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Oxygen free radicals in ARDS, septic shock and organ dysfunction

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Introduction

The acute respiratory distress syndrome (ARDS), septic shock and multiple organ dysfunction syndrome (MODS) are the leading causes of mortality in intensive care units (ICUs), accounting for up to 50% of the deaths in ICUs. It is believed that endotoxin released from the bacterial cell wall initiates the physiological and biochemical abnormalities that characterize ARDS and septic shock. Biochemical injury can activate various cells such as macrophages, neutrophils, endothelial and epithelial cells resulting in the release of a number of mediators including cytokines, chemokines, platelet-activating factor, interferon-γ, complement prostanoids, leukotrienes and proteases. This sequence of events leads to neutrophil activation with the release of oxygen free radicals (OFR). These inflammatory mediators are important for killing various pathogens, but if the response is overexpressed then it may cause systemic infection in distal organs and can lead to death. The following is a brief description of recent studies that address the role of OFR in human ARDS, septic and MODS.

Quinlan GJ, Lamb NJ, Tilley R, Evans TW, Gutteridge JMC (1997) Plasma hypoxanthine levels in ARDS: implications for oxidative stress, morbidity and mortality. Am J Respir Crit Care Med 155: 479–484

Plasma protein thiol levels are significantly lower in patients with ARDS who do not survive the disease, suggesting they suffer from severe oxidative stress. This study measured plasma levels of pro-oxidant substrates for xanthine oxidase, hypoxanthine and xanthine and correlated them with the loss of plasma protein thiol groups. Twenty-nine patients with ARDS (APACHE II 13.2 ± 0.85) were studied at multiple time points to relate hypoxanthine levels to the severity of lung injury and survival. The same indices were measured in normal subjects and in two different control groups at risk from ARDS: patients undergoing pulmonary resection and critically ill individuals with sepsis. Where possible, measurements were also made in samples of bronchoalveolar lavage (BAL) fluid. In ARDS patients, plasma hypoxanthine levels in the non-survivors were significantly increased, compared with survivors, and elevated over the patients undergoing pulmonary resection, the ICU control patients and the normal control subjects. Plasma levels of hypoxanthine and protein thiol on the first day of admission to ICU were also significantly different between the non-surviving patients with ARDS and the survivors. A significant, negative correlation was observed between low protein thiols and high hypoxanthine levels. BAL fluid hypoxanthine levels significantly increased in the patients with ARDS compared with the normal control subjects. This study confirms that patients with ARDS have severe oxidative stress.

Metnitz PG, Bartens C, Fischer M, Fridrich P, Steltzer H, Druml W (1999) Antioxidant status in patients with acute respiratory syndrome. Intensive Care Med 25: 180–185

To determine endogenous antioxidant concentrations and lipid peroxidation, this study included eight patients with ARDS. Blood samples were taken when the diagnosis was made (d0) and after 3 (d3) and 6 days (d6) during therapy. The antioxidants alpha-tocopherol, ascorbate, beta-carotene and selenium were reduced from onset of illness in the patients compared to the reference range obtained from a group of healthy controls. In the patients with ARDS, the plasma lipid peroxidation level was significantly increased, suggesting a massive oxidant stress. This study indicates that reduction of endogenous antioxidant capacity may result in an imbalance between oxidant and antioxidant in patients with ARDS.

Borrilli E, Roux-Lombard P, Grau GE, Girardin E, Ricou B, Dayer J-M, Suter PM (1996) Plasma concentrations of cytokines, their soluble receptors and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. Crit Care Med 24: 392–397

As mentioned above, clinical studies appear to confirm the central role of the imbalance between oxidant and antioxidant activity in pathological processes involving neutrophil activation, such as sepsis and ARDS. It is reported that endogenous vitamin C is the first scavenger to enter the bloodstream and protect cell membranes against lipid peroxidation.

This study by Borrelli and colleagues was designed to evaluate plasma concentrations of tumour necrosis factor-α (TNF-α) and its soluble receptors, interleukin-6, as well as antioxidant vitamin C in 16 patients at high risk of developing MODS. Ten patients developed MODS and five of them died. Plasma TNF-α concentrations, soluble TNF-α receptors 55 (sTNF-αR-p55) and 75 (sTNF-αR-75) and interleukin-6 were higher in patients developing MODS compared with patients who did not develop MODS, whereas the vitamin C level was significantly decreased in patients with MODS during all ICU stays. This study suggests that an increased plasma concentration of cytokines and a decreased antioxidant vitamin C can contribute to the development of MODS in the critically ill patient at risk.

Galley HF, Howdle PD, Walker BE, Webster NR (1997) The effects of intravenous antioxidants in patients with septic shock. Free Radic Biol Med 23: 768–774

Oxidative stress is implicated in septic shock, but whether antioxidant therapy has a place in the treatment of septic shock is unclear. This study addressed this question. Thirty patients with septic shock randomly received either antioxidants, *N*-acetyl-L-cysteine plus vitamin C and E, or placebo. Basal vitamin C was low in all patients. In the 16 patients receiving antioxidants, vitamin C increased but the total antioxidant capacity, determined by an enhanced chemiluminescence technique, was unaffected. Lipid peroxidation was elevated in all patients but did not increase further in the patients receiving antioxidants. The antioxidant replacement therapy resulted in statistically significant haemodynamic changes. A decrease in systemic vascular resistance was associated with an increase in cardiac index in the antioxidant-treated patients. Systemic vascular resistance was decreased but blood pressure was maintained as a result of increased cardiac output. *N*-acetyl-L-cysteine is also known to enhance cardiac contractility. Enhancing cardiac performance without peripheral vasodilation may be a useful approach in the management of patients with sepsis and septic shock. This study supports the role of OFR in the inflammatory process and suggests an alternative therapeutic strategy for treatment of the haemodynamic derangement of septic shock.

Spapen H, Zhang H, Demanet C, Vleminckx W, Vincent J-L, Huyghens L (1998) Does *N*-acetyl-L-cysteine influence cytokine response during early human septic shock? Chest 113: 1616–1624

To assess the effects of adjunctive treatment with *N*-acetyl-L-cysteine on molecular mechanisms in human septic shock, we studied 22 patients within 4 h of diagnosis of septic shock. In addition to haemodynamics and blood gases, plasma concentrations of TNF-α, interleukin-6, interleukin-8, interleukin-10 and sTNF-αR-p55 were measured at 0, 2, 4, 6 and 24 h. *N*-acetyl-L-cysteine improved oxygenation and static lung compliance at 24 h, but had no significant effect on systemic and pulmonary haemodynamics, oxygen delivery or oxygen consumption. *N*-acetyl-L-cysteine acutely decreased interleukin-8 and sTNF-αR-p55 levels but had no significant effect on plasma TNF-α, interleukin-6 or interleukin-10 levels. Mortality rate was similar in the *N*-acetyl-L-cysteine-treated and untreated patients, but survivors who received *N*-acetyl-L-cysteine had fewer ventilator days and were discharged earlier from the ICU. This study suggests that treatment with the antioxidant *N*-acetyl-L-cysteine may improve lung function and shorten ICU stay in patients with early septic shock. The attenuated interleukin-8 production, a pivot mediator of septic lung injury, may have contributed to the lung-protective effects of *N*-acetyl-L-cysteine.

Discussion

In physiological conditions, the generation of small amounts of OFR is neutralized by scavenging substances such as superoxide dismutases, vitamin A, vitamin C, vitamin E and methionine; when OFR generation increases, defence systems fail and damage occurs. A massive increase in plasma lipoperoxides and a decrease in circulating endogenous antioxidants are reported in patients with ARDS and sepsis who develop MODS. These clinical investigations suggest the involvement of OFR as a key factor in human ARDS and sepsis immunopathophysiology.

A variety of sources of OFR are present in ARDS and septic patients leading to activation of xanthine oxidase and the respiratory burst of phagocytes. The possible sources of OFR during ARDS, sepsis and MODS are: (1) the mitochondrial respiratory chain during low oxygen availability, (2) the metabolic cascade of arachidonic acid, (3) the protease-mediated enzyme xanthine oxidase and (4) granulocytes and other phagocytes activated by complement, bacteria, endotoxin, lysosomal enzymes, etc. OFR are the highly reactive intermediates of the mono-reduction of molecular oxygen. OFR can result in profound disturbances of cell biochemistry such as protein denaturation, polysaccharide depolymerization, cellular and interstitial structure destabilization.

Oxygen free radical stress is probably operative in many critically illnesses. A number of clinical studies emphasize that modulating OFR stress may be one important intervention to control the systemic inflammatory response associated with ARDS and sepsis. Many antioxidants, such as vitamin E, dimethyl sulfoxide, glutathione, *N*-acetyl-L-cysteine, applopurinol, 21-aminosteriods as well as a variety of nitrones, have been tested in animal models and have improved the evolution of septic shock. In patients with ARDS, *N*-acetyl-L-cysteine improved systemic oxygenation, reduced the need for ventilatory support and decreased lung injury score [Chest (1994)105: 190–194, J Crit Care (1997)12: 177–182]. In another study in patients with sepsis-related ARDS, the administration of the antioxidants *N*-acetyl-L-cysteine and procysteine has been shown to shorten the duration of acute lung injury, increase cardiac index and replenish red blood cell glutathione [Chest (1997) 112: 164–172]. However, a recent ARDS clinical trial with procysteine has been terminated early, because there was an unexpected mortality rate in the treatment group. A study in patients with septic shock demonstrated that *N*-acetyl-L-cysteine increased oxygenation in most patients studied but haemodynamics, gastric intramucosal pH and survival improved in only some of them [Crit Care Med (1994) 22: 1738–1746]. The timing between the onset of sepsis and the administration of the drug may be an important factor influencing the response to the therapy. It seems likely that an effective intracellular and extracellular antioxidant screen is necessary to protect tissues from injury. To date, no drug with an antioxidant activity has been conclusively proven to be effective in controlling OFR associated with ARDS and septic shock in a clinical trial. However, there is no question that a novel therapeutic approach balancing oxidant and antioxidant and pro- and anti-inflammatory responses for the treatment of these deadly diseases is required.

Interestingly, using molecular modelling studies, a stable and active class of superoxide dismutase (SOD) mimics, M40403, has been recently discovered [Science (1999) 286: 304–306]. M40403 had high catalytic SOD activity and was chemically and biologically stable in vivo. Injection of M40403 into rat models of inflammation and ischaemia-reperfusion injury decreased myeloperoxidase activity (an index of neutrophil activation) and the cytokines TNF-α and interleukin-1β (IL-1β), and protected the animals against tissue damage. In addition to the direct effects of superoxide anion in these models, it is possible that some of the beneficial anti-inflammatory and cytoprotective effects of M40403 are due to the prevention of peroxynitrite formation through the removal of superoxide anion before it reacts with nitric oxide. Such mimics may result in better clinical therapies for diseases mediated by superoxide radicals.