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Oxidative stress in severe pulmonary trauma in critical ill patients. Antioxidant therapy in patients with multiple trauma — a review

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Abstract

Multiple trauma patients require extremely good management and thus, the trauma team needs to be prepared and to be up to date with the new standards of intensive therapy. Oxidative stress and free radicals represent an extremely aggressive factor to cells, having a direct consequence upon the severity of lung inflammation.

Pulmonary tissue is damaged by oxidative stress, leading to biosynthesis of mediators that exacerbate inflammation modulators. The subsequent inflammation spreads throughout the body, leading most of the time to multiple organ dysfunction and death.

In this paper, we briefly present an update of biochemical effects of oxidative stress and free radical damage to the pulmonary tissue in patients in critical condition in the intensive care unit. Also, we would like to present a series of active substances that substantially reduce the aggressiveness of free radicals, increasing the chances of survival.

Key words: lung injury, inflammation; oxidative stress, antioxidant therapy; multiple trauma; critically ill patient

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Multiple trauma patients are, and will always be, a challenge for the intensive care unit (ICU) [1, 2]. Most often, patients with multiple traumas develop serious lung problems due to several complications arising from injury, infections or from mechanical ventilation. The management of the respiratory system has a special importance [3], due to the constant and critical need of tissue oxygenation of the body [3–6]. Recorded data in Trauma Register DGU (Germany) [6], and presented by Huber *et al.* [6], highlight a high mortality rate with pulmonary trauma patients: 17.5% (16.5% male and 20.5% female). In retrospective group studies (2002–2011) patients with an ISS score higher than 16. 48% were patients who have suffered lung contusion, out of which, 39% pneumothorax, 28% hemothorax, 12% lung lacerations, 3% thoracic vessel injuries [6].

Acid-base imbalances [7], low oxygenation [8] and cellular death [9] are just some of the complications of a deficient respiratory system, that lead to multiple organ damage [10].

In turn, the pulmonary tissue is affected by injuries, inflammations (Systemic Inflammatory Response Syndrome

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— SIRS), and infections (Acute Respiratory Distress Syndrome — ARDS, Ventilator-Associated Pneumonia — VAP) [11]. Together, those clinical aspects accelerate biochemically the production of free radicals with devastating effects for the cell and by default for the whole biological system [12–14]. Thus, this stimulates the so-called 'oxidative stress' [15, 16], which has a significant contribution in the clinical status of the patient. Pulmonary dysfunction leads to a series of complications that make recovery impossible [6] through the activation of the hyper-metabolism induced by severe trauma.

In this paper, we propose an update to the action of free radicals and oxidative stress on the pulmonary tissue in patients with multiple traumas and also an update to the current research concerning therapy with antioxidants.

BIOCHEMICAL ASPECTS OF FREE RADICALS AND THE ACTIONS OF OXIDATIVE STRESS

Biochemical reactions that take place in cells are all driving forces that sustain life [17]. In physiological conditions, oxygen is used by our body for cellular respiration, defence, detoxification and embryonic development. Due to physiological imbalance or traumas, the oxygen is transformed in non-physiological species, which are toxic for the body and are called free radicals. Free radicals are unstable molecules, ions or clusters of atoms, with an extremely high reactivity toward molecules around them [17–22].

The oxidative stress affects mainly the cellular organelles [23]. These alterations of physiological functions are caused by extremely reactive free radical compounds that influence enzymatic and membrane activities. The extremely high reactivity of these free species becomes very important when it comes to the study of tissue complications, especially in the case of patients with multiple trauma, when because of the significant injuries, the patient develops hyper-metabolism [24, 25]. The biochemical alterations at the cellular level imply oxidative reactions of the DNA, structural modifications of the proteins and oxidative modifications of lipids [26] (Fig. 1).

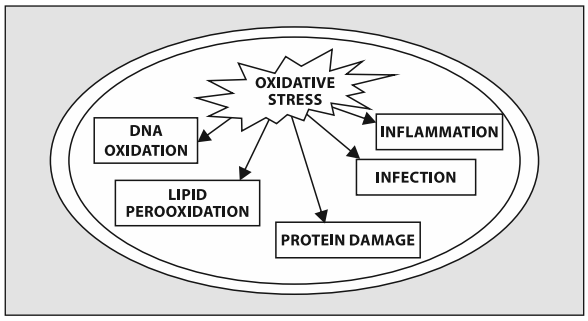

Figure. 1. The action of oxidative stress on tissues

Reactive oxygen species are produced in high quantities through endogenous metabolisms [27], while at the same time, there are also a large class of exogenous factors that increase the production of free radicals. Such mechanisms that can generate free radicals inside the body are represented by: the activation of neutrophils, the electron transport chain at the mitochondrial level, arachidonic acid metabolism, oxide-reduction of xanthine [28] or nitric oxide synthesis [27, 29–31]. The respiratory chain [32–34] has a key role at the cellular level, being responsible for the conversion of oxygen in water molecules. At the neutrophils' level, the major source of oxygen is the enzymatic complex NAD(P)H oxidase. Moreover, severe infections of the pulmonary tissue can lead to massive synthesis of reactive species of oxygen and accumulation. The enzymatic processes that take part in the defence of the tissues transform a part of the oxygen in reactive species that lead to tissue inflammation [35]. In the pulmonary tissue, the most important source or free radicals are the neutrophils, eosinophils, leucocytes or different enzyme modulators [36].

The biochemical process activities lead to the overproduction of inflammatory molecules with immediate response on inflammation spreading [37, 38]. Chang *et al*. suggest that in this case proteoglycans have a determinant role, since they are responsible for the response given by the aggression [39]. The level of inflammatory mediators determines the level of inflammatory response [40]. The endotoxin, the activation of the complement, the cytokines, the arachidonic acid's metabolites, liposomal enzymes and kinines, histamine, the nitric oxide or the mediators derived from the endothelium, are the aggressive participants in the decompensation of the patient's clinical status. The complications arise together with micro-embolisms, pulmonary artery hypertension and the alteration of the respiratory functions [41–48]. Neutrophils stimulation through different biochemical mechanisms produces high quantities of hydrogen peroxide [49–51]. The biosynthesised oxidants have a role in destroying bacteria, but the adverse effects produce a series of tissue inflammations. The accumulation of neutrophils and the exacerbated biosynthesis of inflammatory cytokine, combined with the ICU conditions (VAP, SEPSIS, etc.) lead to a severe destruction of the pulmonary tissue [51–53]. Active oxygenated species, and implicitly oxidative stress, affects the lung, especially through lipid peroxidation, the increased production of pro-inflammatory molecules, protein oxidation and inactivation of antioxidants [54]. The abnormal oxidation of proteins from the pulmonary tissue that is made possible by the compounds of the oxidative stress is directly implicated in the pathogenesis of a series of pulmonary diseases. The lipid oxidation is associated with the generation of a big number of toxic compounds with direct and severe implications in the destruction of cells

Table 1. Substances with antioxidant capacity

Study	Antioxidant	Outcome	Reference
Ribeiro et al.	CANNABIDIOL	Antioxidant effects	[87]
		Reduce lung inflammation	
		Attenuation of acute lung injury	
		20 mg kg^{-1} — 1 single dose	
Benetti et al.	SULPHURED HYDROGEN	Inhibits the acumulation of neutriphiles	[88]
		Activates the production of enzimatic engoden antioxidants	
Wu et al.	EICOSAPENTAENOIC AICD	Reduces cellular apoptosis	[89]
		Modulates mitochondrial activity	
Santos et al.	OLEANIC ACID	Strong antioxidant properties	[90]
		Administration intra-peritoneal injection	
Choi et al.	DESOXYRHAPONTIGENIN	Modulates cytokine biosynthesis	[91]
Torres et al.	METHYLPREDNISOLONE	Positive effects in inflammation and sepsis	[92]
		Slows down the oxidative damage	
		Activation of antioxidative enzymes	
Kutsukake et al.	PIOGLITAZONE	Significantly reduces the concentration of IL-6, TNF-α	[93]
		Blocks haemocyte infiltration	
		Significant positive effects in acute lung injury	
Straaten et al.	VITAMIN C	Modulates antioxidant enzyme activity	[94]
		Blocks the production of free radicals	
		Reduce the stationing in ICU	
		Reduce mortality	
		Protects lung tissue from biochemical injuries cause by oxidative stress	
Wischmeyer et al.	GLUTAMINE	Reduces the level of oxidative stress biomarkers	[95]
		Significantly reduces mortality	
Ayvaz et al.	METHYLENE BLUE	Positive effects in sepsis	[96]
		Positive effects in lung injury	
		Significantly reduces lung tissue injuries	
Qin et al.	ULISTATIN	Reduces considerably the systemic effects of the inflammation	[97]
		Reduces significantly the complications that can arise from lung injuries	
		Reduces the effects of free radicals	
Liu et al.	SALIDROSIDE	Reduces the plasmatic concentration of TNF-α, IL-6 and IL-1	[98]
		Blocks the specific receptors — peroxisome proliferator	

IL — interleukine; TNF-α — tumor necrosis factor alfa; ICU — intensive care unit

through membrane damage, inhibition of the biochemical processes of the cell and in the end its death [55–58].

A lung injury is often brought by the oxygen therapy — hyperoxia induced by mechanical ventilation in the management of severe respiratory dysfunctions [25, 59–61]. There are a series of controversies related to the parameters used in mechanical ventilation, especially when we are talking about an inflammated lung. The severe pulmonary destruction and inflammation can have severe consequences at a patient with multiple trauma, the majority leading to Multiple Organ Dysfunction Syndrome (MODS) [62, 63] and death [64–66].

Many critically ill patients are being brought in the emergency units in haemorrhagic shock [67, 68]. Inadequate resuscitation and the complications that may arise in this case, makes the recovery of the patient hard or impossible [69–71]. An aggressive and inadequate fluids resuscitation can produce high quantities of reactive species of oxygen through the re-oxygenation of the tissue [15]. Once the tissue's reperfusion takes place, an important source of reactive oxygen appears, the main biosynthesis being xanthone-oxydaze reactions. For this matter, a series of active compounds [72–75] that can reduce the inflammations resulting from the fluids generated by resuscitation have

been studies. The compounds that had a great contribution in the good post-resuscitation management are acid valproic [72], or N-acetylcysteine [73]. The complete impact of the oxidative stress and free radical on the pulmonary tissue and the biochemical and physiological explications of all the clinical manifestation that appear in a patient with multiple traumas remain unclear and need further research.

THERAPY WITH ANTIOXIDANTS

Destructive effects of free radicals and oxidative stress are minimalized naturally by the organism through the defensive antioxidant system. The antioxidants are compounds that inhibit or slow down the oxidative damage [76–78] brought to a molecule by a free radical [79–81]. The antioxidants react in various ways [82] — inhibitors of the oxidative reaction determined by free radicals, saturation with oxygen singlet, blocking the chain of oxidative reactions, transforming hydroxyl-peroxides in stable compounds, inhibiting some pro-oxidative enzymes or through synergy with other antioxidants [77, 83–86] (Table 1).

The body has such anti-oxidative compounds, naturally – anti-oxidative enzyme (glutathionperoxidase, catalase or superoxide-dismutase) [86, 87], metals or other compounds chelation agents (coenzyme, vitamin, acid uric, peptide, Cu, Zn etc.) [88–90]. The cellular membrane is protected by the attack of the oxidative stress by ubiquinone, which can be found in high quantities in the Golgi mechanism and in the liposomal membranes [91, 92]. Nowadays, intensive research is being done on a series of biologically-active substances that can minimize and even block the mechanisms that biosynthesise free radicals, in order to avoid pulmonary tissue complications. It is known both scientifically and practically that the loss of control of the pulmonary infections or inflammations is directly linked with the spreading of these to the rest of the body which result in true physiological and pathological catastrophes.

Ribeiro *et al.* [87] studied the effect of cannabidiol on severe pulmonary tissue affections on laboratory rats. They emphasised the anti-inflammatory potential of this compound, demonstrating the beneficial effects brought by the reduction of lung injury when the inflammatory process has already evolved in the patient, and thus demonstrating the ability of the compound to be effective even if the lung is already inflammated.

In many scientific papers the beneficial effect of the sulphureted hydrogen on the inflammated lung is presented [88, 93–97]. Benetti *et al*. [88] demonstrates that through the administration of the sodium mono-hydrogen-sulphate (NaHS) that generates sulphureted hydrogen, the accumulation of neutrophils and of eosinophils is inhibited.

Eicosapentaenoic acid – enriched phospholipids extracted from sea cucumber *Cucumaria frondosa*, also has an inhibition effect on the reactive oxygenated species [89, 98–105]. Wu *et al*. [89] remarks that this antioxidant compound alters the metabolic way of the mitochondrial apoptosis [89].

Santos *et al*. [90] demonstrated that the intra-peritoneal injection of oleanolic acid at one hour after the lung injury controls the oxidative and inflammatory process, while avoiding important modification from a physiological and histological point of view.

The endotoxin responsible for the tissue inflammation and the pro-inflammatory effects of the reactive oxygenated species [106-109] are inhibited by another compound called desoxyrhapontigenin [61], which is recommended by Choi *et al*. to be used for its anti-oxidative and anti-inflammatory properties [91]. Other studies recommend the use of small quantities of corticosteroids for long periods of time (1–2 mg kg^{-1} day^{-1}) [91]. Those reduce considerably the systemic effects of the inflammation. Ayvaz *et al*. [96] demonstrate in their study on laboratory animals that intravenous administration of 2 mg kg^{-1} of methylene blue reduces considerably the quantity of nitric oxide, endothelial nitric oxide synthase. Furthermore they observed positive effects on lung tissue ischemia reperfusion damage.

A study on laboratory mice by Torres *et al*. [92], demonstrates that the administration of methylprednisolone [92] activates the antioxidant compounds of the pulmonary tissue. The association of pioglitazone in patients' therapy in ICU reduces significantly the complication that can arise from lung injuries. These effects have been studied by Kutsukake *et al*. [93], demonstrating that through the administration of this active compound the tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) concentrations (Fig. 2) are significantly reduced, and also haemocyte infiltration, inflammation and cellular death is reduced (Fig. 3) [93]. The levels of pro-inflammatory cytokines that are released

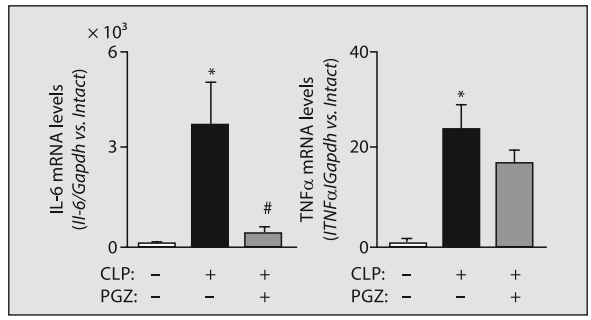

Figure 2. Effects of pioglitazone on IL-6 and TNF-α mRNA levels in visceral adipose tissue of CLP mice. Total RNA extracted from adipose tissue in each group was subjected to real-time polymerase chain reaction analysis. Values are the means ± SD of the mean. CLP: cercal ligation and puncture induced visceral–adipose–tissue inflammation, PGZ: pioglitazone-treated CLP (10 mg kg^{-1} for 7 days) [93] (with Elsevier agreement)

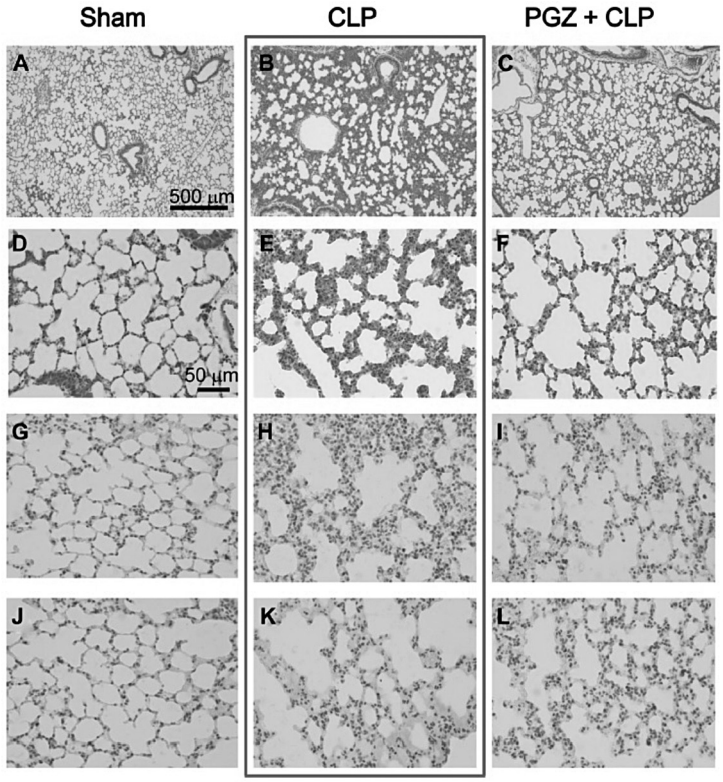

Figure 3. The effect of pioglitazone on CLP-induced lung injury. Lung tissue was collected 24 h after CLP. Paraffin-embedded sections were stained with hematoxylin-eosin (A-F) and immune-stained with CD11b/c (G-L). Figures show comparisons among the sham group (A, D, G, J), CLP group (B, E, H, K), and pioglitazone-treated CLP group (C, F, I, L). Each panel shows a picture from an individual animal [93] (with Elsevier Agreement)

uncontrollably in the pulmonary tissue are also inhibited by ulistatin [110] or salidroside [111]. The beneficial effects of these active compounds on the reduction of plasmatic concentrations of TNF-α, IL-6 si IL-1 [30, 110] have been demonstrated and studied. Salidroside inhibits the inflammatory response by blocking the specific receptors — peroxisome proliferator — activated receptors (PPAR-γ) [111].

Glutamine, is the most abundant unessential amino acid. Its antioxidant proprieties are intensely studied. Numerous beneficial proprieties that this amino acid brings to critically ill patients due to its effect on cellular defence pathways, modulation of the inflammatory response and prevention of organ injuries cause by free radicals [112] were discovered. The administration of glutamine in pulmonary infections reduces, according to studies, reduce hospital mortality and retention time in the ICU. Wischmeyer *et al*. [95], in their study regarding the administration of glutamine on critical patients report that intravenous administration of 0,3–0,5 g kg^{-1} day^{-1} significantly improves the clinical status of the patients.

Straaten *et al*. [94] report the importance of administration of vitamin C in critical patients. Numerous studies show that vitamin C reduces considerably the production of free radicals. Furthermore, in sepsis activates the action of macrophages, regulates the production of cytokines, modulates the inflammatory response, reduces neutrophil oxidative burst and regulates the antioxidant-oxidant balance. Administration of doses of vitamin C varies depending on the case, but in many articles it's recommended an intake of 1000–1500 mg day^{-1} of vitamin C intravenously for 3–5 days [94].

Another antioxidant remedy that was reported in specialized studies is omega 3 fatty acids. Numerous beneficial effects of these active substances were shown especially in critically ill patients with lung trauma — ARDS, sepsis. Administration on entirely path of supplements with a high omega 3 fatty acids reduce mortality with 19 % according to studies [113,114].

Other compounds with remarkably good anti-oxidative and anti-inflammatory effects have been studied for the purpose of reducing the inflammatory effects of the oxidative stress on pulmonary tissue, among which pentoxifylline [115], apocynin-nitrone [116], narginin [117], sphingisylphosphorylcholine [118], usnic acid [119], zinc aspartate [120], trapidil [121] or melatonin [122].

CONCLUSION

A critically ill patient suffers a series of complications due respiratory problems. The pulmonary tissue becomes inflammated due to infections, trauma or genetic determinism, which induces in the end the spreading of the inflammation and multiple organ death. The conditions of the intensive therapy — nursing, the lavage of endotracheal intubation tube, or the mechanical ventilator — lead as well to complications in the lungs, sometimes provoking important injuries. The extracellular membranes are damaged through the action of free radicals, forming toxic compounds that have a crucial impact on the physiological status of the lung, accelerating the destructive inflammatory processes.

Oxidative stress and free radicals contribute directly to the degradation of the physiological state of the pulmonary tissue, complicating the management of the patient with multiple traumas. Current research offers a series of alternatives that minimizes the adverse effects of the oxidative stress on the pulmonary tissue. The protocolization of antioxidant therapy and the investigation of biomarkers responsible for oxidative stress becomes a necessity, being useful in minimization of inflammatory effects caused by free radicals.

In conclusion, it can be affirmed that a serious thought should be given when considering these aspects of oxidative stress on the lung. Severe complications that arise due to severe inflammations, infections or a partially-working lung can only substantially or completely reduce the chances of survival in ICU. We consider that current research regarding intensive care in multiple trauma cases for reduction of pulmonary, and implicitly systemic, inflammation and infection are extremely important nowadays and should be taken into consideration. Our paper's limitations are given by the lack of presentation of all compounds that have antioxidant properties and that are used in the control of pulmonary and tissue inflammations for patients that are in a critical state.

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