Free Rad. Res., Vol 34, pp. 439-443
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The Iron Paradox of Heart and Lungs and its Implications for Acute Lung Injury

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Accepted for publication by Prof. B. Halliwell

(Received 14 September 2000; In final form 7 August 2000)

Iron is an essential requirement for the growth, development, and long term survival of most aerobic organisms. When control over safe iron sequestration is lost or compromised, leading to the release of low molecular mass forms of iron, the heart appears to be particularly sensitive to iron toxicity with cardiomyopathies often developing as a consequence. Iron toxicity, leading to iron-overload, is often treated in humans with the iron chelator desferrioxamine mesylate. Such treatment regimens designed to protect the heart can, however, often lead to lung injury and, in fact, several compounds with known iron chelating properties can induce severe lung dysfunction and injury. Based on these clinical observations and our recent laboratory data, we propose that the lungs actively accumulate reactive forms of iron for use in cellular growth and proliferation, and for the oxidative destruction of microbes, whereas the heart responds in the opposite way by actively removing iron which it finds extremely toxic.

Keywords: Iron signalling, sepsis, acute lung injury, iron toxicity, chelation, iron regulatory proteins

Abbreviations: ARDS, acute respiratory distress syndrome; TfR, transferrin receptor; CPB, cardiopulmonary bypass; IRPs, iron regulatory proteins; HO, haemoxygenase; GSH-Pase, glutathione peroxidase; SOD, superoxide dismutase; DFO, desferrioxamine mesylate; LMrFe, low molecular mass iron; ALI, acute lung injury; BAL, bronchoalveolar lavage

INTRODUCTION

Low molecular mass iron (LMrFe) is present inside cells, and in certain biological fluids, where the iron is associated with ligands such as citrate, phosphate, and acetate. The iron ions can readily be removed from such complexes by chelators with a stronger affinity for iron. Such iron is an essential growth factor for bacteria and is a catalyst for chemical reactions leading to the formation of powerful oxidants (reviewed in[1]). This explains why the body has evolved protective stratagies to keep iron safely sequestered. An example of how dangerous the body regards iron during infection is seen as the classical hypoferraemic response[2] of sepsis. The majority of deaths amongst critically ill patients requiring intensive care are attributable to sepsis leading to multiorgan system failure; the lung being most commonly afflicted. Indeed, some 40% of patients with sepsis develop acute lung injury (ALI) or its extreme manifestation, the acute respiratory distress syndrome (ARDS).

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Mortality amongst patients with ARDS remains high. The purpose of this commentary is to propose possible reasons why.

Whilst examining some of the factors influencing the antioxidant/pro-oxidant balance of plasma and other fluids in patients with ARDS, we observed a considerably disturbed iron chemistry as a feature of the disease[3,4]. We also studied, as a control group of patients at risk of developing ARDS, patients undergoing cardiopulmonary bypass (CPB) surgery. Interestingly too, CPB patients had serious abnormalities in their iron chemistry[5,6], leading us to explore in animal models, the molecular mechanisms that might be involved[7].

Endotoxaemia, developed in the rat, suggested that iron turnover and control in the heart and lungs were often opposite in response for these two organs (see Table I). Ferritin, a predominantly intracellular iron storage protein, and transferrin receptors (TfR) which are responsible for cellular uptake of iron, from iron-loaded transferrin, are subject to post-transcriptional control by the iron regulatory proteins (IRPs) (for a review see[8]). Based on the measurement of mRNA and protein levels, the heart by down-regulating the expression of TfR whilst maintaining, or even increasing ferritin levels, appeared to be decreasing mobile intracellular iron levels. In lung tissue, however, the opposite appeared to occur with an up-regulation of TfR expression and a decrease in cellular ferritin levels (see Table I).

We suggest that the different responses to endotoxin seen in these two organs are adaptations to accommodate both antioxidant and antimicrobial defence mechanisms. The data appear to support the known sensitivity of the heart to iron toxicity (Table 2). The high oxygen demand of the heart coupled to its low levels of constitutive antioxidants (see Table III) make it particularly susceptible to oxidative insults. The down regulation of TfR expression by the heart during sepsis, leading to decreased tissue accumulation of iron, may therefore be viewed as an antioxidant response to iron. This response can also be seen as antimicrobial, since low intracellular iron levels would limit the possibility of myocardial infection.

The response in the lungs, however, appears to be entirely different since iron seems to be necessary for normal lung function and, indeed, its removal by chelation causes serious lung injury (see Table IV). Since chelation of iron appears to cause lung injury, it seems unlikely that this type of tissue damage is mediated through reactive oxygen species. In support of a role for chelatable iron in normal lung function, low molecular mass iron (LMFe) has been found in bronchoalveolar lavage (BAL) fluid of normal individuals[9]. Levels of LMrFe were found to be increased in BAL fluid of patients with ARDS who survived the disease, whereas they were absent in those who died from ARDS[9]. In the latter case, severe lung leak allowed plasma transferrin to enter BAL and complex the LMrFe[9]. Why the lungs require low molecular mass forms of iron is not yet fully understood, although ongoing synthetic, proliferative, and protective processes seem likely. Indeed, it has been shown that decreased intracellular iron levels suppress epithelial cell surface plasmin generation necessary for repair of lung tissue damage[10]. Another possible explanation may, however, reside in the catalytic properties of iron whereby it can facilitate the formation of highly damaging species from superoxide, hydrogen peroxide, and hypochlorous acid (reviewed in reference[1]). Chelatable iron might, therefore, have a key role in host defence at the alveolar surface. The lung is an organ directly and continuously exposed to 21% oxygen, environmental pollutants, toxins, and microbes. It has its own constitutive and inducible antioxidant systems (reviewed in[11,12]) that would serve to protect against oxidative stress, although some are different from those seen in other organs, (see Table III). Lung lining fluid is unusual in having high levels of reduced glutathione (reviewed in[12]) and this together with ascorbate and urate

(reviewed in[13]) would tend to maintain iron in the reduced ferrous state and promote its catalytic properties. The low levels of unsaturated lipids in lung surfactant would also be compatible with a system in which reactive iron played a key role in host defence. Iron is a growth promoter for most bacteria[2] but, in normal healthy subjects, iron in the alveolar lung space may, in the short term, function to promote antimicrobial activity rather than microbial growth. During an acute inflammatory episode, however, such as occurs during sepsis, the role of iron in the lung may well become reversed as the balance between iron and reactive oxygen species is significantly changed.

TABLE I Some Changes in the Regulation of Iron Following an Endotoxin Challenge

		Heart	*Lungs*	*Refs*
A.	Change in mRNA			
	Transferrin receptors (TfR)	significantly decreased	significantly increased	[14]
	Ferritin			
	Heavy chains	no change	no change	[14]
	Light chains	no change	no change	
B.	Change in protein			
	Transferrin receptors (TfR)	significantly decreased	no change	[14]
	Ferritin (both forms)	no change	significantly decreased	[14]

TABLE II Iron Toxicity to the Heart

Condition	*Comments*	*Refs.*
Thalassaemia	Transfusional iron overload. LMrFe in plasma. Cardiomyopathies, hypopituitarism, diabetes as complications	Reviewed in [15]
Haemochromatosis	Hereditary. High body iron stores, LMrFe in plasma. Cardiomyopathies, hypopituitarism, diabetes, liver tumours	Reviewed in [15]
Oncology treatments with doxorubicin	Antibiotic (antitumour), iron chelator. Cardiomyopathies	Reviewed in [16]
High body iron stores in males	Postulated to be a reason for the higher incidence of heart disease in young males compared to females	[17]

LMrFe = Low molecular mass iron

TABLE III ***Some Antioxidant Responses* in *Heart and Lungs***

	Heart	*Lungs*	*Refs.*
Dietary Antioxidants	Epidemiological links between low long-term intake of antioxidants and risk of heart disease	No such links between antioxidant intake and acute lung disease. Dietary links between vitamin intake and chronic lung disease	[18,19]
Constitutive Antioxidants	Low levels of: SOD and catalase, compared with lung tissue, and GSHPase compared with liver and kidney. H-chain (ferroxidase) ferritin predominates, but deletion results in early embryonic death	Atypical pattern of extracellular antioxidants, possibly to deal with higher iron levels	Reviewed in [11,12]
Inducible Antioxidants: Stress by: Iron toxicity	HO-1 induction slow	HO-1 induction rapid. Low molecular mass iron is a product of HO-1 acting on haem.	[7]

TABLE IV Lung Damage Possibly Due to the Chelation of Iron

Condition	*Comments*	*Refs.*
Thalassaemia	Desferrioxamine (DFO) infusion can cause serious lung damage	[21]
Oncology treatments with Bleomycin	Lung tissue low in bleomycin hydrolase. Bleomycin is an iron chelator. ARDS can develop	[22]
Iron poisonings and treatment with desferrioxamine	DFO used to treat accidental and deliberate overdoses with iron. ARDS can develop	[23]
Wilson's disease and rheumatoid arthritis treated with D-Penicillamine	D-Penicillamine not specific as a copper chelator and can remove iron. Lung damage is a complication of treatment	[24,25]
Oleic acid and models of acute lung injury	Oleic acid used to develop ARDS in animal models. Oleic acid reported to strongly bind iron	[26] [27,28]

SUMMARY

We conclude, the lungs by evolving to use low molecular mass forms of iron for their normal functioning, became perilously susceptible to oxidative damage through the inflammatory response, and as a result of insult by environmental factors. Acute respiratory distress syndrome may represent an extreme example of such susceptibility.

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