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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 hypoxic 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, sildenafil, 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

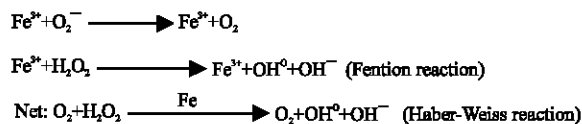
INTRODUCTION

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

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):



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 *et 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 <i>et al.</i> (2007)	Newboru 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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (2007)	Neonatal rats	Captopril	30 mg/kg/day between 7th and 21 day of hyperoxia	Alleviation of lung injury and fibrosis by captopril
George <i>et al.</i> (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 <i>et al.</i> (2009)	Neonatal rats	Melatonin	4 mg kg ⁻¹ i.p. for 14 days	Improvement of oxidant/antioxidant imbalance in lung injury
Li <i>et al.</i> (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 <i>et al.</i> (2008)	Newboru 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 <i>et al.</i> (2006)	Rat pups	Rosiglitazone	3 mg kg ⁻¹ i.p. for 24 h	Prevention of morphologic, molecular and immunohistochemical changes in lung injury
Du <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (2003)	Fetal baboon	AEOL 10113 (Catalytic antioxidant metaloporphyrine)	Continuous i.v. infusion of for 10 days	Reduction of oxygen toxicity in prematurely boru infant
Shim <i>et al.</i> (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 <i>et al.</i> (2009)	Neonatal rats	Alpha-phenyl N-tert-butyl nitro (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 <i>et al.</i> (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 <i>et al.</i> (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 of normal lung compliance and suppression of airway inflammation
Demir <i>et al.</i> (2008)	Newborn rat pups	Clarithromycin, Montelukast and Pentoxifylline	Each drug in combination or alone for 10 days	Combination treatment is superior to placebo in treatment of lung injury
Town <i>et al.</i> (1993)	Preterm guinea pigs	Dexamethasone	10 mg/kg/day for 72 h	Blunting neutrophil influx and induction antioxidant effect, without effect on survival
Ramsay <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (2009)	Rat pups	Sildenafil	50-150 mg/kg /day s.c.	Prolonged median survival, reduction of fibrin deposition, improvement of alveolarization and angiogenesis
Ladha <i>et al.</i> (2005)	Rat pups	Sildenafil	100 mg/kg/day s.c. for 14 days	Prevention of alveolar growth, lung angiogenesis, decreased pulmonary vascular resistance,
Bryan <i>et al.</i> (1993)	Male rats	Allopurinol	Daily injection for 14 days	Decrease neutrophil alveolar response but has no effect on lung injury
Jenkinson <i>et al.</i> (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 <i>et al.</i> (2005)	Neonatal rats	Recombinant human VEGF (rhVEGF)	rhVEGF-165 for 10 days	rhVEGF treatment during recovery enhanced vessel growth and alveolarization
Looney <i>et al.</i> (2009)	Neonatal rats	Activated protein C (APC)	APC by different routes	Failure to improvement of lung injury indices
Davis <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (1988)	Rabbits	Ibuprofen	Ibuprofen p.o for 4 days	Failure in prevention of lung injury
Hageman <i>et al.</i> (1989)	Adult rabbits	Prostaglandin E1 (PGE1)	0.1, 0.06 or .003 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 <i>et al.</i> (1985)	Neonatal rats	Vitamin E (Vit E)	150 mg/kg Vit. E for 7 days	Preservation of pulmonary capillary endothelium from hyperoxia
Chakraborti <i>et al.</i> (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 <i>et al.</i> (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.: Intraperitoneally, s.c.: Subcutaneously, i.v.: Intravenous, p.o: Per oral, U:unit, mcg: Microgram, ppm: Part per million, kg: Kilogram, h: Hour, d: Day; SOD: Superoxide dismutase, CAT: Catalase, MAPK: Mitogen-activated protein kinases, VEGF: Vascular endothelial growth factor

hyperoxia-induced lung injury, each drug targeted a part of this system (Ahmad *et al.*, 2006; Ciencewicz *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 sildenafil (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 possess 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 Fe³⁺ 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 loses 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 H₂O₂ 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 H₂O₂ and O₂⁻ (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

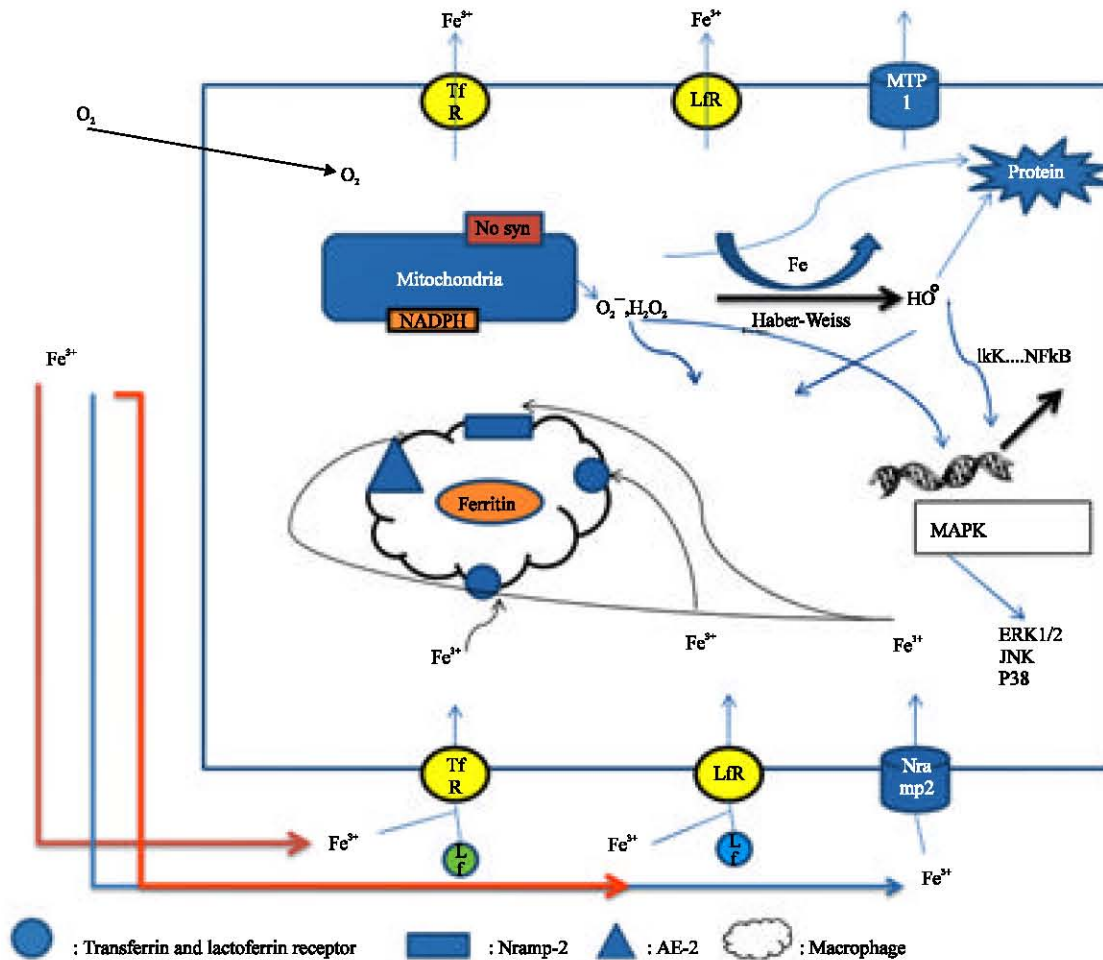


Fig. 1: Pathways of iron transport and iron-mediated damage within the lung epithelial cell; Tf: Transferrin, Lf: Lactoferrin, TfR: Transferrin Receptor, LfR: Lactoferrin Receptor, OH[•]: Hydroxyl radical, H₂O₂: Hydrogen peroxide, O₂⁻: Superoxide anion, kappa: IKK: IκB kinase, NFκB: Nuclear Factor κ 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 ferrereduction 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 H₂O₂ 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 DMT1 increases 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 through ascorbate-mediated cytochrome b ferrireduction (Ghio *et al.*, 2003). Anion-exchange protein is a novel system in the lung for transferrin-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 extracellular 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 (Demnery *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 Hexidentate 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;

Paraskevaïdis *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 bronchoalveolar lavage (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 lipopolysaccharide. 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 Fe³⁺ (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 thalasseamia (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.

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