PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B, Vol. 68 (2014), No. 5/6 (692/693), pp. 200–206.
DOI: 10.2478/prolas-2014-0024

Review

THE ROLE OF OXIDATIVE STRESS MARKERS IN DEVELOPING OF ACUTE RESPIRATORY DISTRESS SYNDROME

Marina Šarkele*#, Agnese Ozoliņa*, Olegs Sabeļņikovs*, Andrejs Šķesters**, Alise Silova**, Inta Jaunalksne***, Eva Strīķe*, Angelika Krūmiņa****, and Indulis Vanags*

* Department of Anaesthesiology and Reanimatology, Rīga Stradiņš University, Rīga Stradiņš University, Dzirciema iela 16, Rīga, LV-1007, LATVIA; lu_xus@inbox.lv

** Laboratory of Biochemistry, Rīga Stradiņš University, Rātsupītes iela 5, Rīga, LV-1067, LATVIA

*** Pauls Stradiņš Clinical University Hospital, Pilsoņu iela 13, LV-1002, LATVIA

**** Department of Infectology and Dermatology, Rīga Stradiņš University, Linezera iela 3, LV-1006, LATVIA

Corresponding author

Communicated by Rafails Rozentāls

Acute respiratory distress syndrome (ARDS) is common and multi factorial, clinically described as an inflammatory lung disorder that is associated with major morbidity and high mortality in intensive care patients. Recently, investigators have revised the AECC criteria from 1994. To diagnose ARDS and discover its severity we presently use Berlin definition criteria. An important role in developing of ARDS may be through a disbalance between reactive oxygen species (ROS), which have both oxidant and antioxidant compartments. The pathogenesis of ARDS is very complex, and unfortunately, the dynamic development of ARDS in an individual patient is difficult to recognise. ROS can initiate cellular tissue damage by modifying lipids, proteins and DNA, which can seriously compromise cell life ability or induce a large number of cellular responses through generation of secondary reactive species, leading, at last, to cell death by necrosis or apoptosis. Studies have shown that many patients with organ malfunction at admission to the intensive care units (ICU) show decreased antioxidative properties, worsening the harmful effects of lipid peroxidation. That is the reason why predicting development of ARDS has great value for intensive care specialists.

Key words: *oxidative stress markers, acute respiratory distress syndrome, biomarkers, antioxidants, oxidants, reactive oxygen species.*

INTRODUCTION

Patients in the intensive care unit (ICU) are likely to suffer from acute respiratory failure (ARF) with a risk of developing acute lung injury (ALI) and its more severe complication, acute respiratory distress syndrome (ARDS) with 30–50% mortality (Bernard *et al.*, 1994; Ferguson *et al.*, 2007). Hospital mortality in Scandinavia decreased by 1% per year ($p = 0.03$) during the studied period held, from 50% in 1988–1992 to 33% in 2006–2010. The ten-year survival of ARDS survivors was 68% compared with 90% survival of a reference population ($p < 0.001$). The incidence of ARDS has almost doubled, but hospital mortality was shown to decrease since 1990 during 23 years of observation in Scandinavia (Sigurdsson *et al.*, 2013).

Patients with ARF, and particularly those diagnosed with ARDS, represent a great economic burden, because of the requirement of long-lasting and possibly harmful ventilator support, eventually including extracorporeal membrane oxygenation (ECMO) and other advanced management techniques.

The acute respiratory distress syndrome (ARDS) is common and multi factorial, clinically described as an inflammatory lung disorder, which is associated with great morbidity and high mortality in intensive care patients. An important role in developing of ARDS may by played by a disbalance between reactive oxygen species (ROS), which have both oxidant and antioxidant compartments. The pathogenesis of ARDS is very complex, and unfortunately, the dynamic development of ARDS in an individual patient is difficult to recognise. That is the reason why predicting development of ARDS has great value for intensive care specialists.

DEFINITIONS

During the last two decades, ALI and ARDS have been defined according to the American–European Consensus Conference (AECC) criteria, where ARDS was diagnosed as a

"syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension" (Bernard *et al.*, 1994). In short, the definition is based on the following criteria: (1) acute onset; (2) PaO_2/FIO_2 < 300 mm Hg for ALI and PaO_2/FIO_2 < 200 mm Hg for ARDS; (3) bilateral infiltrates on the frontal chest radiograph; and (4) pulmonary artery pressure < 18 mm Hg, or no clinical evidence of left atrial hypertension (Bernard *et al.*, 1994) (Table 1).

The severity of the disease was evaluated using Murray lung injury score (Table 2).

In 1988, Murray and colleagues proposed an expanded definition of ARDS, taking into account various pathophysiological features of the clinical syndrome (Murray *et al.*, 1988). The Murray scoring system includes four criteria for the development of ALI/ARDS: a "scoring" of hypoxemia, a "scoring" of respiratory system compliance, chest radiographic findings, and level of positive end-expiratory pressure. Each criterion receives a score from 0 to 4 according to the severity of the condition. The final score is obtained by dividing the collective score by the number of components that were used. A score of zero indicates no lung injury, a score of 1–2.5 indicates mild to moderate lung injury, and a final score of more than 2.5 indicates the presence of acute respiratory distress syndrome (Murray *et al.*, 1988).

Recently, investigators have revised the AECC criteria from 1994 (Bernard *et al.*, 1994; Ranieri *et al.*, 2012). The AECC definition required that onset of respiratory failure is acute, without indicating a specific timeframe (e.g., hours, days, or weeks). In a study by Fergusson *et al.* (2005), during the period of acceptance, when the criteria were strictly applied (bilateral chest X-ray infiltrates) in routine work, the sensitivity remained at 84%, but the specificity was at only 51%. Acute lung injury, as in a subgroup with a milder hypoxemia (i.e., with PaO_2/FiO_2 201–300 mmHg) was suggested to be under-recognised by clinicians. The clinicians concluded that PaO_2/FiO_2 may vary with FiO_2, and in response to differences in ventilator settings, particularly to variations in PEEP.

Since PEEP can affect the reliability and specificity of PaO_2/FiO_2 to classify the severity of ARDS, a minimum PEEP level of 5 cm H_2O (or non-invasive CPAP for mild ARDS) has been included in the updated Berlin definition, where ALI is defined as mild form of ARDS, as shown in Table 3 (Ranieri *et al.*, 2012). Table 3 distinguishes three different stages (mild, moderate, and severe) of ARDS to provide better and more precise separation of prognosis and interventional decisions. Several observational studies suggest that the majority of patients are identified within 72 h of the recognition of underlying risk factors, with nearly all patients identified within seven days. The meaning of "acute onset" has been redefined as a condition developing within one week of a known clinical insult or new/worsen-

Table 1

AMERICAN–EUROPEAN CONSENSUS CONFERENCE ON ARDS: RECOMMENDED CRITERIA FOR ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Injury	Criteria
ALI	Acute onset $PaO_2/FiO_2 \leq 300$ mm Hg Bilateral infiltrates on frontal chest radiograph Pulmonary artery wedge pressure ≤ 18 mm Hg (when measured), or no clinical evidence of left atrial hypertension
ARDS	Acute onset $PaO_2/FiO_2 \leq 200$ mm Hg Bilateral infiltrates on frontal chest radiograph Pulmonary artery wedge pressure ≤ 18 mm Hg (when measured), or no clinical evidence of left atrial hypertension

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; PaO_2, arterial oxygen tension; FiO_2, fraction of inspired oxygen.

Table 2

THE LUNG INJURY SCORE (Murray score)

1. Chest radiogram score		
No alveolar consolidations		0
Alveolar consolidation confined to 1 quadrant		1
Alveolar consolidation confined to 2 quadrant		2
Alveolar consolidation confined to 3 quadrant		3
Alveolar consolidation confined to 4 quadrant		4
2. Hypoxemia score		
PaO_2/FiO_2	≥ 300	0
PaO_2/FiO_2	225–299	1
PaO_2/FiO_2	175–224	2
PaO_2/FiO_2	100–174	3
PaO_2/FiO_2	< 100	4
3. PEEP score (when ventilated)		
PEEP	≤ 5 cmH_2O	0
PEEP	6–8 cmH_2O	1
PEEP	9–11 cmH_2O	2
PEEP	12–14 cmH_2O	3
PEEP	≥ 15 cmH_2O	4
4. Respiratory system compliance score (when available)		
Compliance	≥ 80 ml/ cmH_2O	0
Compliance	60–79 ml/ cmH_2O	1
Compliance	40–59 ml/ cmH_2O	2
Compliance	20–39 ml/ cmH_2O	3
Compliance	≤ 19 ml/ cmH_2O	4
The final value is obtained by dividing the aggregate sum by the number of components that were used.		
		Score
No lung injury		0
Mild to moderate lung injury		0.1–2.5
Severe lung injury		> 2.5

PaO_2 / FiO_2, arterial oxygen tension to inspired oxygen concentration ratio; PEEP, positive end expiratory pressure.

Table 3

THE BERLIN DEFINITION OF ARDS*

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities — not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g, echocardiography) to exclude hydrostatic edema if no risk factor presented
Oxygenation[b]	Mild — 200 mm Hg ≤ PaO_2/FiO_2 ≤ 300 mm Hg with CPAP or PEEP ≥ 5 cm H_2O[c] Moderate —100 mm Hg ≤ PaO_2/FiO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O Severe — PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥ 5 cm H_2O

* Ranieri *et al*., 2012. CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end- expiratory pressure; a, chest radiograph or computed tomography scan; b, if altitude is higher than 1000m, the correction factor should be calculated as follows: (PaO_2/FiO_2 x (barometric pressure/ 760)); c, this may be delivered noninvasively in the mild acute respiratory distress syndrome group.

ing of already existing respiratory failure. Another concern is that the chest X-ray criterion has moderate inter-observer reliability, even among experts (Ranieri *et al.*, 2012; Meade *et al.*, 2000). To make the chest radiograph criterion more clear, it should include "diffuse" bilateral opacities consistent with pulmonary oedema, which are not fully explained by effusions, lung collapse, or nodules/masses. On the other hand, CT scan abnormalities are not included in the definition (Table 3).

Etiology. ARDS is a multi-factorial disease that may occur due to environmental causing factors in genetically predisposed critically ill individuals.

ALI and ARDS can develop due to pulmonary (direct) or extrapulmonary (indirect) reason. Direct ALI causes (pneumonia, aspiration of gastric content, contusion, embolus, inhalation injury and reperfusion) account for approximately 55% of all ALI cases, and indirect ALI (extrapulmonary sepsis and trauma, burn injury, mass transfusion of blood components, bypass surgery, intoxication and acute pancreatitis) account for 20%. In one-fifth of all patients, there appear to be mixed factors leading to ALI and the remaining 4% actually cannot be explained by any underlying pathophysiology. Sepsis is the most commonly encountered condition among all mentioned underlying the development of ALI, with severe sepsis accounting for 46% of direct and 33% of indirect ALI cases (Perl *et al.*, 2011).

PATHOPHYSIOLOGY

The pathology leading to ALI/ARDS has not been well understood until recently. It is likely to be as heterogeneous as the underlying conditions that induce them.

Oxidative or, in other words, nitrosative stress is a condition that is characterised by increased levels of reactive oxygen species. It is recognised to be one of the most important features of many acute and chronic diseases, not only in the aging process.

As mentioned above, generation of reactive oxygen species (ROS) in lung infection plays a significant role in development of ARDS and worldwide attention to this has tended to increase, since many physiological and pathophysiological conditions are related to oxidative-antioxidative cell modification. A free radicals can be defined as chemical substances containing unpaired electrons and that are paramagnetic. Most of the oxygen derived free radicals are unstable molecules, short-lived and highly reactive. For these reasons, ROS can initiate cellular tissue damage by degrading lipids, proteins and DNA, which can seriously influence cell life ability or induce a large number of cellular responses due to generation of secondary reactive species, leading to cell death by necrosis or apoptosis.

Free radicals can be removed by some metalloenzymes (e.g., superoxide dismutase, glutathione peroxidase, and catalase) as well as by the non-enzymatic antioxidant protective system (e.g., tocopherol, β-carotene, glutathione, lipoic acid, and uric acid), the main function of which is to reduce their chemical activity.

Another important process in oxidative stress formation is lipid peroxidation. This is a complex process whereby polyunsaturated fatty acids in phospholipids of cellular membranes undergo reaction with oxygen to form lipid peroxides and hydroperoxides (LH, LOOH). The LOOH and conjugated dienes that are formed can decompose to form a variety of other products, including alkanals, alkenals, hydroxyalkenals, malondialdehyde (MDA), reactive carbonyl intermediates, such us α,β-unsaturated aldehydes-4-hydroxinonenal (4-HNE) and volatile hydrocarbons. Malondialdehyde is an indicator that can be used to detect lipid peroxidation. Another indicator might be thiobarbituric acid (TBA), which together with MDA can form a complex MDA_TBA, which could be related to the activity of oxidative stress in ARDS patients. However, MDA is regarded to be an unspecific marker of lipid peroxidation due to analytical difficulties, and thus in combination with TBA it may be more specific (Lapenna *et al.*, 2001). Volatile aldehydes have been studied as specific markers of lipid peroxidation in asthma/chronic obstructive pulmonary disease (Corradi *et al.*, 2004) and ARDS (Weigand *et al.*, 2004). Aldehydes of all types are considered as toxic second messengers, due to their ability to react with protein molecules. This may result in severe damage caused by loss of enzyme activity, destruction of amino acids and polymerization, as well as genotoxicity induced by binding to DNA (Valko *et al.*, 2006).

In a study (Lichtenstern *et al.*, 2009) comparing ARDS and liver failure patients, MDA levels were more than four times higher in arterial and mixed venous blood of ARDS patients than those of patients who suffered from liver in-

sufficiency. There was no difference detectable for MDA concentrations in arterial and mixed venous blood of ARDS patients (p = 0.78). However, in the ARDS group, both volatile aldehydes showed much higher arterial than mixed venous levels, representing significant gradients between both compartments (Lichtenstern *et al.*, 2009).

In sepsis patients, a significant increase of MDA levels was observed to develope, compared to those in burn trauma patients, on the second day (Mühl *et al.*, 2011). Lipid peroxidation reaction in biological membranes causes the impairment of membrane functioning, because of inactivation of membrane-bound receptors and enzymes, as well as increased non-specific permeability to ions (Palmieri *et al.*, 2007).

It has been shown that many patients with organ malfunction at admission to intensive care units (ICU) show impaired antioxidative properties, worsening the harmful effects of lipid peroxidation. For this reason, antioxidative nutrients such as selenium may be beneficial in the treatment of critical ill patients (Heyland *et al.*, 2005).

A dominant role in ARDS pathophysiology is played by imbalance between oxidant and antioxidant species. Previous studies have shown that decreased concentrations of water-soluble antioxidants (urate, glutathione, ascorbate) are present in the distal airways in patients with ALI (Bowler *et al.*, 2003).

Elevated concentrations of hydrogen peroxide (Baldwin *et al.*, 1986; Sznajder *et al.*, 1989) as well as isoprostanes (Carpenter *et al.*, 1998) due to peroxidation of membrane phospholipids in vivo have been observed in the exhaled breath condensate in ARDS patients. This group of patients showed a significant decrease of antioxidants like α-tocopherol and selenium, while the level of lipid peroxidation in plasma was increased (Richard *et al.*, 1990; Quinlan *et al.*, 1996; Metnitz *et al.*, 1999; Kumar *et al.*, 2000)

In patients with recognised distress syndrome, concentrations of lipid peroxides are significantly higher, compared to those in controls and patients who are at risk for developing ARDS (Kumar *et al*., 2000). Moreover, patients at risk for ARDS or with already diagnosed syndrome showed a significant decrease in polyunsaturated fatty acids (PUFA), representing an important fatty acid deficiency disease (Gutteridge *et al.*, 1998). Kumar *et al.* (2000) showed a significant decrease in the levels of nitric oxide in patients with established ARDS.

As part of ARDS pathophysiology, accumulation of neutrophils has been observed, which is important in patients with developing acute lung injury (Lee *et al.*, 2001). The physiologic role of neutrophils can be characterised not only by production and release of ROS, but also by release of proteases favouring pathogen translocation. Effective neutralisation of neutrophil proteases and free radicals by lung antioxidants (glutathione) and antiproteases (a1-antitrypsin, a2-macroglobulin) can possibly prevent developing lung injury.

Inflammation of the lung may result in activation of macrophages and neutrophils, which indicates the release of free radicals due to respiratory burst. In addition, commonly used high inspiratory concentrations of oxygen may contribute to generation of free radicals (Lang *et al.*, 2002), not only in critically ill patients, but also during long general anaesthesia. This shows a dependence of oxidative stress markers on ventilation strategy, which is used in treatment of patients with acute respiratory failure.

Another aspect that should be considered is that the mode of ventilation during ARDS may also influence antioxidant gene expression followed by antioxidant release. The mode of ventilation has a proved impact on gene expression in lung tissue, as it has been observed that a non-ventilated lung had increased levels of proinflammatory genes (e.g. interleukin-1b) in bronchial epithelium cells after high-frequency ventilation (Copland *et al.*, 2003).

As severe sepsis is one of known causes for developing ARDS, there is a need to understand the role of nitrosative stress in sepsis. According to Mühl *et al.* (2011), severe sepsis is accompanied by oxidative stress and pathological leukocyte endothelial cell interactions, as the laboratory parameters used for the evaluation of sepsis and several markers of pro- and antioxidant status differ between sepsis and non-sepsis burn patients. The tendency of changes in these parameters may result in major oxidative stress in developing of sepsis in burn patients; septic patients showed a significantly elevated leucocyte count and different C-reactive protein levels during a 5-day period (Mühl *et al.*, 2011). Oxidative stress is a major contributing factor to the high mortality rates associated with severe sepsis and many other diseases associated with major inflammation (Everton *et al.*, 2009). Previous studies have confirmed severe oxidative stress in sepsis patients, demonstrating reduced plasma, total antioxidant capacity, and elevated levels of malondialdehyde and 4-hydroxynonenal. Oxidative stress caused by sepsis induces an imbalance between the production of free radicals and endogenous available antioxidants (Alonso de Vega *et al.*, 2002).

Diseases in which high levels of protein carbonyl (PC) groups have been observed include Alzheimer's disease, rheumatoid arthritis, diabetes, sepsis, chronic renal failure, and respiratory distress syndrome (Dale-Donne *et al.*, 2003). Protein carbonyl groups (aldehydes and ketones) are produced on protein side chains in oxidised condition. These molecules are described as chemically stable species, compared with those mentioned above, which can be useful for their detection to predict disease. Increased concentrations of protein carbonyls have been documented in ARDS patients (Sittipunt *et al.*, 2001). The carbonyl content of broncho-alveolar lavage (BAL) fluid proteins were observed to be significantly increased in patients with diagnosed ARDS (5.0 **F** 1.3 nmol carbonyl/ml BAL fluid, p = 0.0004) and moderately increased in patients at risk for de-

veloping ARDS caused by coronary bypass surgery (1.3 **F** 0.2 nmol/ ml, p = 0.027), compared with a control group (0.8 **F** 0.2 nmol/ ml) (Lenz *et al.*, 1999). In addition, there are a large number of potential oxidative modifications, of which only a few have been systematically studied, for example the already mentioned protein carbonyl group products.

Acute respiratory distress syndrome is associated with a complicated process of ROS expression, NO generation and consumption. Concentrations of NO molecules will differ in the unstable changing cytokine environment according to the origin of airway inflammation followed by neutrophil activation, production of reactive oxygen species and acidity of endothelial and epithelial cells (Marczin and Royston, 2001).

ANTIOXIDANTS

The massive production of ROS is generally inactivated by endogenous and/or exogenous antioxidant molecules (Cui *et al.*, 2004).

The balance between the physiological production of ROS and their inactivation in cells is based on effective enzymatic and non-enzymatic antioxidant systems (Behl *et al.*, 2002), as summarised in Figure 1.

As a first line of protection, preventive antioxidants act by binding to specific promoters of oxidation and transition metal ions, like iron and copper, which contain unpaired electrons. As a result, the formation of free radicals is elevated. Preventive antioxidants also include enzymatic antioxidants like superoxide dismutase (SOD), glutathioneperoxidase (GPx) and catalase (CAT). These enzymes act on specific ROS following their formation and degrade them to less harmful products (Ccui *et al.*, 2004; Wilcox *et al.*, 2004).

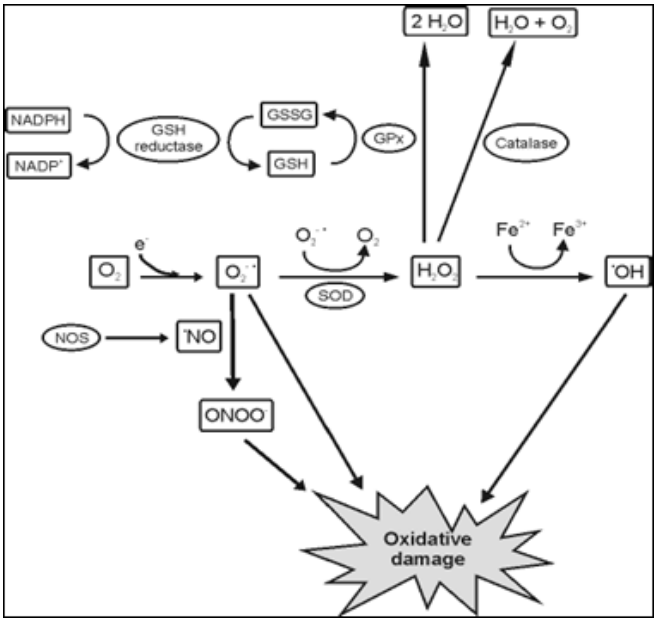

Fig. 1. Formation of reactive oxygen and nitrogen species and some of the endogenous antioxidant defence mechanisms. SOD, superoxide dismutase; GSH, reduced glutathione; GSSG, oxidised glutathione; GPx, glutathione peroxidase.

One of the most effective intracellular enzymatic antioxidants is superoxide dismutase. This enzyme catalyses the dismutation of the superoxide anion to molecular oxygen and hydrogen peroxide. The H_2O_2 formed in this reaction is later destroyed by the action of catalases and glutathione peroxidases.

Catalase is a heme-containing enzyme, mainly localised in the peroxisomes of mammalian cells, which decomposes hydrogen peroxide to water and molecular oxygen.

Superoxide dismutases act together with catalases — at the antioxidant forefront with a function to destroy free oxygen radicals. In this way, these enzymes significantly decrease the free radical concentration in the cell and minimise oxidative damage causing cellular death. There are three forms of metal-containing superoxide dismutases: SOD1 (Cu, Zn-SOD) located in the cytoplasm, SOD2 (MnSOD) in the mitochondria, and, finally, SOD3 (Cu, Zn-SOD) is extracellular form that can be found at the production site. Decreased SOD activity may be associated with a variety of mutations in Cu/Zn-SOD, which can characterise several neurodegenerative diseases (Stasser *et al.*, 2005).

The selenium containing peroxidises, of which glutathione peroxidase may be the most important example, catalyse the reduction of hydroperoxides (H_2O_2 or ROOH) in the presence of the reduced form of glutathione (GSH) (Matés *et al.*, 2000), which oxidises two molecules of GSH to GSSG (the oxidised form of glutathione), which can subsequently be reduced to GSH again by glutathione reductase (Nordberg *et al.*, 2001). The tripeptide glutathione exists either in the reduced (GSH) or oxidised (GSSG) form and is present in all cells. Its main functions include: restoration of oxidised proteins, detoxification of hydrogen peroxide, and lipid hydroperoxides. Another important function provided by glutathione is transport of amino acids through the plasmatic membrane, regeneration of some antioxidants like α, β, γ, δ- tocopherols to active forms. The main clinical value of glutathione is protection of brain tissue from oxidative stress (Nordberg *et al.*, 2001; Valko *et al.*, 2006; Drake *et al.*, 2003; Masella *et al.*, 2005). The glutathione level was observed to be significantly elevated in burn trauma patients at the first and third day after admission in ICU, while superoxide dismutase enzyme activity showed no significant changes among the control, sepsis and thermal injury groups. On the other hand catalase activity was increased in sepsis patients on the first day compared to the burn trauma group (Mühl *et al.*, 2011). Previous studies confirmed the hypothesis that alveolar antioxidants may be decreased in bronchoalveolar lavage fluid in burn patients (Comhair *et al.*, 2002).

Previous study (Schmidt *et al.*, 2004) showed that ARDS patients had increased neutrophil and decreased macrophage counts in the broncho-alveolar lavage fluid. Total

BALF protein was highly elevated in ARDS, while total phospholipid levels did not differ significantly between patients and controls. In healthy controls, GSH was the most common antioxidant molecule. Patients with ARDS (0.13 mM) showed higher concentrations of GSSG compared with controls (0.03 mM). F_2-isoprostane levels, as markers for lipid peroxidation, were significantly elevated in ARDS patients, indicating oxidant stress. The concentration of GSH was not different in ARDS as compared with controls. The analysis of α-tocopherol showed a significant increase in ARDS patients. When the patients with ARDS were divided into primary ARDS and secondary ARDS group, only minor differences were observed in GSH levels (Schmidt *et al.*, 2004).

Another study performed by Sakr and co-workers (Sakr *et al.*, 2007) shows the relation of selenium levels to sepsis and SIRS. On ICU admission, 92% of patients had plasma selenium levels below 74 μg/L — which is the reference level for healthy patients. Plasma selenium levels showed a decrease in all patients with SIRS, especially when associated with sepsis, despite 100 μg/day administration of selenium. The degree of organ dysfunction appeared to be a major factor explaining the drop in selenium concentration. A plasma selenium level of 36 μg/L was found to predict ICU mortality with high sensitivity and specificity. Serum selenium levels were low in all groups of patients compared to those of controls, but the greatest decrease was seen in the patients with severe organ failure, especially in those with established infection.

In conclusion, dynamic changes of oxidative and antioxidative markers are not clearly understood in critically ill patients with acute respiratory failure and as a result in acute respiratory distress syndrome. A variety of contradicting data have been published in recent and previous studies, and no consensus have been found yet. As a result, oxidative stress is a wide field for investigations and improvements by scientists and clinical experts.

REFERENCES

Alonso de Vega, J. M., Díaz, J., Serrano, E., Carbonell, L. F. (2002). Oxidative stress in critically ill patients with systemic inflammatory response syndrome. *Crit. Care Med.*, **30**, 1782–1786.

Baldwin, S. R., Simon, R. H., Grum, C. M., Ketai, L. H., Boxer, L. A., Devall, L. J. (1986). Oxidant activity in expired breath of patients with adult respiratory distress syndrome. *Lancet*, **1**, 11–14.

Behl, C., Moosmann, B. (2002). Antioxidant neuroprotection in Alzheimer's disease as preventive and therapeutic approach. *Free Radic. Biol. Med*., **33**, 182–191.

Bernard, G. R., Artigas, A., Brigham, K. L., Carlet, J., Falke, K., Hudson, L., Lamy, M., Legall, J. R., Morris, A., Spragg, R. (1994). The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Amer. J. Respir. Crit. Care Med*., **149** (3 Pt 1), 818–824.

Bowler, R. P., Velsor, L. W., Duda, B., Chan, E. D., Abraham, E., Ware, L. B., Matthay, M. A., Day, B. J. (2003). Pulmonary edema fluid antioxidants are depressed in acute lung injury. *Crit. Care Med*., **31**, 2309–2315.

Carpenter, C. T., Price, P. V., Christman, B. W. (1998). Exhaled breath condensate isoprostanes are elevated in patients with acute lung injury or ARDS. *Chest*, **114**, 1653–1659.

Comhair, S. A., Erzurum, S. C. (2002). Antioxidant responses to oxidant-mediated lung diseases. *Amer. J. Physiol*., **283**, L246–L255.

Copland, I. B., Kavanagh, B. P., Engelberts, D., McKerlie, C., Belik, J., Post, M. (2003). Early changes in lung gene expression due to high tidal volume. *Amer. J. Respir. Crit. Care. Med*., **168**, 1051–1059.

Corradi, M., Pignatti, P., Manini P., Andreoli, R., Goldoni, M., Poppa, M., Moscato, G., Balbi, B., Mutti, A. (2004). Comparison between exhaled and sputum oxidative stress biomarkers in chronic airway inflammation. *Eur. Respir. J*., **24**, 1011.

Cui, K., Luo, X., Xu, K., Ven Murthy, M. R. (2004). Role of oxidative stress in neurodegeneration: Recent developments in assay methods for oxidative stress and nutraceutical antioxidants. Prog. Neuropsychopharmacol. *Biol. Psych*., **28**, 771–799.

Dalle-Donne, I., Ranieri, R., Giustarini, D., Milzani, A., Colombo, R. (2003). Protein carbonyl groups as biomarkers of oxidative stress. *Clin. Chim. Acta*, **329**, 23–38.

Drake, J., Sultana, R., Aksenova, M., Calabrese, V., Butterfield, D. A. (2003). Elevation of mitochondrial glutathione by gamma-glutamylcysteine ethyl ester protects mitochondria against peroxynitrite-induced oxidative stress. *J. Neurosci. Res*., **74**, 917–927.

Everton Andrades, M., Ritter, C., Dal-Pizzol, F. (2009). The role of free radicals in sepsis development. *Front Biosci* (*Elite Ed*) No. 1, 277–287.

Ferguson, N. D., Frutos-Vivar, F., Esteban, A., Gordo, F., Honrubia, T., Penuelas, O., Algora, A., Garcia, G., Bustos, A., Rodriguez, I. (2007). Clinical risk conditions for acute lung injury in the intensive care unit and hospital ward: A prospective observational study. *Crit. Care*, **11** (5), R96.

Ferguson, N. D., Frutos-Vivar, F., Esteban, A., Fernandez-Segoviano, P., Aramburu, J. A., Najera, L., Stewart, T. E. (2005) Acute respiratory distress syndrome: Under recognition by clinicians and diagnostic accuracy of three clinical definitions. *Crit. Care Med*., **33**, 2228–2234.

Gutteridge, J. M. C., Quinlan, G. J., Yamamoto, Y. (1998). Are fatty acid patterns characteristic of essential fatty acid deficiency indicative of oxidative stress? *Free Radic. Res*., **28**, 109–114.

Heyland, D. K., Dhaliwal, R., Suchner, U., Berger, M. M. (2005). Antioxidant nutri- ents: A systematic review of trace elements and vitamins in the critically ill patient. *Int. Care Med*., **31**, 327.

Kumar, K. V., Rao, S. M., Gayani, R., Mohan, I. K., Naidu, M. U. (2000). Oxidant stress and essential fatty acids in patients with risk and established ARDS. *Clin. Chim. Acta*, **298**, 111–120.

Lang, J. D., McArdle, P. J., O'Reilly, P. J., Matalon, S. (2002). Oxidant-antioxidant balance in acute lung injury. *Chest*, **122**, Suppl. 6, 314S–320S.

Lapenna, D., Ciofani, G., Pierdomenico, S. D., Giamberardino, M. A., Cuccurullo, F. (2001). Reaction conditions affecting the relationship between thiobarbituric acid reactivity and lipid peroxides in human plasma. *Free Radic. Biol. Med*., **31**, 331.

Lee, W. L., Downey, G. P. (2001). Neutrophil activation and acute lung injury. *Curr. Opin. Crit. Care,* **7**, 1–7.

Lenz, A. G., Jorens, P. G., Meyer, B., De Backer, W., Van Overveld, F., Bossaert, L., Maier, K. L. (1999). Oxidatively modified proteins in bron choalveolar lavage fluid of patients with ARDS and patients at-risk for ARDS. *Eur. Respir. J*., **13** (1), 169–174.

Lichtenstern, C., Hofer, S., Möllers, A., Snyder-Ramos, S., Spies-Martin, D., Martin, E., Schmidt, J., Motsch, J., Bardenheuer, H. J., Weigand, M. A. (2011). Lipid peroxidation in Acute Respiratory Distress Syndrome and liver failure. *J. Surg. Res*., **168**, 243–252.

Marczin, N., Royston, D. (2001). Nitric oxide as mediator, marker, modulator of microvascular damage in ARDS. *Brit. J. Anaesth*., **81** (2), 179–183.

Perl, M., Lomas-Neira, J., Venet, F., Chung, C. S., Ayala, A. (2011). Pathogenesis of indirect (secondary) acute lung injury. *Expert Rev. Respir. Med*., **5** (1), 115–126.

Masella, R., Di Benedetto, R., Vari, R., Filesi, C., Giovannini, C. (2005). Novel mechanisms of natural antioxidant compounds in biological systems: Involvement of glutathione and glutathione-related enzymes. *J. Nutr. Biochem*., **16**, 577–586.

Matés, J. M. (2000). Effects of antioxidant enzymes in the molecular control of reactive oxygen species toxicology. *Toxicology*, **153**, 83–104.

Meade, M. O., Cook, R. J., Guyatt, G. H., Groll, R., Kachura, J. R., Bedard, M., Cook, D. J., Slutsky, A. S., Stewart, T. E. (2000). Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome. *Amer. J. Respir. Crit. Care Med*., **161** (1), 85–90.

Metnitz, P. G., Bartens, C., Fischer, M., Fridrich, P., Steltzer, H., Druml, W. (1999). Antioxidant status in patients with acute respiratory distress syndrome. *Intens. Care Med*., **25**, 180–518.

Murray, J. F., Matthay, M. A., Luce, J. M., Flick, M. R. (1988). An expanded definition of the adult respiratory distress syndrome. *Amer. Rev. Respir. Dis*., **138**, 720–723.

Mühl, D., Woth, G., Drenkovics, L., Varga, A., Ghosh, S., Csontos, C., Bogiţr, L., Wéber, G., Lantos, J. (2011). Comparison of oxidative stress & leukocyte activation in patients with severe sepsis & burn injury. *Indian J. Med. Res*., **134**, 69–78

Nordberg, J., Arner, E. S. (2001). Reactive oxygen species, antioxidants and the mammalian thioredoxin system. *Free Radic. Biol. Med*., **31**, 1287–1312.

Palmieri, B., Sblendorio, V. (2007). Oxidative stress tests: Overview on reliability and use. *Eur. Rev. Med. Pharm. Sci*., **11**, 309–342.

Quinlan, G. J., Lamb, N. J., Evans, T. W., Gutteridge, J. M. (1996). Plasma fatty acid changes and increased lipid peroxidation in patients with adult respiratory distress syndrome. *Crit. Care Med*., **24**, 241–246.

Ranieri, V. M., Rubenfeld, G. D., Thompson, B. T., Ferguson, N. D., Caldwell, E., Fan, E., Camporota, L., Slutsky, A. S. (2012). Acute respiratory distress syndrome: The Berlin Definition. *JAMA (The Journal of the American Medical Association),* **307** (23), 2526–2533.

Richard, C., Lemonnier, F., Thibault, M., Couturier, M., Auzepy, P. (1990). Vitamin E deficiency and lipoperoxidation during adult respiratory distress syndrome. *Crit. Care Med*., **18**, 4–9.

Sakr, Y., Reinhart, K., Bloos, F., Marx, G., Russwurm, S., Bauer, M., Brunkhorst, F. (2007). Time course and relationship between plasma selenium concentrations, systemic inflammatory response, sepsis, and multi-organ failure. *Brit. J. Anaesth*., **98**. 775–784.

Schmidt, R., Luboeinski, T., Markart, P., Ruppert, C., Daum, C., Grimminger, F., Seeger W, Gunther A. (2004). Alveolar antioxidant status in patients with acute respiratory distress syndrome. *Eur. Respir. J*., **24**, 994–999.

Sigurdsson, M. I., Sigvaldsson, K., Gunnarsson, T. S., Moller, A., Sigurdsson, G. H. (2013). Acute respiratory distress syndrome: Nationwide changes in incidence, treatment and mortality over 23 years. *Acta Anaesthesiol. Scand*., **57**, 37–45.

Sittipunt, C., Steinberg, K. P., Ruzinski, J. T., Myles, C., Zhu, S., Goodman, R. B., Hudson, L. D., Matalon, S., Martin, T. R. (2001). Nitric oxide and nitrotyrosine in the lungs of patients with acute respiratory distress syndrome. *Amer. J. Respir. Crit. Care Med*., **163** (2), 503 – 10.

Stasser, J. P., Eisses, J. F., Barry, A. N., Kaplan, J. H., Blackburn, N. J. (2005). Cysteine-to-serine mutants of the human copper chaperone for superoxide dismutase reveal a copper cluster at a domain III dimer interface. *Biochemistry*, **44**, 3143.

Sznajder, J. I., Fraiman, A., Hall, J. B., Sanders, W., Schmidt, G., Crawford, G., Nahum, A., Factor, P., Wood, L. D. (1989). Increased hydrogen peroxide in the expired breath of patients with acute hypoxemic respiratory failure. *Chest*, **96**, 606–612.

Valko, M., Rhodes, C. J., Moncol, J., Izakovic, M., Mazur, M. (2006). Free radicals, metals and antioxidants in oxidative stressinduced cancer. *Chem. Biol. Interact*., **160**, 1–40.

Weigand, M. A., Snyder-Ramos, S. A., Mollers, A. G., Bauer, J., Hansen, D., Kochen, W., Martin, E., Motsch, J. (2000). Inhaled nitric oxide does not enhance lipid peroxidation in patients with acute respiratory distress syndrome. *Crit. Care Med*., **28**, 3429.

Wilcox, J. K., Ash, S. L., Catignani, G. L. (2004). Antioxidants and prevention of chronic disease. *Crit. Rev. Food Sci. Nutr*., **44**, 275–295.

Received 19 June 2014

OKSIDATĪVĀ STRESA MARĶIERU LOMA AKŪTA RESPIRATORA DISTRESA SINDROMA ATTĪSTĪBĀ

Akūts respirators distresa sindroms (ARDS) ir bieži sastopams, multifaktoriāls iekaisīgas dabas plaušu audu bojājums, kas saistās ar izteiktu komorbiditāti un augstu mirstību intensīvās terapijas pacientu vidū. Nesen pētnieki pārskatīja ARDS diagnostiskos kritērijus kopš 1994. gada. Pašlaik ARDS tiek diagnosticēts, izmantojot Berlīnes definīcijas kritērijus. Svarīga loma ARDS attīstībā ir oksidantu un antioksidantu līdzsvara traucējumiem. Patoģenēzē liela nozīme piemīt tā saucamajām reaktīvajām skābekļa daļiņām. Dinamiskā ARDS attīstībai ir vairāku faktoru ietekme, līdz ar to jālieto individuāla pieeja katram pacientam, kas saistās ar apgrūtinātu prognozi un tālākās ārstēšanas taktikas izvēlē. Reaktīvās skābekļa daļiņas uzsāk šūnu bojāeju, izmainot lipīdus, olbaltumvielas un DNS, kas nopietni apdraud šūnu turpmāko dzīvotspēju, kas savukārt sekmē sekundāro reaktīvo daļiņu izdalīšanās un šūnu nāvi apoptozes vai nekrozes dēļ. Pētījumi parāda, ka daudziem pacientiem ar orgānu mazspēju, iestājoties intensīvajā terapijā, raksturīga pazemināta antioksidantu aktivitāte, kas pastiprina lipīdu peroksidācijas izraisītos negatīvos efektus. Minētie fakti pierāda nepieciešamību pēc iespējas sekmīgāk un agrīnāk prognozēt ARDS attīstību un turpmāko gaitu kritiski slimiem pacientiem.