# Acute respiratory distress syndrome in adults

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***The acute respiratory distress syndrome (ARDS) can arise from a range of predisposing insults. Mortality rates are high for patients with ARDS and survivors require extended and expensive intensive care treatment. This article presents evidence that implicates the production of toxic and damaging reactive oxygen species in the pathogenesis of ARDS.***

The acute respiratory distress syndrome (ARDS) is an acute inflammatory condition characterized by non-cardiogenic pulmonary oedema. It was first formally described in 1967 (Ashburgh et al, 1967). ARDS can arise as a result of a diverse and ever growing list of predisposing causes, often not directly involving the lung (Wyncoll and Evans, 1999).

When first described, ARDS was thought of as solely a respiratory condition, but is now thought to represent only the pulmonary manifestation of an acute pan-endothelial inflammatory insult (Dorinsky and Gadek, 1990; St John and Dorinsky, 1994). Indeed, the majority of deaths from ARDS do not result from respiratory failure but are attributable to multiple organ dysfunction syndrome (MODS) (Dorinsky and Gadek, 1990; St John and Dorinsky, 1994). Mortality rates for patients with ARDS vary between 30 and 70%, depending in part on the nature of the precipitating condition. Advances in intensive care management of ARDS patients have meant that mortality rates within individual centres have fallen from 65% to less than 35% over a 10-year period (Abel et al, 1998). Nevertheless, the intensive care required to treat patients with ARDS is prolonged and represents a considerable fiscal burden for the NHS.

## PATHOPHYSIOLOGY

The pathophysiology of ARDS is complex and probably involves the activation of inflammatory pathways of multiple types. Recently, our own research efforts have involved an in-depth assessment of the role of reactive oxygen species (ROS) in these processes. We have shown that ROS (sometimes termed oxygen free radicals) production is inherent to the disease process. Thus, plasma markers of lipid (Quinlan et al, 1994a, 1996) and protein oxidative damage (Quinlan et al, 1994b) are elevated in patients with ARDS compared with appropriate controls, demonstrating a marked oxidative burden.

Low molecular mass redox active iron (LmrFe) is a key catalyst for several reactions involving ROS which lead to the formation of aggressive and toxic reactants capable of causing molecular damage. Our studies have shown deficiencies in antioxidant protection specific for iron-catalysed ROS formation in patients with ARDS compared to controls (Gutteridge et al, 1994a). We have also demonstrated the presence of LmrFe, suggesting a state of iron overload exists in ARDS complicated by MODS (Gutteridge et al, 1994b). Iron chemistry is also disrupted in the lungs of such patients, and in non-survivors we have significant evidence of increased iron mobilization compared to that seen in survivors (Gutteridge et al, 1996).

Similar findings are apparent in patients at risk of developing ARDS, undergoing surgery necessitating cardiopulmonary bypass (Pepper et al, 1995). In these circumstances, iron overload was related to oxidative damage of plasma lipids (Quinlan et al, 1994c), and to the development of mild lung injury (Messent et al, 1997). There is consequently strong evidence implicating abnormalities in iron metabolism and related ROS production in the pathophysiology of ARDS, and ongoing studies using in-vivo models have confirmed original observations (Anning et al, 1999).

## SOURCES OF ROS

The sources of ROS formed in patients with ARDS include hyperoxia as a result of ventilatory support, the respiratory burst of activated inflammatory cells and the effects of ischaemia/reperfusion injury (*Figure 1*). We have found evidence linking a range of markers of oxidative damage found in the lungs with the degree of lung neu-

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trophil activation in patients with ARDS (Lamb et al, 1999a), thereby indicating that neutrophils are a major source of ROS in the lung.

Second, plasma hypoxanthine levels are significantly elevated in non-surviving patients with ARDS on the first day of admission to the intensive care unit, as well as throughout their stay, when compared to survivors (Quinlan et al, 1997). Hypoxanthine is a marker of ischaemia, but is also a substrate for the xanthine dehydrogenase/oxidase enzyme system. Xanthine oxidase (XOD) is formed from the dehydrogenase form of the enzyme during ischaemia. XOD catabolizes hypoxanthine and xanthine to uric acid and, in the process, produces the ROS superoxide and hydrogen peroxide (for a review see Parks and Granger, 1986). Patients with ARDS generally, and non-survivors in particular, therefore have the potential to generate ROS by this mechanism. Indeed, a significant correlation has been shown between hypoxanthine levels and a marker of protein oxidative damage.

Furthermore, XOD has been detected in plasma at elevated levels in plasma from patients with ARDS and sepsis (Grum et al, 1987; Galley et al, 1996). This mechanism of ROS production may be of particular relevance to endothelial cell damage associated with these patients, as XOD is known to bind readily to the endothelium (Adachi et al, 1993).

## PROBLEMS WITH VENTILATION

Ventilatory support with high inspired oxygen concentration is known to contribute to the pro-oxidant burden faced by patients in intensive care units and to lead to oxidative damage (Ben Baouali et al, 1994). As part of their ventilatory strategy patients with ARDS may be given inhaled nitric oxide (NO). NO has several pharmacological actions but is used as a vasodilator for the treatment of pulmonary hypertension in patients with ARDS, which also reduces shunt and improves oxygenation in the approximately 60% of patients who respond.

Although clinical trials have failed to show a survival benefit, inhaled NO has nevertheless been found to be effective on an individual patient basis. However, NO reacts with the ROS superoxide anion ($O_2^-$) rapidly at equimolar concentrations, to form the powerful oxidant peroxynitrite anion ($ONOO^-$). This species is capable of inflicting oxidative damage on biological molecules and is also a nitrating agent (reviewed in Beckman and Koppeno, 1996). The precise mechanisms by which nitration occurs are still a matter for debate but it is known that this modification can affect the function of numerous biological processes (reviewed in Ischiropoulos, 1998). Tyrosine and tryptophan residues are favoured nitration sites and the measurement of nitro-tyrosine levels is commonly used as a marker of peroxynitrite formation. We have found evidence of tyrosine nitration in BAL fluid proteins from patients with ARDS (Lamb et al, 1999a), the levels of which were significantly elevated in patients receiving inhaled NO therapy (Lamb et al, 1999b). These findings indicate that peroxynitrite is being formed in the lungs of patients with ARDS as part of an acute inflammatory process (NO is formed endogenously

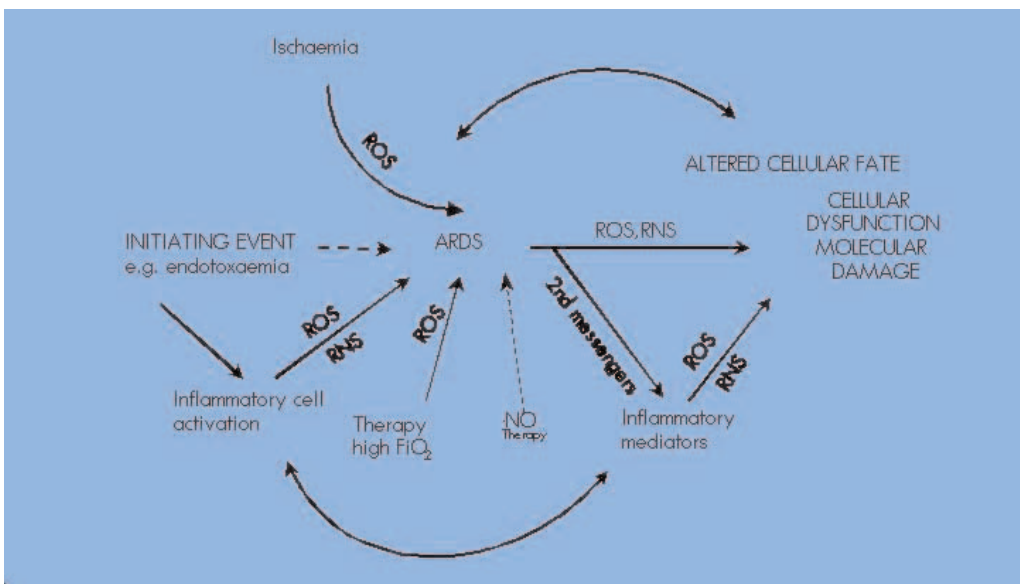


*Figure 1. Involvement of reactive oxygen species (ROS) in acute respiratory distress syndrome (ARDS). $FiO_2$ = inspired oxygen concentration; NO = nitric oxide; RNS = reactive nitrogen species.*

under such conditions) and that inhaled NO therapy increases the levels of peroxynitrite formed in the lungs of these patients. Nitration of surfactant protein A is known to decrease the effectiveness of lung surfactant (Haddad et al, 1996) and there are numerous other reported effects associated with nitration (reviewed in Ischiropoulos, 1998). The functional significance, if any, of these findings is unclear and warrants further study, particularly in view of the obvious benefits gained from this intervention.

## CONCLUSIONS

Patients with ARDS are subjected to severe oxidative stress that is generated by a variety of mediators including neutrophil activation, ischaemia/reperfusion and ventilatory support (both with and without inhaled NO — see *Figure 1*). Abnormalities in iron chemistry and metabolism may exacerbate such oxidative stress by catalysing the formation of more toxic ROS from normally innocuous species. To date, antioxidant interventions have failed to improve outcome in this patient population (Domenighetti et al, 1997), probably because of the complex nature of oxidant–antioxidant interactions in vivo and possible disruptions caused to ongoing processes.

A better approach for treatment in the future may be to upregulate specific endogenous protective strategies rather than trying the blanket approach of an all encompassing antioxidant. Identification of those individuals with a genetic predisposition for the development of ARDS may ultimately lead to the design of effective therapies to combat this devastating syndrome. HM

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### KEY POINTS

- Acute respiratory distress syndrome (ARDS) is an acute form of lung injury that can lead to mortality, although not usually as a result of the primary respiratory insult.
- ARDS arises from a variety of predisposing causes often not directly related to the lung.
- ARDS represents a considerable fiscal burden for the NHS.
- The production of reactive oxygen species has been implicated as a contributing factor to the onset and progression of ARDS.
- Identifying those individuals with a genetic predisposition for the development of ARDS will ultimately lead to the design of effective treatment regimens for this syndrome.