OXIDATIVE STRESS IMPLICATIONS IN VARIOUS LUNG DISEASES. FOCUSING ON ONE LUNG VENTILATION

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OXIDATIVE STRESS IMPLICATIONS IN VARIOUS LUNG DISEASES. FOCUSING ON ONE LUNG VENTILATION (Abstract): One the most intriguing biomedical fact nowadays is that many of the existent diseases exhibit a certain molecular component expressed through oxidative damage. In this way, it seems also that lung diseases have an oxidative stress component which is clearly shown by impairment in oxidant/antioxidant mechanisms balance. In several pathological cases, each and every cell present in lung tissue may be capable to produce reactive oxygen species (ROS) as a part of the inflammation signaling. ROS are also produced in normal conditions, but a strong antioxidant defence system acts in order to transfer the impaired electrons of the ROS reducing them to neutral species. In this way, in one lung ventilation (OLV) surgical maneuver an increase in the ROS production occurs mainly due to 100% use of oxygen during artificial ventilation. Unfortunately, the only way in which the oxidative damage can be minimized is by carefully and correctly executing this maneuver. Moreover, no antioxidant therapy can be considered working or safe yet, although some animal modeling showed promising results. Keywords: REACTIVE OXYGEN SPECIES, THORACIC SURGERY, LUNG RESECTION, COMPLICATIONS, ANTIOXIDANT THERAPY.

Nowadays, it is generally known that living organisms on Earth can survive only due an appropriate concentration of oxygen in the breathing air. Both plants and animals’ metabolic pathways are based on a continuing exchange of atomic particles between reactive species and pathway partners. At the same time, it seems that these reactive species also play an important part in the process that make living bodies age and finally die. As the oxygen species formed in respiration chain participate in all homeostatic reactions, energy production, enzymatic activation, pathways regulation and so on, it seems that the same species can also easily participate in order to end cellular activity by activating the well-known self-destructive mechanism called apoptosis. This paradox can be well observed in lung diseases (LD) where the oxygen privation leads to serious tissue damage (1). It was only currently that we understood that reactive oxygen species (ROS) can also play a crucial role in LD and that the lung tissue may be extremely vulnerable when exposed to oxidative
stress during a LD, a surgical procedure, or after specific post-operative maneuvers such as lung-ventilation. Therefore it seems that oxidative stress damage may be of great importance when it comes on LD due to lung vulnerability to the toxic effects of oxygen and the oxygen damage can occur and radically change pathologies features.

The pathology of oxidative stress begins when an imbalance in oxidant-antioxidant systems occurs. The accumulation of ROS can cause damage to DNA, lipids, proteins, and carbohydrates. There are methods to measure oxidative stress shown for example by increased lipid peroxidation products, or the DNA oxidation, and protein carbonyl formation in lung tissue. As the lipid peroxidation can be an excessive ROS production marker, the oxidized lipids may possess signaling potential. It is the case of the isoprostanes, by-products of membrane lipid peroxidation involved in bronchoconstriction occurrence and airway hyper-responsiveness in asthma that can also be powerful vasoconstrictors in pulmonary arterial hypertension or acute lung injury (2, 3).

One lung ventilation (OLV) is currently used in video-assisted surgery and also in open lung surgery. OLV purpose is to decrease the blood flow through pulmonary circulation that could lead to temporary ischemia followed by reperfusion after restoring ventilation, in combination with iatrogenic hyperinflation, all of which can imply in ROS production (4).

It is interesting that both common lung diseases and artificial lung ventilation involve oxidative stress damage to lung tissue, but no comparative or cumulative study was made. This review aims to present several aspects considering the oxidative stress occurring generally in the common lung diseases and particularly during or after surgeries that require the assistance of artificial lung ventilation. Surprisingly, it seems that even a surgery tool may mimic or increase oxidative stress leading eventually to lung tissue damage.

OXIDATIVE STRESS MECHANISMS IN LUNG DISEASES

Many studies show that endogenous oxidative-antioxidative mechanisms may be critical in LD (as reviewed by - 5). As the reactive species of oxygen and nitrogen are ubiquitous in nature, they must be produced by both endogenous and exogenous sources. Endogenous sources may be the cellular organelles responsible for respiratory chain and hydrogen peroxide metabolism (6, 7). In other words, when the unpaired electrons from the mitochondrial transport chain occur during oxidative phosphorylation, they are reduced by the molecular oxygen which leads to superoxide production which easily changes into hydrogen peroxide. This is the time when the peroxisomes are activated and their enzymes contribute to the catalysis of these reactive oxygen species (ROS), but being an enormous source of oxidative stress (8-10).

Studies show that there are many important cellular enzymes that are implicated in lung diseases pathologies (11-14). NADPH oxidase, cytochrome P450, lipooxygenases may be just some of these enzymes that are produced by various cells in the lung tissue alongside ROS and other molecules.

In this way, neutrophils use to produce a significant ROS concentration due to their antibacterial activity. Therefore, it is in their membrane where the NADPH oxidase generates superoxide which further
activates the reaction cascade in phagocytosis. Alongside the NAPDH oxidase, the myeloperoxidase also is involved in the phagocytosis oxidative reactions mainly producing an extremely reactive Chloride species, the hypochlorous acid (15, 16). However, it has been known that the neutrophils are very few in lung tissues having an extreme mobility during inflammation from the circulation into the lung tissue. Also attracted by the chemical signal of inflammation, the peripheral monocytes may produce significant damage in lung tissue due to their impressive capacity of producing large amounts of superoxide leading to acute injuries (17). In the same way as neutrophils, the alveolar macrophages and eosinophils act like potent ROS producers through the NADPH oxidase activity (18), but the first being active also in physiologic conditions (19) and the latter mostly in allergies or infections (20). Eosinophils also possess peroxidase potential, surprisingly similar to myeloperoxidase.

Endothelial cells, on the other hand, are known to produce ROS in pathological conditions, also being of a great number in lung tissue. Oxidative stress occurs due to these cells during and after hypoxia (21) and in some cases during inflammation (22, 23). They mainly produce superoxide, sent by membrane channels to extracellular compartments of lung tissues, and hydroxyl radicals (24). Smooth muscle cells can also produce ROS through NADPH-like oxidase complexes and may produce airway hyperactivity (25, 26).

Pneumocytes in the alveolar epithelia and lung fibroblasts also possess intense metabolisms being involved in inflammation and tissue reconstruction. Type II pneumocytes may be precursor for type I therefore in the differentiation process a certain oxidative stress occurs (27, 28). Lung fibroblasts are attracted by inflammation signals (such as cytokines) and produce ROS intracellularly and extracellularly (29).

Therefore it seems that each type of cells present in the lung tissue may actually generate ROS, either in physiologic or pathologic conditions. It is not yet sufficiently clear whether if an imbalance in the cellular system of ROS formation and degradation act as a clean pathological trigger. Extremely important should be the fact that most of the ROS play important roles in signalling processes of several survival pathways such as apoptosis.

ROS production from exogenous sources may also play an important role in LD. Environmental toxins or diet could also promote the onset of LD. Classical examples may be the exposure to different herbicides or pesticides that could lead to lung injuries in human by increasing inflammatory factors expression and mitochondrial dysfunction. Also the ethanol poisoning has been shown to lead to lung diseases (30-32) and even ROS-induced cysteine modification in the lungs (33). Even the well-known anti oxidative factors found in the usual diet can influence the inflammatory processes leading to unwanted side effects (34). Other examples may include oxidative stress induction by environmental toxins (arsenic, asbestos, and tobacco) that disrupt the cytochrome P450 metabolism (35). All of these changes affect the pulmonary inflammatory response and can finally contribute to lung cancer onset (36-38).

In addition, ROS have been suggested to have a major influence on the rate of postoperative complications after thoracic surgeries assisted by two-lung ventilation.
or one-lung ventilation. It seems that lipid peroxidation may be involved in the atrial fibrillation, a common complication following pulmonary resections (39). Due to high reactive properties, changes in impaired electrons oxygen molecules may be rather difficult to assess, although it might be more suitable to evaluate the ROS production by evaluating the changes that they may lead to different molecules such as proteins. For example, an increase in carbonyl groups may be the result of the increase of hydroxyl radicals which generate protein dimerization following ammonium radical oxidation. Covalent binding of cysteine or methionine protein residues may be associated with excessive oxidation of sulphydryl groups.

In OLV, it is highly possible that due to the 100% use of oxygen, several changes in oxidative mechanisms occur. As one of the lungs is inactive, the other one must take over the entire activity so that it must provide the entire body the oxygen it needs. In this way, a higher concentration of oxygen must pass through the lung and reach blood. Therefore, it has been shown that higher myeloperoxidase and lower SOD activities may act together in common lung injury caused by hyperoxia due to protein carbonyls formation and high cytokines signalling (40). In the same way, when switching from two-lung to one-lung ventilation, a shunt fraction increases, and oxygenation is impaired. In this way, hypoxemia during OLV may be predicted measuring lung function and distribution of perfusion (41).

ANTIOXIDANT DEFENCE MECHANISMS

While the lung is directly exposed to the environmental oxygen, antioxidant defence is very important (42). Antioxidant defence exists as biochemical systems that help the cells or tissues to restore the proper oxidative balance in order to maintain cellular homeostasis. Obviously, a great part of this defence consists of enzymatic complexes aiming to catalyse the reduction of ROS into low reactive species such as water or to transfer their active potential to other biological important molecules such as NADP(H). The first enzyme in the defence is the superoxide dismutase (SOD) which transforms superoxide in oxygen and hydrogen peroxide. SOD is active both in intracellular and extracellular space with not clear role in antioxidant mechanisms but efficiently decreasing lipid peroxidation and membrane damage (43). As the hydrogen peroxide is produced, the catalase (CAT) and glutathione systems (GS) have the purpose of reducing it to water and oxygen. In spite of SOD, CAT is only active intracellularly (in peroxisomes) alongside the reduced form of glutathione (GSH) (44, 45). Due to the fact that reduction potential of GS bases on the ratio between the oxidized and reduced (GSH) forms of glutathione, and adding that GSH concentration in the alveolar lavage fluid is 100 fold higher than in plasma (44), it seems that GS is a highly active antioxidant system in lung tissues.

Moreover, there are other enzymatic systems that may play direct or indirect roles in the defence against oxidative stress. Among these lie the peroxiredoxins which can reduce hydrogen peroxides, or the thioredoxins which reduce sulphydryl bonds and they are all implicated in a whole tableau of mutual cellular effort to counteract the damaging effects of normally produced ROS.

Besides the important enzymes that re-
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duce the ROS and lipid peroxides such as thioredoxins and GS which in fact were shown to be involved in LD as important protective factors (46, 47), there are also some non-enzymatic endogenous or exogenous antioxidants that can also protect the lung tissue against the peroxidation radicals (48-50). These non-enzymatic antioxidants are mainly “scavengers” of free radicals, such as vitamin C (51), vitamin E (inhibits oxidation of membrane lipids) (52), uric acid (efficient scavenger of peroxynitrite, present in plasma and airway lining fluid) (53), albumin, bilirubin, glutathione or N-acetylcysteine (NAC).

For example, NAC is a potent drug currently used in LD therapies due its potential of directly reacting with ROS and also serving as GSH precursor (50). In this way, it can prevent oxidative stress produced by neutrophil accumulation (54). Many other antioxidant molecules have been studied in LD therapy (55, 56), but currently most of the attention is channeled through enhancing SOD activity (3, 57). Some of these agents reached the clinical trial level, but unfortunately only at a small scale and none of them have yet become commonly used in practice.

PERSPECTIVES IN ANTIOXIDANT THERAPIES

In contrast to the shown fact that the oxidative stress is an important factor in LD, many studies show that the antioxidant therapeutic approach is a matter of efficiency. It seems that many of the trials failed to succeed due to a great number of reasons.

Many of the reasons generally address to the clinical practice such as dosage, delivery and timing. For example, it is known that in active lung injury burst of oxidative stress in a dynamic activity may occur, therefore it is important to calculate the exact amount of antioxidants which must be delivered in order to surpass the oxidative burst but also to be relatively low in order not to impair the oxidant/antioxidant balance in case of an excess. More than that, it seems that the true challenge is the short half-life of the antioxidants in the tissue delivery context being the case of recombinant SOD enzymes (58, 59) which must quickly reach lung tissue through blood stream, a rather problematic matter. In addition, an efficient delivery should be perfectly timed in order that the antioxidant to reach destination than the irreversible tissue damage occurs.

Another important aspect is that ROS may exhibit more than the damaging role of which therapy is addressed to. There might be several interferences of the treatment with the physiological mechanisms. In this way, the immunological response through phagocytosis may be slowed in the case of an antioxidant treatment of airway inflammation, and therefore lung injury (60, 61). Surprisingly, it seems that several studies in 1996 showed that antioxidant therapy may actually increase lung cancer risk due to cell growth promotion potential (62-64). Moreover, an animal model study in 2014 also claims that antioxidant accelerates lung cancer development (65).

Therefore, a more attentive approach should be considered in antioxidant therapies in terms of genetic variation, and regulation of enzymes. There are many genetic variations including polymorphisms and mutations described for many of the antioxidant defence enzymes. For example, in chronic obstruction pulmonary disease, polymorphisms in antioxidant genes related to GS function and all isoforms of SOD
alter the susceptibility to this disease and also the impact on the disease progression (66, 67). Genetic variations in antioxidant enzymes have also been implicated in susceptibility to asthma (68) and acute lung injury. Their importance is crucial because allows the clinicians to target vulnerability rather than the disease itself meaning that a therapy to prevent would be more efficient than a therapy to cure.

CONCLUSIONS
Oxidative damage may be extremely dangerous in terms of lung functions impairment due to their key role in oxygen supplying for the entire body. Many of the lung diseases access the oxidative pathways causing an excess of ROS both intracellular and extracellular in the lung tissue. One-lung ventilation, a common maneuver during thoracic surgery, has also an oxidant component in which, due to the 100% use of oxygen by one lung, the balance between ROS and antioxidant mechanism is impaired. This maneuver must be carefully handled and controlled because most of the after surgery complications occur based on the mechanisms triggered by the excessively produced ROS. Unfortunately, no direct treatment for after-OLV complications is yet available and no antioxidant treatment or preventive therapy can be developed in the absence of a extreme care in assessing OLV maneuver.

REFERENCES
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35. Gray JP, Mishin V, Heck DE, Laskin DL, Laskin JD. Inhibition of NADPH cytochrome P450 reductase by the model sulfur mustard vesicant 2-chloroethyl ethyl sulfide is associated with increased production of reactive oxygen species. Toxicol Appl Pharmacol 2010; 247: 76-82.
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