	10 ppm NO for 24 h	Alleviation of pathologic feature of lung injury by low dose NO
Radomski *et al.* (1998)	Rat pups	NG-L-nitro-L-arginine methyl ester (L-NAME)	L-NAME 10 mg/kg/day s.c. for 7 to 14 days	Worsening of hyperoxic lung injury, emphasizes of protective role of NO
Pagano *et al.* (2004)	C57BL/6 mice	Cyclosporine A (Cyc A)	25 mg/kg/day 3days before exposure to hyperoxia for 72 h	Decrease lung tissue and mitochondrial damage by Cyc A
Matthew *et al.* (2003)	Murine lung	Cyclosporine A (Cyc A)	50 mg/kg/day i.p. for 72h	Reversal of the hyperoxia-induced increase of one gene (AA125385) with Cyc A treatment has protective role in lung injury
Baba *et al.* (2007)	BALB/C mice	Keratinocyte growth factor gene (KGF)	Intratracheal KGF and then induction of hyperoxia for 72 h	Increase in expression of KGF result in increase of survival
Chang *et al.* (2003)	Fetal baboon	AEOL 10113 (Catalytic antioxidant metaloporphyrine)	Continuous i.v. infusion of for 10 days	Reduction of oxygen toxicity in prematurely born infant
Shim *et al.* (2008)	Rat pups	Endotoxin	Ecoli endotoxin at 1st, 3rd and 5th postnatal day intratrachealy	Improved of lung damage and fibrosis by endotoxin therapy

Table 1: Continued

Study	Model	Drug	Dose/Duration	Conclusion
Chang *et al.* (2009)	Neonatal rats	Alpha-phenyl N-tert-butylnitrone (PBN) (spin trapping agent)	100 mg/kg/day i.p. PBN for 14 days	Attenuation of lung injury by down regulation of inflammatory responses
Ballard *et al.* (2007)	Rat pups	Azithromycine	40 mg/kg/day s.c. for 14 days	Improvement of survival and less emphysematous change, decreased level of IL-6
Auten *et al.* (2001)	Newborn rats	Antineutrophil chemoattractant-1 (CINC-1)	1, 5 or 10 mcg i.p. antibodies against CINC-1 for 2 days	Preservation of alveolar development, maintenance ofnormal lung compliance and suppression of airway inflammation
Demir *et al.* (2008)	Newborns rat pups	Clarithromycin, Montelukast and Pentoxifylline	Each drug in combination or alone for10 days	Combination treatment is superior to placebo in treatment of lung injury
Town *et al.* (1993)	Preterm guinea pigs	Dexamethasone	10 mg/kg/day for 72 h	Blunting neutrophil influx and induction antioxidant effect, without effect on survival
Ramsay *et al.* (2000)	Adult male rats	Dexamethasone	1 mg/kg i.p. for 24 and 48 h	Increase of lung injury because of higher level of p-selectin mRNA expression
Langley and Kelly (1993)	Preterm guinea pigs	N- Acetyl Cysteine (NAC)	200 mg kg^{-1} twice daily i.p. for 72 h	Prevention of the increase in BAL fluid protein concentration, No effect on influx of neutrophils, partly effective
Van Klaveren *et al.* (1997)	Isolated rat type II cells	N- Acetyl Cysteine (NAC)	200 mg/kg/day i.p. from 3 day before exposure to end	Increase of adverse effect on lung epithelial cells
Rodriguez-Pierce *et al.* (1994)	Pregnant rats	Propylthiouracil (PTU)	0.015% in drinking water of timed pregnant rats to end of gestation and during lactation	Increase of survival significant decrease in intraalveolar edema and lipid peroxidation
Ghio *et al.* (1994)	Rats	Synthetic surfactant (Exosurf) Non-surface-active components tyloxapol and cetyl alcohol	Intratracheally instillation of saline, tyloxapol, tyloxapol plus cetyl alcohol, or artificial surfactant	Synthetic surfactant scavenges oxidants and protects against hyperoxic lung injury
De Visser *et al.* (2009)	Rat pups	Sildenafile	50-150 mg/kg /day s.c.	Prolonged median survival, reduction of fibrin deposition, improvement of alveolarization and angiogenesis
Ladha *et al.* (2005)	Rat pups	Sildenafil	100 mg/kg/day s.c. for 14 days	Prevention of alveolar growth, lung angiogenesis, decreased pulmonary vascular resistance,
Bryan *et al.* (1993)	Male rats	Allopurinol	Daily injection for 14 days	Decrease neutrophil alveolar response but has no effect on lung injury
Jenkinson *et al.* (1991)	Premature baboons	Allopurinol	10 mg/kg/day i.v. for 6 days	Significant changes in lung responses and antioxidant defenses compared with placebo
Kunig *et al.* (2005)	Neonatal rats	Recombinant human VEGF (rhVEGF)	rhVEGF-165 for 10 days	rhVEGF treatment during recovery enhanced vessel growth and alveolarization
Looney *et al.* (2009)	Neonatal rats	Activated protein C (APC)	APC by different routs	Failure to improvement of lung injury indices
Davis *et al.* (1993)	Piglets	Recombinant human superoxide dismutase (rhSOD)	5 mg kg^{-1} intratracheally before exposure to 48 h	Prophylactic rhSOD protected the lung by reducing the production of chemotactic mediators
Mikawa *et al.* (1995)	Male rabbits	Recombinant human superoxide dismutase (rhSOD)	10000 U/kg/day i.v. for 36 h	Prevention of hyperoxic lung injury by decreasing chemical mediators
Walther *et al.* (1995)	Premature rabbits	Antioxidant-surfactant liposomes	0.1 mL/15 g birth weight intratracheal injection for 24 h	Potentiating of lung antioxidant capacity in hyperoxia
Aslam *et al.* (2009)	Neonatal rats	Bone Marrow Stromal Cells (BMSC)	BMSC i.v. from day 4 till 14 days	Attenuation of lung injury via the release of immunomodulatory factor
Das *et al.* (1988)	Rabbits	Ibuprofen	Ibuprofen p.o for 4 days	Failure in prevention of lung injury
Hageman *et al.* (1989)	Adult rabbits	Prostaglandin E1 (PGE1)	0.1, 0.06 or .0.03 mcg/kg/min infusion of PGE1 for 65 h	Failure in prevention of lung injury
Berg (2006)	Rats	Zymosan	Zymosan 15 mg i.v. or i.p.	Protection of lung injury by decreasing proteinaceous pleural effusions
Obara *et al.* (1985)	Neonatal rats	Vitamin E (Vit E)	150 mg/kg Vit. E for 7 days	Preservation of pulmonary capillary endothelium from hyperoxia
Chakraborti *et al.* (1999)	Newborn guinea pig	Vitamin C (Vit C)	50 mg vitamin C/100 g body weight for 72 h	Direct antioxidant role in hyperoxic condition
Paine *et al.* (2003)	C57BL/6 mice	Granulocyte Macrophage Colony stimulating factor (GM-CSF)	9 mcg/kg/d GM-CSF for 4 days	Increase of survival by preservation of alveolar epithelial barrier function

MPO: i.p.: Intraperitonealy, s.c.: Subcutaneously, i.v.: Intravenous, p.o: Per oral, U:unit, mcg: Microgeram, ppm: Part per million, kg: Kilogeram, h: Hour, d: Day; SOD: Superoxide dismutase, CAT: Catalase, MAPK: Mitogen-activated protein kinasaes, VEGF: Vascular endothelial growth factor

hyperoxia-induced lung injury, each drug targeted a part of this system (Ahmad *et al*., 2006; Ciencewicki *et al*., 2008; Lee and Choi, 2003; Romashko *et al*., 2003; Sprong *et al*., 1991).

Prevention or declining of inflammatory responses and proinflammatory cytokine release such as interleukine 6 or tumor necrosis factor alpha and improvement in antioxidant defenses by increasing activity of antioxidant enzymes such as superoxide dismutase and catalase and also blockade of neutrophil influx are the major mechanisms found for prevention or treatment of oxidative-induced lung injury (Auten *et al*., 2001; Ballard *et al*., 2007; Chakraborti *et al*., 1999; Chang *et al*., 2003; Davis *et al*., 1993; George *et al*., 1999; Mikawa *et al*., 1995; Obara *et al*.,1985; Ozer *et al*., 2005; Rehan *et al*., 2006; Walther *et al*., 1995).

Other drugs result in improvement of pulmonary angiogenesis, vessel growth, alveolarization and decreasing pathological lung injury (Kunig *et al*., 2005; Ladha *et al*., 2005; Lee *et al*., 2007; Ozer *et al*., 2005). Pentoxifylline (Ter Horst *et al*., 2004), erythropoietin (Ozer *et al*., 2005), lisofylline (George *et al*., 1999) and sildenafile (De Visser *et al*., 2009) are examples of drug that attenuate alveolar fibrin deposition and result in increased survival of animals.

On the other hand some of the drugs especially some commonly used such as N-acetyl cysteine (Langley and Kelly, 1993; Van Klaveren *et al*., 1997), dexamethasone (Ramsay *et al*., 2000; Town *et al*., 1993) or prostaglandine (Hageman *et al*., 1989) have not been successful in treatment of hyperoxia-induced lung injury but even lead to some adverse effects on epithelial lung cells.

Alteration of pathways that lead to cell apoptosis such as mitogen-activated protein kinases (MAPKs) is another way that prevent lung damage (Hageman *et al*., 1989; Matthew *et al*., 2003; Paine *et al*., 2003; Reynolds *et al*., 2010; Veness-Meehan *et al*., 2000; Zimova-Herknerova *et al*., 2008)

DISCUSSION

Iron as a new target: Iron is uptaken into epithelial cells for sequestration within ferritin. Alveolar macrophages elevate ferritin production after exposure to iron. They posses cell surface receptors specific for both haptoglobin and hemopexin to facilitate their removal (Birgens *et al*., 1998; Van Snick *et al*., 1977). Divalent metal transporter 1 (DMT1), Natural resistance-associated macrophage (Nramp) 1,2, transferrin and lactoferrin pathways are involved in iron sequestration in macrophages (Cellier *et al*., 1995) but continuous exposure overwhelms the capacity of ferritin to sequester the metal and finally releases it (Fig. 1). Ferritin is composed of 24 subunits of heavy (21 KD) and light (19 KD) chains and can reserve up to 4500 atom of Fe^{3+} ion. H subunit has ferrioxidase activity converting ferric to ferrous forms to fight against oxidative stress. The ratio between H and L subunits differs in different tissue. Increased H-subunit is found in proliferating tissues (Emerit *et al*., 2001; Harrison and Arosio, 1996). Tumor Necrosis Factor-α and Interleukin-1 transcriptionally induce the H ferritin (Torti and Torti, 2002). Ferritin synthesis is regulated post transcriptionally via the interaction of an iron-regulatory protein (IRP 1 and 2) with Iron Responsive Element (IRE) (Eisenstein, 2000). IRP-1 is an iron-sulfur cluster protein that exists in two forms when iron is abundant. It exists as acytosolic aconitase and IRP-1 that losses its affinity for IRE. The mRNA of ferritin is translated and ferritin synthesis is increased. In the absence of iron, apo IRP-1 put on IRE and the mRNAs of TRF are stabilized and the translation of mRNA of ferritin is suppressed (Papanikolaou and Pantopoulos, 2005; Thomson *et al*., 1999). IRP-2 protein is abundant in iron insufficiency, but it degrades rapidly in iron excess through targeting of unique 73 amino acid sequence (Lavaute *et al*., 2001). Nitric oxide and H_2O_2 activate the IRP-1 through signaling mechanisms and thus mobilize iron from the 4 Fe-4S cubane cluster (Pantopoulos and Hentz, 1998). Down regulation of IRP activity could be a common response to increased formation of H_2O_2 and O_2^- (Pantarulo, 2005). Iron is imported into cells by transferrin and lactoferrin receptors. Transferrin level as a percentage of total protein in BAL fluid is very high (4-5.6%) compared with values for plasma (Mateos *et al*., 1998). Transferrin is produced and secreted at high levels in the lung seeming a major extracellular antioxidant in the lung. However, some of the iron carried by transferrin is not sequestered within ferritin, but rather, released into a catalytically active low molecular weight pool which allows the metal to catalyze ROS (Ghio, 2009).

Lactoferrin is structurally and functionally related to transferrin that comes mainly from the airway rather than alveolar region (Mateos *et al*., 1998), however its localization as sites at which an organism interacts with its environment e.g., secretary epithelium, suggests it plays a role in metal detoxification (Lyer and Lonnerdal, 1993).

Non Transferrin Bound Iron (NTBI) can be transported into cells via transferrin independent pathways and result in the activation of iron responsive

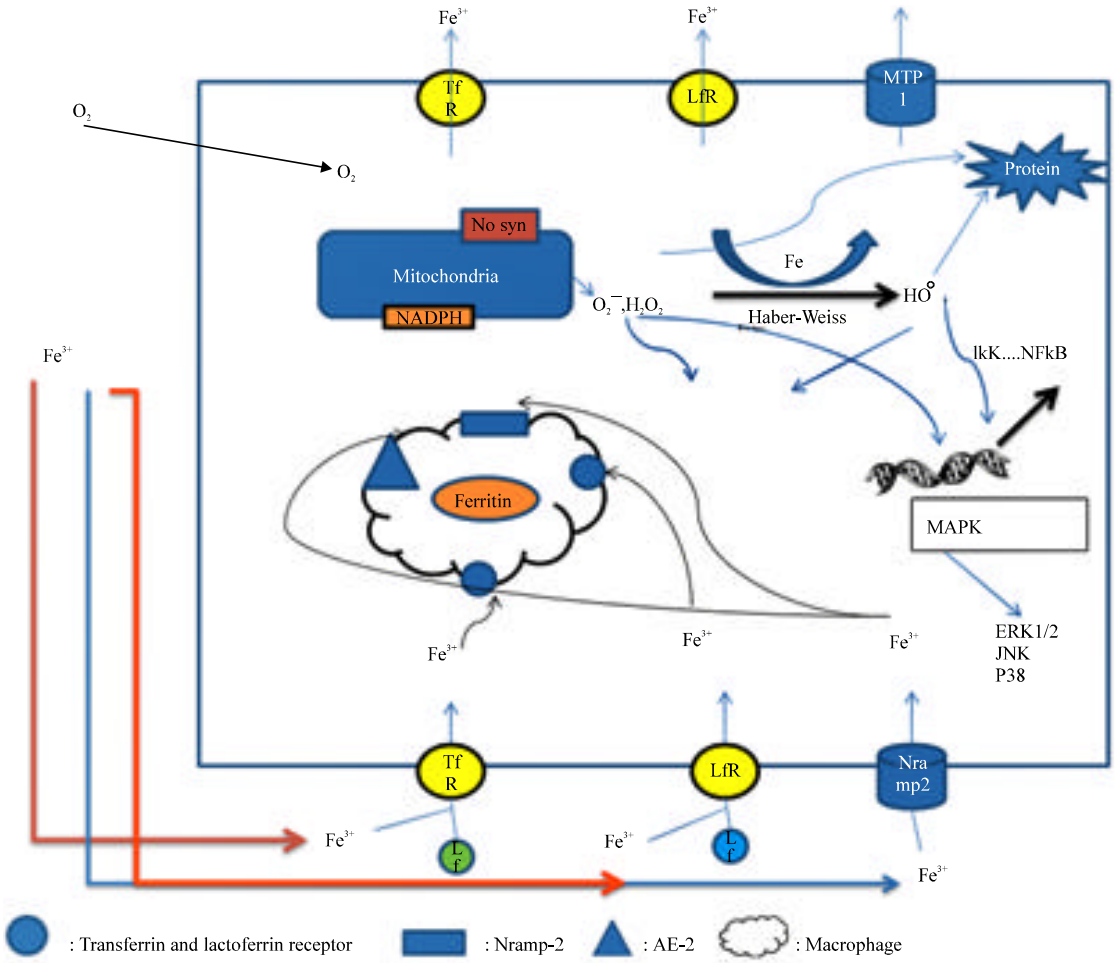

Fig. 1: Pathways of iron transport and iron-mediated damage within the lung epithelial cell; Tf: Transferrin, Lf: Lactoferrin, TfR: Transferrin Receptor, LfR: Lactoferrin Receptor, OH^0: Hydroxyl radical, H_2O_2: Hydrogen peroxide, O_2^-: Superoxide anion, kappa: IKK: IκB kinase, NFκB : Nuclear Factor κ B, Fe: iron, MAPK: Mitogen-activated Protein Kinase, ERK1/2: Extra-cellular signal-regulated Kinase, JNK: Jun-NH2-terminal Kinase, MTP: Metal Transport Protein, Nramp2: Natural resistance-associated macrophage protein, ROS: Reactive Oxygen Species, AE2: Anion Exchange protein 2, NTBI: Non-Transferrin Bound Iron. Iron has critical role in many cellular cell functions, but it can also generate reactive oxygen species that can damage major macromolecules in cells and result in cell death. So cells have different mechanisms to detoxify iron, the major one, is storage in ferritin. Iron mainly imported to cells by transferrin and lactoferrin receptors, Nramp-2 are responsible of NTBI uptake after ferrireduction of iron. To prevent excessive cellular accumulation, iron exported from cells by means of transferrin and lactoferrin receptors and also MTP-1. Alveolar macrophage through same receptors uptake iron for subsequent storage in ferritin and then releases ferritin in airway to diminish iron stress within cells. Overwhelming of these mechanisms result in excess level of free iron which is through Habber-Weiss reaction produce hydroxyl radical from H_2O_2 and superoxide anion. These ROS damage directly and indirectly to major macromolecules within cells and through over expression of some genes activate different pathways and protein such as MAPK and IKK pathways that finally lead to cell necrosis and apoptosis

proteins including ferritin and lactoferrin. NTBI uptake is frequently accomplished using Nramp-2 (DMT-1 or DCT-1) (Vidal *et al*., 1995). mRNA for DMT1increases after lung epithelial cell exposure to iron transcriptional control of IRE isoform, provides a mechanism of regulating Nramp 2 expression to diminish oxidative stress effectively (Lee *et al*., 1998). Nramp2 usually colocalize with transferrin seeming a candidate for both transferrin and non-transferrin-dependent uptake of iron. Ferrireductase activity is required prior to NTBI uptake

and expression of cytochrome b also appears to increase with iron exposure (Ghio, 2009). Superoxide can participate in ferrireduction in lung epithelial cells trough ascrobat-mediated cyt b ferrireduction (Ghio *et al*., 2003). Anion-exchange protein is a novel system in the lung for transferring-independent iron transport, which superoxide dismutase significantly decrease iron import (Ghio *et al*., 2003; Turi *et al*., 2004). Export of intracellular metals can be mediated by either ferritin or transferrin release (Ghio, 2009). Release of ferritin from alveolar macrophages in BAL provides a mechanism to diminish iron stress (Wesselius *et al*., 1994). Metal transporter protein 1 (MTP 1) or ferroportin 1 which present mainly in the apical membrane of airway epithelium, release iron to either the airway or the alveoli rather than to the blood for systemic distribution (Yang *et al*., 2005), however, ferrireduction is required before transport which is done mainly by O_2^-. Anion Exchange 2 (AE2) may also play a part in this release of metal (Yang *et al*., 2002).

Epithelial lining fluid contain several enzymatic and non-enzymatic antioxidant systems such as extracellular forms of superoxide dismutase (Su *et al*., 1997), glutathione peroxidase (Avissar *et al*., 1996), catalase (Cantin *et al*., 1999) as well as several metal-binding proteins (transferrin, ceruloplasmin and lactoferrin) that minimize involvement of transition metal ions in oxidant reaction (Cantin *et al*., 1999). Gland cell take up plasma and interstitial uric acid and secret it along with lactoferrin into the ELF (Pedan *et al*., 1993) where uric acid scavenges inhaled oxidants, reacts with singlet oxygen and also prevents oxidation of GSH and ascorbic acid by chelating transition metal ion (Davies *et al*., 1986).

In pathological condition, all these defenses overwhelmed and in presence of high oxygen concentration, iron result in production of powerful free radicals especially hydroxyl radical which can damage major macromolecules (lipid, DNA, protein) and lead to cell death.

Some studies demonstrate role of iron in lung oxidative injury and hyperoxia. Yang *et al*. (1999) proved that there was no increase in the levels of intracellular antioxidants, inflammatory cytokines and hemeoxygenase-1 in the hypotransferrinemic mouse lung exposed to hyperoxia (95% O_2) compared with those in wild-type mice, however there were elevated expressions of ferritin and lactoferrin in the lung of hypotransferrinemic mice, especially in the alveolar macrophages. The degree of iron sequestration in transferrin was greatly increased in epithelial lining fluid (from 24 to 80%) but not in serum (remained 24%) of animals with respiratory failure, suggesting that the iron originated in the lung compartment (Hallman *et al*., 1994). Instillation of iron containing particles into airways resulted in an increased production of ferritin and lactoferrin and declined transferrin concentrations (Ghio *et al*., 1998). Hemeoxygenase is responsible for the metabolism of heme imported from the extracellulur space; thereby liberate carbon monoxide, bilirubin and ferrous iron. Bilirubin which has been shown to be a potent antioxidant, with albumin-bilirubin complexes being very efficient scavengers of free radicals (Voget *et al*., 1995). Intracellular free iron is sequestered by ferritin and the induction of ferritin by oxidants appear to be coupled to induction of HO-1, there are two isozymes of HO; HO-1 is the inducible enzyme that is induced by oxidants, whereas HO-2 is considered constitutive (Maines, 1988), recently a third isoenzymes, HO-3 which is similar to HO-2 has been described (McCoubrey *et al*., 1997). HO-1 expression in the rat lungs was shown to be increased following 24 to 72 h of a hyperoxic insult (Fogg *et al*., 1999).

Demnery and coworkers in a study exposed HO-2 null mutant mice to >95% O_2 and compared with wild type controls. Similar basal levels were observed, except that the knockout had a twofold increase in total glutathione content and also were sensitized to hyperoxia-induced oxidative injury and mortality (Dennery *et al*., 1998). Wesselius *et al*. (1996) showed that there was dose dependent accumulation of iron and ferritin synthesis in alveolar macrophages exposed to iron-supplemented media. Exposure to hyperoxia (60 and 95% O_2) also decreased iron uptake and to a great extent ferritin synthesis by AM in iron-supplemented media. These data suggest that iron uptake promote hyperoxic injury to AM and the hyperoxia impairs the capacity of AM to sequester iron in ferritin. Therefore iron was increased in lung where it catalyzes oxidative stress contributing to lung injury. Thus lung must have a delicate method for detoxifying iron to prevent its deleterious effects.

Role of iron chelator: Iron chelation has been recently used for conditions without iron overload such as neurodegenerative, infectious, reperfusion injury, cardioprotection and others suggesting the role of iron as an oxidative-induced injury (Hershko, 1994; Kontoghioghes *et al*., 2010). Desferrioxamine (DFO) has a very high affinity for Fe^{3+} and is very efficient in preventing its reduction to Fe^{2+} and the participation of iron in the Haber-Weiss reaction. DFO is a Hexidenate chelator. The maximal coordination of iron is six, so DFO binds to all sites and completely deactivate free iron (Hershko, 1992). DFO has been used in some diseases for prevention or reduction of oxidative stress induced injury (Deboer and Clark, 1992; Drossos *et al*., 1995; Menasche *et al*., 1987; Omar *et al*., 1989;

Paraskevaidis *et al*., 2005; Prass *et al*., 2002), but few of these studies related to lung injury. For example combination of N-acetylcystein plus DFO decreased bronchoalveolarlavage (BAL) fluid protein such as carbonyl protein, inflammatory cells, oxidative damage variables and proinflammatory cytokines in rat after induction of acute lung injury by instillation of lipopolysaccaride. Ritter and coworkers concluded that this combination significantly attenuated lung oxidative damage, mitochondrial superoxide production and histopathological alterations in lung (Ritter *et al*., 2006). In another study, 42 male Wistar rats exposed to coal dust by intratracheal instillation. N-acetylcystein (20 mg/kg/day) alone or in combination with DFO (20 mg/kg/day) could decrease the inflammatory response and the oxidative stress parameters in these rats (Pinhoa *et al*., 2005). Aerosolized DFO could prevent severe pulmonary failure in sheeps exposed to burning cotton towlling (Lalonde *et al*., 1994). DFO due to very poor oral bioavailibilty and a short half-life must be administered by subcutaneous or intravenous infusion. New long acting oral agent such as deferasirox is a tridentate molecule containing 3 active binding sites for iron and has a binding ratio with 2:1 Fe^{3+} (Stumpf, 2007). This drug has better side effect profile in comparison with deferoxamin because of its small size and lipophilic structure that could chelate intracellular iron better than deferoxamine. So, it could be a promising agent for chelation of iron in situation other than thallasseamia (Vanorden and Hagemann, 2006). Currently authors of this paper have a clinical trial ongoing about usefulness of DFO in clinic that its primary results have been promising and is thought to be completed by end of 2010.

CONCLUSION

Oxygen therapy is one of the necessary parts of management of critically ill patients, especially with respiratory failure, but oxygen act as two edge sword in these situations and through oxidative stress process damage to major macromolecules that lead to cell death. Different pathways and molecules that involved in this process are the target of different drugs for prevention or treatment of harmful effect of oxygen. Despite favorable effects of these drugs, they are not completely successful in this condition. Regarding adequate evidence about role of iron in mediating of oxidative stress in hyperoxic conditions, protective effects of iron chelators should be considered reasonable. There are some evidences about positive effects of desferrioxamine alone or in combination when tested in animal models of lung injury or in human but they are not convincing. Further studies are necessary to clarify the importance of intervention with desferrioxamine or new long acting oral agent deferasirox and their risk/benefit in hyperoxia-induced lung injury.

REFERENCES

Abdollahi, M., A.R. Dehpour and F. Shafayee, 2000a. L-Arginine/nitric oxide pathway and interaction with lead acetate on rat submandibulary gland function. Pharmacol. Toxicol., 87: 198-203.

Abdollahi, M., A.R. Dehpour and P. Kazemian, 2000b. Interaction of cadmium with nitric oxide in rat submandibulary gland function. Pharmacol. Res., 42: 591-597.

Abdollahi, M., A. Ranjbar, S. Shadnia, S. Nikfar and A. Rezaiee, 2004. Pesticides and oxidative stress: A review. Med. Sci. Monit., 10: 141-147.

Ahmad, A., S. Ahmad, L.Y. Chang, J. Schaack and C.W. White, 2006. Endothelial Akt activation by hyperoxia: Role in cell survival. Free Radic. Biol. Med., 40: 1108-1118.

Ansari, G., M. Mojtahedzadeh, F. Kajbaf, A. Najafi and M.R. Khajavi *et al*., 2008. How does blood glucose control with metformin influence intensive insulin protocols? Evidence for involvement of oxidative stress and inflammatory cytokines. Adv. Ther., 25: 681-702.

Aslam, M., R. Baveja, O.D. Liang, A. Fernandez-Gonzalez, C. Lee, S.A. Mitsialis and S. Kourembanas, 2009. Bone marrow stromal cells attenuate lung injury in a murine model of neonatal chronic lung disease. Am. J. Respir. Crit. Care Med., 11: 1122-1130.

Auten, Jr. R.L., S.N. Mason, D.T. Tanaka, K. Welty-Wolf and M.H. Whorton, 2001. Anti-neutrophil chemokine preserves alveolar development in hyperoxia-exposed newborn rats. Am. J. Physiol. Lung Cell Mol. Physiol., 281: L336-L344.

Avissar, N., J.N. Finkelstein, S. Horowitz, J.C. Willey and E. Coy *et al*., 1996. Extracellular glutathione peroxidase in human lung epithelial lining fluid and in lung cells. Am. J. Physiol., 14: L173-L182.

Baba, Y., T. Yazawa, Y. Kanegae, S. Sakamoto and I. Saito *et al*., 2007. Keratinocyte growth factor gene transduction ameliorates acute lung injury and mortality in mice. Human Gene. Ther., 18: 130-141.

Babior, B.M., L.D. Lambeth and W. Nauseef, 2002. The neutrophil NADPH oxidase. Arch. Biochem. Biophys., 397: 342-344.

Ballard, H.O., P. Bernard, J. Qualls, W. Everson and L.A. Shook, 2007. Azithromycin protects against hyperoxic lung injury in neonatal rats. J. Investig. Med., 55: 299-305.

Beckett, W.S. and N.D. Wong, 1988. Effect of normobaric hyperoxia on airways of normal subjects. J. Applied Physiol., 64: 1683-1687.

Berg, T.J., 2006. Zymosan priming protects rats against pulmonary oxygen toxicity. Inflamm. Res., 55: 565-571.

Birgens, H.S., L.O. Kristensen, N. Borregaard, H. Karle and H.E. Hansen, 1998. Lactoferrin-mediated transfer of iron to intracellular ferritin in human monocytes. Eur. J. Haematol., 41: 52-57.

Bogdan, C., 2001. Nitric oxide and immune response. Nat. Immunol. Med., 2: 907-916.

Bryan, C.L., R.E. Lewis, S.L. Owens, B. Emanuel and G. Jekinson, 1993. Allopurinol inhibition of neutrophilic alveolar response during hyperoxia. J. Applied Physiol., 75: 357-363.

Cantin, A.M., G.A. Fells, R.C. Hubbard and R.G. Crystal, 1999. Antioxidant macromolecules in the epithelial lining fluid of normal human lower respiratory tract. J. Clin. Invest., 86: 962-971.

Cellier, M., G. Prive, A. Belouchi, T. Kwan, V. Rodrigues, W. Chia and P. Gros, 1995. Nramp defines a family of membrane proteins. Proc. Nat. Acad. Sci. USA., 92: 10089-10093.

Chakraborti, S., S.K. Batabyal and T. Chakraborti, 1999. Role of vitamin C in ameliorating lung damage in response to hyperoxia in developing newborn guinea pig. Med. Sci. Res., 27: 41-43.

Chang, L.L., M. Subramaniam, B.A.Yoder, B.J. Day, M.C. Ellison, M.E. Sunday and J.D. Crapo, 2003. A catalytic antioxidant attenuates alveolar structural remodeling in bronchopulmonary dysplasia. Am. J. Respir. Crit. Care Med., 167: 57-64.

Chang, Y.S., Y.J. Kim, H.S. Yoo, D.K. Sung, S.Y. Kim, S. Kang and W.S. Park, 2009. Alpha-phenyl-N-tert-butylnitrone attenuates hyperoxia-induced lung injury by down-modulating inflammation in neonatal rats. Exp. Lung. Res., 35: 234-249.

Chung-Wai, C., M.T.H. Abreu, T. Suzuki and G.P. Downey, 2003. Oxidative stress and acute lung injury. Am. J. Respir. Cell Mol. Biol., 29: 427-431.

Ciencewicki, J., S. Trivedi and S.R. Kleeberger, 2008. Oxidants and the pathogenesis of lung diseases. J. Allergy Clin. Immunol., 122: 456-468.

Cross, C.E., A. van der Vliet, C.A. O'Neill, S. Louie and B. Halliwell, 1994. Oxidants, antioxidants and respiratory tract lining fluids. Environ. Health Perspect., 102: 185-191.

Das, D.K., D. Bandyopadyay, S. Hoory and H. Steinberg, 1988. Role of polymorphonuclear leukocytes in hyperoxic lung injury. Prevention of neutrophil influx into the lung endothelium during oxygen exposure by ibuprofen. Biomed. Biochim. Acta., 47: 1023-1036.

Davis, W.B., S.I. Rennard, P.B. Bitterman and R.G. Crystal, 1983. Pulmonary oxygen toxicity. Early reversible changes in human alveolar structures induced by hyperoxia. NEJM., 309: 878-883.

Davies, K.J., A. Sevanian, S.F. Muakkassah-kelly and P. Hochstein, 1986. Uric acid-iron ion complexes. A new aspect of the antioxidant function of uric acid. Biochem. J., 235: 747-754.

Davis, J.M., W.N. Rosenfeld, R.J. Sanders and A. Gonenne, 1993. Prophylactic effects of recombinant human superoxide dismutase in neonatal lung injury. J. Applied Physiol., 74: 2234-2241.

De Visser, Y.P., F.J. Walther, H. El-Laghmani, H. Boersma, A. van der Laarse and G.T. Wagenaar, 2009. Sildenafil attenuates pulmonary inflammation and fibrin deposition, mortality and right ventricular hypertrophy in neonatal hyperoxic lung injury. Respir. Res., 109: 30-46.

Deboer, D.A. and R.E. Clark, 1992. Iron chelation in myocardial preservation after ischemia-reperfusion injury: The importance of pretreatment and toxicity. Ann. Thorac. Surg., 53: 412-418.

Demir, K., A. Kumral, N. Duman, S. Sarioglu, O.Yilmaz, D.C. Yesilirmak, A. Kargi and H.Ozkan, 2008. Clarithromycin, montelukast and pentoxifylline combination treatment ameliorates experimental neonatal hyperoxic lung injury. Matern. Fetal Neonatal Med., 21: 407-413.

Dennery, P., D. Spitz, G. Yang, A. Tatarov, C.H. Lee and M. Shegog, 1998. Oxygen toxicity and iron accumulation in the lungs of mice lacking heme oxygenase-2. J. Clin. Invest., 101: 1001-1011.

Drossos, G., A. Lazou, P. Panagopoulos and S. Westaby, 1995. Deferoxamine cardioplegia reduces superoxide radical production in human myocardium. Ann. Thorac. Surg., 59: 169-172.

Du, J., A.L.Z. Du, J.J Jiang, L.F. Tang and X.L. Wu, 2006. Effect of inhaled nitric oxide on surfactant protein A and mannose binding ability in the lung of neonatal rats with hyperoxia-induced lung injury. Zhongguo Dang Dai Er Ke Za Zhi., 8: 486-490.

Eisenstein, R.S., 2000. Iron ragulatory proteins and the molecular control of mammalian iron metabolism. Annu. Rev. Nutr., 20: 627-662.

Emerit, J., C. Beaumont and F. Trivin, 2001. Iron metabolism, free radicals and oxidative injury. Biomed. Pharmacother., 55: 333-339.

Fogg, S., A. Agrawal, H. Nick and G. Visner, 1999. Iron regulates hyperoxia-dependent human Heme oxygenase 1 gene expression in pulmonary endothelial cell. Am. J. Respir. Cell Mol. Biol., 20: 794-804.

George, C.L., G. Fantuzzi, S. Bursten, L. Leer and E. Abraham, 1999. Effects of lisofylline on hyperoxia-induced lung injury. Am. J. Physiol., 276: L776-L785.

Ghio, A.J., P.J. Fracica, S.L. Young and C.A. Piantadosi, 1994. Synthetic surfactant scavenges oxidants and protects against hyperoxic lung injury. J. Applied Physiol., 77: 1217-1223.

Ghio, A., J. Carter, J. Richards, L. Brighton, J. Lay and R. Delvin, 1998. Disruption of normal iron homestasis after bronchial instillation of an iron-containing particle. Am. J. Physiol. Lung Cell Mol. Physiol., 274: L396-L403.

Ghio, A., E. Eozik-Grayck, J. Turi, I. Jaspers, D.R. Mercatante, R. Kole and C. Piantadosi, 2003. Superoxide-dependent iron uptake: A new role for anion exchange protein 2. Am. J. Respir. Cell Mol. Biol., 29: 653-660.

Ghio, A., 2009. Disruption of iron homeostasis and lung disease. Biochem. Biophys. Acta, 1790: 731-739.

Hageman, J.R., S.E. Lee, J. Zemaitis, L.J. Smith and C.E. Hunt, 1989. Prostaglandin E1 infusion fails to prevent hyperoxic lung injury in adult rabbits. Crit. Care Med., 17: 339-344.

Hallman, M., A. Sarnesto and K. Bry, 1994. Interaction of transferrin saturated with iron with lung surfactant in respiratory failure. J. Applied Physiol., 77: 757-766.

Harrison, P.M and P. Arosio, 1996. The ferritins: Molecular properties, iron storage, function and cellular regulation. Biochem. Biophys. Acta, 1275: 161-203.

Hershko, C., 1992. Iron chelators in medicine. Mol. Aspects Med., 45: 276-281.

Hershko, C., 1994. Control of disease by selective iron depletion: A novel therapeutic strategy utilizing iron chelators. Baillieres Clin. Haematol., 7: 965-1000.

Jenkinson, S.G., R.J. Roberts, R.A. de Lemos, R.A. Lawrence and J.J. Coalson *et al*., 1991. Allopurinol-induced effects in premature baboons with respiratory distress syndrome. J. Applied Physiol., 70: 1160-1167.

Kajbaf, F., M. Mojtahedzadeh and M. Abdollahi, 2007. Mechanisms underlying stress-induced hyperglycemia in critically ill patients. Therapy, 4: 97-106.

Kontoghioghes, G.J., A. Kolnagou, C.T. Peng, S.V. Shah and A. Aessopos, 2010. Safety issues of iron chelation therapy in patients with normal range iron stores including thalassaemia, neurodegenerative, renal and infectious diseases. Expert. Opin. Drug Saf., 9: 201-206.

Kunig, A.M., V. Balasubramaniam, N.E. Markham, D. Morgan, G. Montgomery, T.R. Grover and S.H. Abman, 2005. Recombinant human VEGF treatment enhances alveolarization after hyperoxic lung injury in neonatal rats. Am. J. Physiol. Lung Cell Mol. Physiol., 289: L529-L535.

Ladha, F., S. Bonnet, F. Eaton, K. Hashimoto, G. Korbutt and B. Thébaud, 2005. Sildenafil improves alveolar growth and pulmonary hypertension in hyperoxia-induced lung injury. Am. J. Respir. Crit. Care Med., 172: 750-756.

Lalonde, C., K. Ikegani and R. Demling, 1994. Aerosolized deferoxamine prevents lung and systemic injury caused by smoke inhalation. J. Applied Physiol., 77: 2057-2064.

Langley, S.C. and F.J. Kelly, 1993. N-acetylcysteine ameliorates hyperoxic lung injury in the preterm guinea pig. Biochem. Pharmacol., 45: 841-846.

Lavaute, T., S. Smith, S. Cooperman, K. Iwai, E. Meyron-Holtz, S.K. Drake and G. Mitter, 2001. Targeted deletion of the gene encoding iron regulatory protein-2 causes misregulation of iron metabolism and neurodegenerative disease in mice. Nat Genet., 27: 209-214.

Lee, P.L., T. Gelbart, C. West, C. Halloran and E. Beutler, 1998. The human Nramp 2 gene: Characterization of the gene structure, alternative splicing, promotor region and polymorphisms. Blood Cells Mol. Dis., 24: 199-215.

Lee, P.J. and A.M. Choi, 2003. Pathways of cell signaling in hyperoxia. Free Radic. Biol. Med., 34: 341-350.

Lee, J.H., D.K. Sung, S.H. Koo, B.K. Shin and Y.S. Hong *et al*., 2007. Erythropoietin attenuates hyperoxia-induced lung injury by down-modulating inflammation in neonatal rats. J. Korean Med. Sci., 22: 1042-1047.

Li, L.F., S.H. Liao, Y.S. Ko, C.H. Lee and D. Quinn, 2007. Hyperoxia increases ventilators-induced lung injury via mitogen-activated protein kinases, a prospective controlled animal experiment. Crit. Care, 11: R25-R25.

Li, W.B., L.W. Chang, Z.H. Rong, H.C. Liu and Q.S. Zhang *et al*., 2008. Retinoic acid diminished the expression of lung tissue matrix metalloproteinase-2 and matrix metalloproteinase-9 in hyperoxia-exposed premature rats through regulating mitogen-activated protein kinases. Zhonghua Er Ke Za Zhi., 46: 347-353.

Lloyd, R.V., P.M. Hanna, P.M. and R.P. Mason, 1997. The origin of the hydroxyl radical in the Fenton reaction. Free Radic. Biol. Med., 22: 885-888.

Looney, M.R., C.T. Esmon and M.A. Matthay, 2009. Role of coagulation pathways and treatment with activated protein C in hyperoxic lung injury. Thorax, 64: 114-120.

Lyer, S. and B. Lonnerdal, 1993. Lactoferrin, lactoferrin receptors and iron metabolism. Eur. J. Clin. Nutr., 47: 232-241.

Mahmoodpoor, A., M. Mojtahedzadeh, A. Najafi, A. Ahmadi and A. Dehnadi-Moghadam *et al*., 2010. Examination of setarud (IMOD™) in the management of patients with severe sepsis. DARU, 18: 23-28.

Maines, M.D., 1988. Heme oxygenase: Function, multiplicity, regulatory mechanisms and clinical applications. FASEB J., 2: 2557-2568.

Mateos, F., J. Brock and J. Perez-Arellano, 1998. Iron metabolism in the lower respiratory tract. Thorax, 53: 594-600.

Matthew,.E., L. Kutcher and J. Dedman, 2003. Protection of lungs from hyperoxic injury: Gene expression analysis of cyclosporin A therapy. Physiol. Genomics., 14: 129-138.

McCoubrey, W.K., T.J. Huang and M.D. Maines, 1997. Isolation and characterization of a cDNA from the rat brain that encodes hemoprotein heme oxygenase 3. Eur. J. Biochem., 274: 725-732.

Menasche, P., C. Grousset, Y. Gauduel, C. Mouas and A. Piwnica, 1987. Prevention of hydroxyl radical formation: A critical concept for improving cardioplegia. Protective effect of deferoxamine. Circulation, 76: V180-V185.

Mikawa, K., K. Nishina, N. Maekawa and H. Obara, 1995. Attenuation of hyperoxic lung injury in rabbits with superoxide dismutase: Effects on inflammatory mediators. Acta Anaesthesiol. Scand., 39: 317-322.

Mojtahedzadeh, M., M.R. Rouini, F. Kajbaf, A. Najafi, G. Ansari, A. Gholipour, A.R. Mofid 2008. Advantage of adjunct metformin and insulin therapy in the management of glycemia in critically ill patients. Evidence for nonoccurrence of lactic acidosis and needing to parenteral metformin. Arch. Med. Sci., 4: 174-178.

Najafi, A., M. Mojtahedzadeh, A. Mahmoodpoor, M. Aghamohammadi and A. Ahmadi *et al*., 2009. Effect of N-acetylcysteine on microalbuminuria in patients with acute respiratory distress syndrome. Arch. Med. Sci., 5: 408-414.

Naureckas, E.T., P. Factor, O. Benjaminov, E. Hoffer, V. Sriram and J.I. Sznajder, 1994. Pentoxifylline does not protect against hyperoxic lung injury in rats. Eur. Respir. J., 7: 1397-1402.

Nelson, S.K. and J.M. McCord, 1998. Iron, oxygen radicals and disease. Adv. Mol. Cell. Biol., 25: 157-183.

Obara, H., S. Iwai and T. Takada, 1985. The effect of a high dose of vitamin E on the oxygen injured lung. Masui, 34: 286-291.

Omar, R., I. Nomikos, G. Piccorelli, J. Savino and N. Agrawal, 1989. Prevention of postischemic lipid peroxidation and liver cell injury by iron chelation. Gut, 30: 510-514.

Ozer, E.A., A. Kumral, E. Ozer, O. Yilmaz and N. Duman *et al*., 2005. Effects of erythropoietin on hyperoxic lung injury in neonatal rats. Pediatr. Res., 58: 38-41.

Pagano, A., Y. Donati, I. Métrailler and C.B. Argiroffo, 2004. Mitochondrial cytochrome c release is a key event in hyperoxia-induced lung injury: Protection by cyclosporin A. Am. J. Physiol. Lung. Cell Mol. Physiol., 286: L275-L283.

Paine, R., S.E. Wilcoxen, S.B. Morris, C. Sartori, C.E. Baleeiro, M.A. Matthay and P.J. Christensen, 2003. Transgenic overexpression of granulocyte macrophage-colony stimulating factor in the lung prevents hyperoxic lung injury. Am. J. Pathol., 163: 2397-2406.

Pan, L., J.H. Fu, X.D. Xue, W. Xu, P. Zhou and B. Wei, 2009. Melatonin protects against oxidative damage in a neonatal rat model of bronchopulmonary dysplasia. World J. Pediatr., 5: 216-221.

Pantarulo, S., 2005. Iron, oxidative stress and human health. Mol. Aspects Med., 26: 299-312.

Pantopoulos, K. and M.W. Hentz, 1998. Activation of iron regulatory protein-1 by oxidative stress *in vitro*. Proc. Nat. Acad. Sci. USA., 95: 10559-10563.

Papanikolaou, G. and K. Pantopoulos, 2005. Iron metabolism and toxicity. Toxicol. Applied Pharmacol., 202: 199-211.

Paraskevaidis, I.A., E.K. Lliodromitis, D. Vlahakos, D. Tsiapras and A. Nikolaidis *et al*., 2005. Deferoxamine infusion during coronary artery bypass grafting ameliorates lipid peroxidation and protects the myocardium against reperfusion injury: imediate and long-term significance. Eur. Heart J., 26: 263-270.

Pedan, D.B., M. Swiersz, K. Ohkubo, B. Hahn, B. Emery and M.A. Kaliner, 1993. Nasal secretion of ozone scavenger uric acid. Am. Rev. Respir. Dis., 148: 455-461.

Pinhoa, R.A., P.C.L. Silveirab, L.A. Silvab, E.L. Streckc, F. Dal-Pizzold and J.C.F. Moreira, 2005. N-acetylcysteine and deferoxamine reduce pulmonary oxidative stress and inflammation in rats after coal dust exposure. Environ. Res., 99: 355-360.

Prass, K., K. Ruscher, M. Karsch, N. Isaev and D. Megow *et al*., 2002. Desferrioxamine induces delayed tolerance against cerebral ischemia *in vivo* and *in vitro*. J. Cereb. Blood Flow Metab., 22: 520-525.

Quinn, D.A., R.K. Moufarrej, A. Volokhov and C.A. Hales, 2002. Interactions of lung stretch, hyperoxia and MIP-2 production in ventilator-induced lung injury. J. Applied Physiol., 93: 517-525.

Radomski, A., G. Sawicki, D.M. Olson and M.W. Radomski, 1998. The role of nitric oxide and metalloproteinases in the pathogenesis of hyperoxia-induced lung injury in newborn rats. Br. J. Pharmacol., 125: 1455-1462.

Ramsay, P.L., B. Piedboeuf, M. Gamache, R.S. Geske, C.V. Smith and S.E. Welty, 2000. Dexamethasone enhances P-selectin mRNA expression in hyperoxic rat lungs. Inflamm. Res., 49: 655-665.

Rehan, V.K., Y. Wang, S. Patel, J. Santos and J.S. Torday, 2006. Rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, prevents hyperoxia-induced neonatal rat lung injury *in vivo*. Pediatr. Pulmonol., 41: 558-569.

Reynolds, P.R., R.E. Schmitt, S.D. Kasteler, A. Sturrock and K. Sanders *et al*., 2010. Receptors for advanced glycation end-products (RAGE) targeting protect against hyperoxia-induced lung injury in mice. Am. J. Respir. Cell Mol. Biol., 42: 545-551.

Rezaie, A., R.D. Parker and M. Abdollahi, 2007. Oxidative stress and pathogenesis of inflammatory bowel disease: An epiphenomenon or the cause?. Dig. Dis. Sci., 52: 2015-2021.

Ritter, C., A.A. da Cunha, I.C. Echer, M. Andrades and A. Reinke *et al*., 2006. Effects of N-acetylcysteine plus deferoxamine in lipopolysaccharide-induced acute lung injury in the rat. Crit. Care Med., 34: 471-477.

Rodriguez-Pierce, M., I.R. Sosenko, P. Whitney and L. Frank, 1994. Propylthiouracil treatment decreases the susceptibility to oxygen radical-induced lung damage in newborn rats exposed to prolonged hyperoxia. Pediatr. Res., 35: 530-535.

Romashko, J., S. Horowitz, W.R. Franek, T. Palaia and E.J. Miller *et al*., 2003. MAPK pathways mediate hyperoxia-induced oncotic cell death in lung epithelial cells. Free Radic. Biol. Med., 35: 978-993.

Salari, P., M. Mojtahedzadeh and M. Abdollahi, 2005a. Influence of serum epidermal growth factor on mechanical ventilation and survival in patients with acute respiratory distress syndrome. Therapy, 2: 393-398.

Salari, P., M. Mojtahedzadeh, A. Najafi, S. Sadraie, K. Bahaadini, M. Moharreri, N. Hadavandand M. Abdollahi, 2005b. Comparison of the effect of aminophylline and low PEEP vs. high PEEP on EGF concentration in critically ill patients with ALI/ARDS. J. Clin. Pharmacy Therapeutics, 30: 139-144.

Shim, J.W., Y.S. Chang and W.S. Park, 2008. Intratracheal administration of endotoxin attenuates hyperoxia-induced lung injury in neonatal rats. Yonsei Med. J., 49: 144-150.

Soltan-Sharifi, M.S., M. Mojtahedzadeh, A. Najafi, M.R. Khajavi and M.R. Rouini, 2007. Improvement by N-acetylcysteine of acute respiratory distress syndrome through increasing intracellular glutathione and extracellular thiol molecules and anti-oxidant power: Evidence for underlying toxicological mechanisms. Human Exp. Toxicol., 26: 697-703.

Sprong, C., Y.M.W. Janssen and P.J.A. Borm, 1991. The role of reactive oxygen species, cytokines and cytochrome P450 in pulmonary damage due to hyperoxia. Med. Hypotheses., 34: 296-299.

Stumpf, J., 2007. Deferasirox. Am. J. Health-Syst. Pharm., 64: 606-616.

Su, W.Y., R. Folz, J.S. Chen, D.J. Capro and L.Y. Chang, 1997. Extacellular superoxide dismutase mRNA expressions in human lung by *in situ* hybridization. Am. J. Respir. Cell Mol. Biol., 16: 162-170.

Ter Horst, S.A., G.T. Wagenaar, E. de Boer, M.A. van Gastelen and J.C. Meijers *et al*., 2004. Pentoxifylline reduces fibrin deposition and prolongs survival in neonatal hyperoxic lung injury. J. Applied Physiol., 97: 2014-2019.

Thomson, A.M., J.T. Rogers and P.J. Leedman, 1999. Iron regulatory proteins,iron-responsive elements and ferritin mRNA translation. Int. J. Biochem. Cell Biol., 31: 1139-1152.

Torti, F. and S. Torti, 2002. Regulation of ferritin genes and proteins. Blood, 99: 3505-3516.

Town, G.I., G.J. Phillips, M. Landreau, J. Louden, S.T. Holgate and F.J. Kelly, 1993. Dexamethasone treatment fails to reduce oxygen-induced lung injury in the preterm guinea pig. Effects on pulmonary inflammation and antioxidant status. Biochem. Pharmacol., 46: 1565-1572.

Turi, J., F. Yang, M. Garrick, C. Piantadosi and A. Ghio, 2004. The iron cycle and oxidative stress in the lung. Free Radic. Biol. Med., 36: 850-857.

Van der Vliet, A., C.E. Cross and C.A. O'Neill, 1999. Determination of low-molecular mass antioxidant concentrations in human respiratory tract lining fluids. Am. J. Physiol., 276: L289-L296.

Van Klaveren, R.J., D. Dinsdale, J.L. Pype, M. Demedts and B. Nemery, 1997. N-acetylcysteine does not protect against type II cell injury after prolonged exposure to hyperoxia in rats. Am. J. Physiol., 273: L548-L555.

Van Snick, J.L., B. Markowetz and P.L. Masson, 1977. The ingestion and digestion of human lactoferrin by mouse peritoneal macrophages and the transfer of its iron into ferritin. J. Exp. Med., 146: 817-827.

Vanorden, H. and T. Hagemann, 2006. Deferasirox an oral agent for chronic iron overload. Ann. Phamacother., 40: 1110-1117.

Vazin, A., M. Mojtahedzadeh, A. Najafi, A. Khalilzadeh and M. Abdollahi, 2005a. Relationship between duration, fatality rate and severity of disease and serum epidermal growth factor in human acute lung injury. Therapy, 2: 255-259.

Vazin, A., M. Mojtahedzadeh, E. Salehifar, N. Rastkari, S. Khalaj, A. Rezaie and M. Abdollahi, 2005b. Future drugs for treatment of acute respiratory distress syndrome. Int. J. Pharmacol., 1: 9-16.

Veness-Meehan, K.A., F.G. Bottone and A.D. Stiles, 2000. Effects of retinoic acid on airspace development and lung collagen in hyperoxia-exposed newborn rats. Pediatr. Res., 48: 434-444.

Vidal, S., A.M. Beluchi, M. Cellier, B. Beatty and P. Gross, 1995. Cloning and characterization of a second human Nramp gene on chromosome 12q13. Mamm. Genome., 6: 224-230.

Voget, B.A., J. Alam, A.J. Croatt, G.M. Veraallott and K.A. Nath, 1995. Acquired resistance to acute oxidative stress: Possible role of heme oxygenase and ferritin. Lab. Invest., 72: 474-483.

Walther, F.J., R. David-Cu and S.L. Lopez, 1995. Antioxidant-surfactant liposomes mitigate hyperoxic lung injury in premature rabbits. Am. J. Physiol. Lung Cell Mol. Physiol., 269: L613-L617.

Wesselius, L., M.E. Nelson and B.S. Shikne, 1994. Increased release of ferritin and iron by iron-loaded alveolar macrophages in cigarette smokers. Am. J. Respir. Crit. Care Med., 150: 690-695.

Wesselius, L., W. Wade, K. Baily, S. Vamos, A. O'brien-lander and Th.Weigmann, 1996. Iron uptake promotes hyperoxic injury to Alveolar macrophages. Am. J. Respir. Crit. Care Med., 159: 100-106.

Yang, F., J. Coalson, H. Bobb, J. Carter, J. Banu and A. Ghio, 1999. Resistance of hypotransferrinemic mice to hyperoxia-induced lung injury. Am. J. Physiol. Lung Cell Mol. Physiol., 277: L1214-L1223.

Yang, F., X. Wang, D.J. Haile, C. Piantadosi and A. Ghio, 2002. Iron increases expression of iron-export protein MTP1 in lung cells. Am. J. Physiol. Lung Cell Mol. Physiol., 283: L932-L939.

Yang, F., D.J. Haile, X. Wang, L.A. Dailey, J.G. Stronchuerner and A. Ghio, 2005. Apical location of ferroportin 1 in airway epithelia and its role in iron detoxification in the lung. Am. J. Physiol. Lung Cell Mol. Physiol., 289: L14-L23.

Zimova-Herknerova, M., J. Myslivek and P. Potmisil, 2008. Retinoic acid attenuates the mild hyperoxic lung injury in newborn mice. Physiol. Res., 57: 33-40.