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Review

The Impact of General Anesthesia on Redox Stability and Epigenetic Inflammation Pathways. Crosstalk on Perioperative Antioxidant Therapy

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Abstract: Worldwide, the prevalence of surgery under general anaesthesia has increased significantly, on one hand because of modern anaesthetic and pain control techniques, and on the other hand because of better diagnosis and increased complexity of surgical technique. Together with the development of new concepts in the surgical field, the attention of researchers and clinicians turned to minimizing the impact of surgical trauma and offering minimal invasive procedures. This fact is due to the recent discoveries in the field of cellular and molecular mechanisms, that have revealed a systemic inflammatory and pro-oxidative impact that not only lasts in the perioperative period, but also impacts the long term, contributing to more difficult recovery, increased morbidity, and mortality, and finally a negative financial impact. Detailed molecular and cellular analysis have shown an overproduction of inflammatory and pro-oxidative species, that are responsible for an augmentation of the systemic inflammatory status and more difficult postoperative recovery. Moreover, it was shown that there are a series of changes in certain epigenetic structures, the most important being the microRNAs. Based on these findings, a series of modern, targeted therapeutic approaches have been proposed, with the final goal of blocking these mechanisms and reducing the redox state. Recent studies carried out had a positive clinical impact regarding antioxidant therapy and have shown that it can be used in the perioperative period with beneficial clinical impact. This review describes and details the most important molecular and cellular mechanisms that impact the surgical patient undergoing general anaesthesia, and it presents a series of antioxidant therapies that can reduce systemic inflammation.

Keywords: general anesthesia; redox; inflammation; antioxidants; hypermetabolism; microRNAs; biomarkers; oxidative stress; Vitamin C

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1. Introduction

Anaesthesia allows performance of surgical procedures in a rapid, safe and pleasant manner producing analgesia, absence of awareness and adequate muscle relaxation when needed [1–3]. A critically important aspect of perioperative anaesthetic care is maintenance of homeostasis, including hemodynamic stability, oxygenation, ventilation, and temperature. The World Health Organization (WHO) and the World Bank (WB) expect that by 2026 the burden of diseases requiring surgery and aesthesia will override that of HIV, tuberculosis and malaria, measured in disability adjusted life-years. As anaesthesia providers are an integral part of the delivery of safe and effective surgical care, it is of paramount importance to develop the necessary tools to minimize mortality and morbidity in the perioperative period [4].

Surgical stress induces an imuno-inflammatory response which is not necessarily proportional to the degree of tissue damage. It has been suggested that in addition to the surgical injury, there are other factors contributing to the inflammatory response in the perioperative period, including general aesthesia itself, mechanical ventilation, administration of blood products, and antiemetic drugs [5]. Moreover, numerous studies have highlighted a number of molecular changes induced by anaesthetic substances, involving the expression of inflammation and hypermetabolism during general anaesthesia. Abnormal imuno-inflammatory response, either over or under expressed, has been associated with various relevant postoperative conditions, including infections, pulmonary complications, delirium and postoperative cognitive dysfunction [6], renal injury [7], and cancer recurrence [8–10].

This review article aims to integrate current knowledge regarding the effects of commonly used anaesthetic agents on the inflammatory response developed in the postoperative period. A better understanding of the impact of anaesthetic agents on the immune system, adequate state of anaesthesia and ensuring homeostasis stability during surgery may improve perioperative management and postoperative outcome. Moreover, by applying perioperative methods for reducing the impact of oxidative stress and inflammation can lead to better results in regard with postoperative recovery and can also lead to less adverse effects and increased patient satisfaction.

2. Redox disturbance and inflammation during general anaesthesia and surgery procedures

A degree of inflammation during surgery is unavoidable and it represents the first necessary mechanism in wound healing. It involves complex pathways that alter endocrine, hemodynamic, metabolic, redox, and immune responses [11]. The main link between localized injury and systemic inflammatory response is represented by the damage-associated molecular pattern (DAMP) molecules, also called alarmins [12]. On a regular basis, these molecules have a physiological role inside the cell, but acquire additional functions when they are exposed to the extracellular environment: they can activate antigen presenting cells (APCs), have chemotactic properties and exhibit immunoenhancing activity, stimulating both the innate and adaptive immune system [13]. Alarmins include high mobility group box 1 (HMGB1), heat shock proteins (HSPs), defensins, cathelicidin, eosinophil-derived neurotoxin (EDN), S100 proteins, purine metabolites and DNA or RNA located outside the nucleus or mitochondria. Hence it represents a very diverse and structurally different group of molecules released by damaged or dying cells [14]. Interestingly, these ”danger” sensing molecules exert their functions by interacting with specific receptors expressed on damaged or dying cells, but not on apoptotic cells [15].

As the first line of defence following tissue injury, a pro-inflammatory reaction is developed through migrating macrophages and granulocytes at the place of injury, which further stimulates the release of various pro-inflammatory cytokines [16–18]. This response is rapidly contained by an anti-inflammatory response, with the aim of fine tuning and of producing a balance between the defence and healing processes [19].

From a biochemical viewpoint, oxidative stress is characterised by an imbalance between oxidant and antioxidant factors, although prooxidative species have a higher share. The most reactive of all these species are hydrogen peroxide, hydroxyl radicals, superoxide anions, reactive nitrogen species, reactive lipid species and oxidative fragments resulting from protein denaturation [20–22]. Free radicals can be formed both intra- and extracellularly due to certain exogen factors that manage to penetrate human biological systems. The most common intracellular sources incriminated in the production of oxidant substances are nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitochondria, the endoplasmic reticulum, lysosomes, cytochrome P450 and peroxisomes [23] . The body has a series of enzymatic systems with important antioxidant properties such as superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT), as well as certain antioxidant molecules, such as glutathione (GSH), vitamin E, vitamin C, melatonin, uric acid, and a series of polyphenols. The most well-known and widely researched oxidative reduction mechanism is

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that of SOD, which is responsible for the molecular conversion of superoxide anions to hydrogen peroxide, that will further lead to the formation of water through an enzymatic catalysation induced by CAT and GPX [24,25]. The reduction of oxidative species by GSH with the formation of glutathione disulphide (GSSG) is another mechanism for oxidative reduction [26]. Furthermore, reactive oxygen species are also involved in modifying cellular signalling pathways responsible for the cellular proliferation, differentiation, autophagia, and apoptosis. Responsible for this is the activation of pro-inflammatory mechanisms that lead to the formation of cytokines by activating nuclear factor κB (NF-κB), AMP-activated protein kinase, hypoxia-inducible factor, and Kelch-like ECH-associated protein 1 (KEAP1) [27]. During pro-oxidative states, at a cellular level, the mitochondria is responsible for generating oxidative factors involved in the augmentation of the redox state with its further molecular and cellular effects. The mechanism is known as mitochondrial reactive oxidative species production (mitoROS) [28,29]. The following mechanisms are involved in the production of reactive oxygen species at mitochondrial level: activity of complex I, II, and III in the mitochondria. From a molecular point of view, complex I is responsible for the entrance of electrons from the NADH complex in the respiratory chain, and therefore through the interaction of flavinmononucleotides with oxygen will result the hydroxyl anion that will be afterwards released in the mitochondrial matrix [30–32]. Complex II is involved in the production of reactive species through the oxidation of succinate to fumarate, a part of the Krebs cycle. Increased amounts of ROS are produced by complex II when complexes I and III are blocked at a molecular level. Following redox activity, complex III is responsible for the production of high amounts of hydrogen peroxide that is able to diffuse in the mitochondrial matrix [33,34]. Once the pro-oxidative damage of biological systems responsible for the adequate functioning of the mitochondria has been done, increased amounts of ROS will lead to mitochondrial death and to the accumulation of highly oxidative species inside the cell. Physiologically, the mechanisms responsible for inhibiting the prooxidative destructive mechanisms inside the cell are GSH, thioredoxin (Trx) and glutaredoxin (Grx) [35]. Recent studies have shown in increased oxidative reduction activity inside the mitochondria for SOD, that functions through blocking the redox activity of oxygen ions in hydrogen peroxide. Ribas et al., have underlined the fact that during enzymatic antioxidant activity in the mitochondria, the most important activity is that of SOD2 (manganese-dependent superoxide dismutase, MnSOD) [36], while in the intermembrane space of SOD1 (Cu,Zn-SOD). Through the activity of the SOD molecular family, reactive oxygen species are transformed in hydrogen peroxide that has a less pronounced oxidative character. Enzymatic antioxidant species such as glutathione reductases, peroxidases and peroxiredoxins are activated for the total inhibition of redox activity. They will dissociate hydrogen peroxide into water and oxygen. Regarding the Trx and Grx antioxidant enzymes, researchers have discovered different species such as Trx2 and thioredoxin reductase-2 (TrxR2) responsible for the reduction of oxidative stress by the modulation of NADPH mechanisms and by taking control over the migration of electrons inside the mitochondria [37–40]. The family of Grx antioxidant enzymes includes Grx2 and Grx5, responsible for the modulation of molecular mechanisms that produce oxygen ions in complex I by catalysation of tiol groups in GSH [41]. An increase in redox state at the level of cellular organelles will lead to a decrease in ATP production due to the migration of electrons towards the water used in the formation of hydrogen peroxide. Other important molecular sources in the production of oxidative species inside the cell are characterized by the interaction between reactive oxygen ions with D-aspartate oxidase, xanthine oxidase , polyamine oxidase, [42,43] (ACOX), L-αhidroxyacid oxidase, D-amino acid oxidase and L-pipecolic oxidase. Due to insufficient electrons for ATP production at mitochondrial level, the whole cell will be affected by the so-called energy failure phenomenon, that has important implications for the whole body and will have the utmost clinical impact in critically ill patients [44–48].

A very important goal during surgery and general anaesthesia is the maintenance of an adequate cerebral blood flow that will sustain normal cerebral metabolic activity and sufficient brain oxygenation. The literature has shown a 2 – 10% rate of severe cerebral ischemia cases during cardiovascular surgery, and 0.05 – 7% during non-cardiac surgery [49–51]. Biochemically, important amounts of ROS and RNS are produced during ischemia-reperfusion. Moreover, an important increase in the intracellular Ca^{2+} levels has also been demonstrated, as well as an exacerbation of the neurotoxic properties of glutamate. Ye Wang et al., have studied the molecular effects induced by curcumin encapsulated nanoparticles on oxidative stress in the cerebral tissue that has undergone ischemia-reperfusion injury. This group has proven a decrease in the oxidative attach on the endothelial tissue, as well as a decrease in the blood-brain barrier (BBB) [52–54].

Recent studies have discussed different theories regarding the cerebral metabolism and regional cerebral blood flow (eCBF) [55,56]. The importance of maintaing an optimal cererbral blood flow comes from the continuous need of insuring global or regional oxygenation. Weiss et al, in an experimental study regarding cerebral oxygen

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consumption during ischemia and reperfusion, have identified a direct correlation between O2 supply/consumption and ischemia/reperfusion syndrome. The authors have used two study groups comprising of laboratory animals, as follows: one group (n=9) where cerebral ischemia was induced, and a second group (n=9) where reperfusion was induced. The study animals received 90% isoflurane anaesthesia with a mixture of oxygen and gas, through and ETT tube, with the endpoint of a partial pressure of oxygen over 100 mmHg. In order to achieve cerebral ischemia, they blocked the medial cerebral artery for an hour in the case of group 1, while for group 2 they have reperfused the same artery for two hours. Cerebral blood flow was determined by using The C^{14}-iodoantipyrine autoradiographic technique [57]. Sakai et al., in a study regarding cerebral protection given by anaesthetic agents have reported an improvement in neurological function after focal ischemia. When carrying out the study the researchers have used lab animals that were induced cerebral ischemia through the temporary occlusion of the medial cerebral artery. They have proven a reduction in the incidence of neurological deficits in the animals that suffered from cerebral ischemia under general anaesthesia with isoflurane, compared to the control group. Moreover, the authors have shown that the cerebral protection induced by isoflurane persists up to 8 weeks after ischemia [58].

Another important oxidative mechanism in the case of IR injury is based on the iNOS activity and on increased NO concentrations. The redox implications of NO are a very interesting topic as they have an increased reactivity towards other molecules. A specificity of this pathway is the formation of peroxynitrite free radicals following the interaction between NO and the superoxide radical [59,60]. The attack mechanisms of peroxynitrite at cellular level are the attack towards the mitochondrial membrane, DNA oxidation, blocking DNA repair mechanisms and cell energy failure [61,62].

Neuronal OS occurring during cerebral ischemia are divided in three major groups of nitric oxide synthases: end endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS) [63,64]. Recent studies have shown an increase in the activity of these enzymes during cerebral ischemia, with a significant NO production increase. Silver et al., in a study regarding the expression of NO in patients suffering from Moyamoya disease that had undergone bypass surgery with a temporary occlusion of the M4 branch of the middle cerebral artery, have shown increased expression for mixed venous nitride (NO_2) occurring immediately after the occlusion of the cerebral artery. Moreover, the authors concluded that the NO_2 expression is directly proportional to the degree of cerebral ischemia [65].

During cerebral ischemia, due to the released OS and increased flow of reactive species the BBB can be affected, leading to a migration of T lymphocytes, macrophages, natural killer cells, and polymorphonuclear leucocytes. Among the most widely studied reactive species involved in the BBB destruction are transforming growth factor betta (TGF-β), interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin 1-beta (IL-1β), interferon beta (IFN-β) and tumor necrosis factor alpha (TNF-α) [49,66–69]. Boutin et al., have proven the destructive impact of Il-1 in ischemic brain injury. Moreover, there are numerous mechanisms that correlated increased IL-1β production with an increase in BBB permeability [70].

The most representative chemokines involved in the molecular mechanisms of IR are the monocyte chemoattractant protein-1 (MCP-1/CCL2). The main activity of MCP-1 is the central recruitment of activated lymphocytes, macrophages, and monocytes. Hartley et al., have studied the implications of CCL2 in the changes that occur at BBB level after ischemia. By blocking CCL2 with an antibody, the permeability of the BBB is [71]significantly reduced, together with the distribution of the tight-junction proteins . A similar study carried out by Stamatovic et al., has reported that MCP-1 plays an essential role in leukocyte recruitment and in the increase of BBB permeability [72] .

One of the main parts of general anaesthesia is represented by mechanical ventilation. This therapeutic segment has significant implications on the OS expression in the surgical patient. An increased interest for the problem arises in the case of lung transplant, major cardiac surgery and lung surgery with one-lung ventilation. The most common mechanisms at cellular and molecular levels constitute the lung ischemia reperfusion injury (LIRI). By reducing or even interrupting pulmonary blood flow, the reactive species production in the endothelium will be accelerated. Another site for the excessive production of ROS is represented by the alveolar macrophage. The reperfusion phase is characterised by pro-inflammatory cytokine release, activation of NOS and neutrophile recruitment [73–76].

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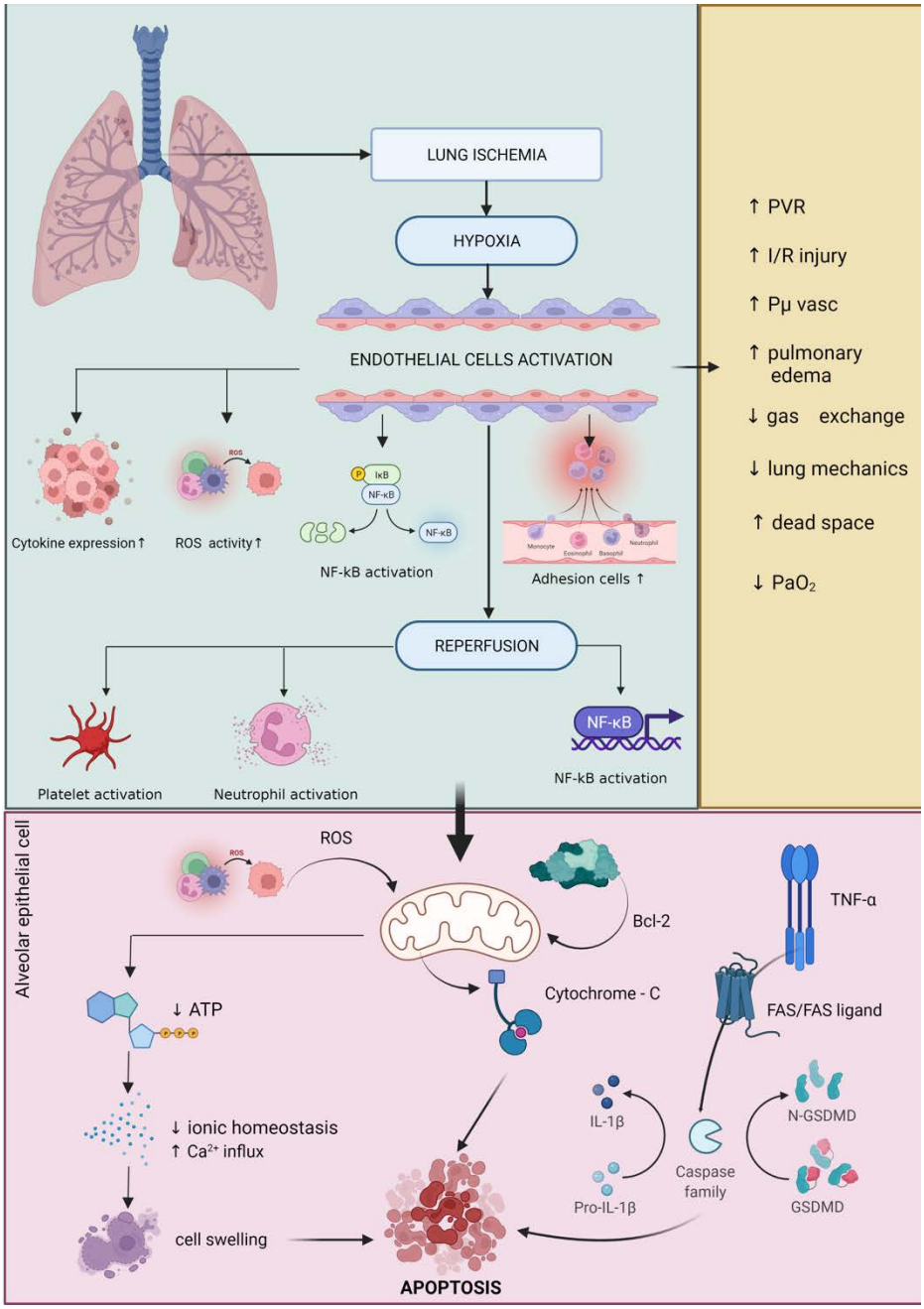

Figure 1. Schematic representation of lung ischemia reperfusion injury

An increase in the expression of reactive oxygen species leads to changes in the cellular and molecular activities in lung tissue. The main sites affected by these changes are the expression of calcium/calmodulin-dependent NO, nicotinamide adenine dinucleotide phosphate (NADPH), and nuclear factor kappa B (NF-kB). The result of the acceleration of these processes inside the cell is pulmonary oedema that is the result of an increase in pulmonary vascular resistance and endothelial damage. During mechanical ventilation these secondary phenomena lead to decreased ventilation and impaired gas exchange in the alveoli. After reperfusion, pulmonary vascular resistance can increase up to 100% mainly due to vasoconstriction and endothelial damage in the lung microvasculature. Increased vascular resistance, worsening pulmonary oedema, and increased extravascular lung water lead to impaired gas exchange and impaired lung mechanics. All of these phenomena will negatively impact the clinical status of the patient through a sudden decrease in arterial partial oxygen pressure, increase peak airway pressure and alveolar-arterial oxygen gradient (A-a/DO2) [77,78]. Recent studies have shown that during pulmonary reperfusion microvascular permeability can increase up to 10 times. It was suggested that the initial stage depends on the production of interleukin-8 (IL-8), interleukin 12 (IL-12), interleukin-18 (IL-18), and tumor necrosis factor alpha (TNF-α), while the second stage is responsible for the production

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of activated neutrophiles and pro-oxidative factors such as interleukin-8 (IL-8), leukocyte adhesion molecule CD18, endothelial P-selectin, and endothelial intracellular adhesion moleculue-1 [73].

Changes in the redox balance represent another frequent phenomenon in the case of LIRI, as excessive production of reactive oxygen species (ROS) has been shown to happen right after the reperfusion. In the lung there are a series of potential ROS generators such as activated xanthine oxidase, neutrophiles, mitochondria, NADPH oxidase system, and NO synthase. Chen et al., has shown in a study that mitochondrial damage plays a more important role in the ischemia process and a less important one in the reperfusion process. The oxidative phenomenon is augmented by the reduction of oxygen delivery in the mitochondria that leads to a decreased oxidative phosphorylation process and a decrease in ATP production [79]. Decreased ATP production will lead to a dramatic decrease in the mitochondrial membrane potential, leading to calcium transfer outside the mitochondria and the initiation of cellular apoptosis. Damage to the mitochondrial membrane and permeabilization of the membrane will lead to an increase destruction of certain proteins that are vital for the normal functioning of the mitochondrial system, such as the citocrom-C. Furthermore, releasing cytochrome-C in the cytosol will lead to the activation of caspase-9 and to an increase in the apoptotic process at cellular level [80,81]. NOS found in the lung can be subdivided in 4 species: endothelial NOS (eNOS) inducible NOS (iNOS), neuronal NOS (nNOS) and mtNOS. Studies have shown an increased pro-inflammatory activity for [82–85]mtNOS, as well as an increased anti-inflammatory activity for iNOS and eNOS [82–85].

Stefan Fischer et al., have shown in their study that apoptosis is only present after the reperfusion of lung tissue, that the activity increases dramatically and that the peak is reached after two hours. Apoptosis is initiated by the activation of both intrinsic and extrinsic mechanisms, with the mitochondria playing the role of modulating factor in both pathways [86]. The intrinsic pathway is also known as the mitochondrial pathway and is initiated by the action of cytokines and free radicals. It is characterised by changes in permeability of the mitochondrial membrane through the Bcl2 proteins. On the other hand, the extrinsic pathway is characterised by the activation of certain signalling proteins such as TNF receptor, angiotensin 2, and FAS/FAS ligand [87,88].

Ischaemia in the lung tissue will lead to the activation of caspase-8 through the FAS/FAS ligand system. The next phase is represented by the activation of caspase-7, caspase-6, and caspase-3 that led to DNA fragmentation through the poly-ADP ribose polymerase [87]. During ischemia-reperfusion syndrome researches have shown a rapid release of vasoconstrictor and vasodilatory mediators inside the lung, all derived from arachidonic acid, C3 and C5a complement fragments, thrombin, transcription factor, and a series of pro- and anti-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-10 (IL-10), interleukin-18 (IL-18), interferon-γ (INF-γ), and tumour necrosis factor-α (TNF-α).

The consequence of various anaesthetic drugs on the immune cells have been extensively investigated in *in vitro* studies. Cultures of immune cells such as neutrophils, lymphocytes and/or NK-cells are separated and exposed to clinical concentrations of anaesthetics, but at the same time the cells are isolated from the whole network and interaction with other immune cells or mediators which may not reflect the clinical situation.

Several studies have shown that propofol has immuno-inhibitory activity through actions on the non-specific immune system, impairing monocyte and neutrophil functions like chemotaxis, phagocytosis, and oxidative burst. Some studies have suggested that this activity is due to the lipid solvents found in the formula. The inhibition of the chemotactic and phagocytic function of neutrophils may be caused by a decrease in intracellular calcium. The effects of propofol seem to be dose dependent and occur at clinically relevant concentrations [89,90]. Propofol has been found to suppress the functions of polymorphonuclears, lymphocyte proliferation and cytokine release in response to endotoxemia only in patients already immunocompromised, but not in healthy volunteers. Hoff et al. investigated the effects of propofol and ketamine on TNF-α gene expression in peripheral blood mononuclear cells and found that lipopolysaccharide endotoxin stimulated TNF-α mRNA steady state transcripts were significantly increased in the presence of propofol (+42%) and decreased in the presence of ketamine (–31%) compared to control cell groups [91].

The effects of most anaesthetics are mediated at least partially through GABA-A receptors. Several studies have demonstrated that these receptors can be found on the immune cell membranes and can be influenced by anaesthetic drugs. GABA can activate ion channels on macrophages and monocytes and decreased cytokine secretion and T cells proliferation. Moreover, drugs that influence the GABA concentration such as, vigabatrin and muscinol seem to have the same effects. There is extensive crosstalk between the central nervous system and the immune system, and these findings offer a possible explanation as to why chronic propofol administration in intensive care patients increases the

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risk of infection. On the contrary, monocyte GABA-A receptors are not influenced by diazepam, therefore the use of benzodiazepines as sedative agents may be more appropriate where infection is a life-threatening problem.

The effects of inhalational anaesthetics are also mainly inhibitory, including suppressed neutrophil function, altered lymphocyte proliferation and decreased cytokine release by mononuclear cells. In contrast to halogenated inhalational anaesthetics, which are known to suppress pro-inflammatory cytokines in murine pulmonary cells, volatile anaesthetics induced an increased gene expression of pro-inflammatory cytokines. Moreover, some studies have shown that the effects of inhalational anaesthetics are dose and time dependent [92–94].

A 2013 study suggested that the NF-κB signalling pathway contributes to sevoflurane and isoflurane-induced neuroinflammation, by increasing the levels of IL-6 (isoflurane by 410% and sevoflurane by 290%) the nuclear levels of NF-κB (isoflurane by 170% and sevoflurane by 320%). Other studies have confirmed that isoflurane can increase levels of interleukin IL-6, which has been associated with learning and memory impairment in animals [95,96].

The immunosuppressive effects of morphine are well documented in numerous studies and extend at many levels in the inflammatory cascade. Among the effects of morphine: altered cytokine release and lymphocyte proliferation, activated enzymes involved in macrophage and lymphocytes apoptosis, inhibition of cell adhesion and increased secretion of stress hormones. Synthetic opioids, except for Fentanyl, seem to have less pronounced impact on the immune system, probably due to the fact that they do not interact with the **μ**2 opioid receptors on immune competent cells [97,98].

Intravenous rocuronium bromide induces pain during injection and/or withdrawal movement, the exact mechanism of which is not yet understood. One study found that rocuronium bromide induces inflammation in calf cells, by inhibiting endothelial nitric oxide synthase, suppressing nitric oxide production, activating cyclooxygenase-2 and increasing prostaglandin E2 synthesis, which in turn may be the cause of pain during injection [99].

Challenges in isolating various immune variables from the complex immunological network in clinical scenarios lead to far fewer *in vivo* than in vitro studies. Inhalational agents are of great importance not only to the patients, but also to the personnel attending the operating theatre due to their volatile nature. Chronic occupational exposure to low doses of isoflurane were correlated with fewer total T and T helper (CD4+) lymphocytes in a dose and time dependent manner [100]. The *in vivo* effects of sevoflurane and isoflurane largely reflect the in vitro studies. Several studies have demonstrated that these two agents can reduce the levels of reactive species of oxygen, inhibit chemotaxis, inhibit activation of neutrophils and, hence, decrease neutrophil adhesion to human endothelial cells, decrease IL6 and TNF-α, suppressed PMNs migrations and functions through various pathways, altered cytokine release from macrophages and decrease in NK cytotoxic activity. A study comparing two different anaesthetic techniques, TIVA vs. balanced inhalational anaesthesia, found that perioperative cell mediated immunity was less influenced by TIVA, suggesting that the stress response in patients undergoing anaesthesia with a volatile agent is more pronounced [101–106] .

A 2019 study addressing the effects of propofol on neutrophil function, lipid peroxidation and inflammatory response during elective coronary artery bypass grafting in patients with impaired ventricular function found that the addition of propofol contributes to a lesser increase of IL-6 levels, and a greater decrease of IL-10 compared to placebo. No effects were seen on IL-8. In addition, malondialdehyde (MDA), a marker of lipid peroxidation and free radical injury, measured in the coronary artery sinus, was lower in the Propofol group at 1, 3, 5 and 60 minutes after reperfusion ($p<0.01$), suggesting that propofol attenuates free-radical-mediated lipid peroxidation and systemic inflammation in patients with impaired myocardial function undergoing CABG [107].

A study by Potocnik et al., on patients undergoing thoracic surgery and one lung ventilation used either propofol or sevoflurane to maintain the anaesthesia. They found that IL6, IL8 and CRP levels where higher in the propofol group, while IL10 was higher in sevoflurane group. The oxygenation index 6 hours after the surgery was lower in the propofol group compared to sevoflurane ($p = 0.02$), maintained 24h after the surgery ($p=0.019$). The number of postoperative adverse events was significantly higher in the propofol group ($p<0.05$) and included ARDS, pneumonia, and SIRS [108]. In a similar manner, but on patients undergoing craniotomy, propofol proved to be less inflammatory than sevoflurane with lower IL-6/IL-10 concentration ratio during and at the end of surgery ($p = 0.0001$) and higher IL10 [109].

A 2019 study compared the effects of propofol with those of desflurane on inflammation and ischemia reperfusion syndrome during robot assisted laparoscopic radical prostatectomy (RALRP) and found that propofol based anaesthesia significantly attenuated the increase in IL-6 levels during RALRP (4.68 ± 2.76 pg/mL vs. 8.57 ± 3.72 pg/mL; $p < 0.001$), but with similar effects on TNF-α, CRP, and NO levels [110].

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American Heart Association (AHA) recommends that patients at risk of myocardial ischemia during surgery, who are hemodynamically stable, should undergo general anaesthesia with inhalational agents [111].
These recommendations and the benefits of these agents were emphasized in numerous studies. A study conducted on 74 patients scheduled for coronary artery bypass graft surgery under cardioplegic arrest, showed that 10 minutes of preconditioning with sevoflurane decreased the release of brain natriuretic peptide in the perioperative period. Moreover, the levels of plasma cystatin C were lower in sevoflurane preconditioned patients, suggesting improvement in both cardiac and renal function after major heart surgery [112].
A review by Fukazawa et al., presented extensive evidence, both in vitro and in vivo, that modern inhalational halogenated anaesthetics play an important role in the pathophysiology leading to AKI, by inhibiting renal tubular and endothelial cell necrosis and apoptosis and inducing anti-inflammatory effects at this level, by activating pathways responsible for anti-inflammatory and cytoprotective signalling molecules, such as releasing TGF-β1, activating CD73 and inducing IL-11 and generating adenosine [113]. A systematic review concluded that patients undergoing cardiac surgery had a significantly lower increase in creatinine level in the first two days after surgery, lower intensive care unit stay and hospitalization when anesthetised with volatile anaesthetics compared to TIVA Propofol. However, there was no statistically significant difference in mortality between the groups [114]. Furthermore, current anaesthetics seem to offer neuroprotection against mild or moderate ischemic injury sustained for 2 - 4 weeks but have no influence on severe ischemia. These effects are mediated by antagonizing postsynaptic glutamate receptors and enhancing GABA-A mediated hyperpolarization and by inhibition of several processes that lead to neural apoptosis (increased levels of antiapoptotic proteins like Bcl-2 and reduced cytochrome c release) [115–117].
The benefits of inhalational anaesthetics extend beyond the operating theatre, with extensive research suggesting that sedation with sevoflurane or isoflurane in the intensive care unit plays an important role in preventing ventilatory associated lung injury (VILI). Release of pro-inflammatory markers, such as IL-1b and MIP-1β, and reactive oxygen species, as well as neutrophil transmigration into the alveolar compartments of the lungs are rapidly prevented in the early stages of VILI if sedation is switched from intravenous to inhalational [118]. Moreover, inhalational anaesthetics seem to influence glycaemic control in the perioperative period. Blood glucose levels were found to be higher with volatile agents, like sevoflurane and isoflurane, compared to propofol maintained anaesthesia. This response was attributed to impaired glucose clearance and increased glucose production and inhibition of normal insulin production .

Kalimeris et al., have studied the antioxidant effects of propofol in patients undergoing carotid endarterectomy. The study protocol included 21 patients in the control group, in which general anaesthesia (GA) administered using sevoflurane, and the study group in which GA was administered using propofol (N=23). The biomarkers used for the quantification of oxidative stress included the expression of P-selectin and S100B protein, the lactate levels, nitrate, nitrite, and malondialdehyde. The study has shown statistically significant differences regarding S100B levels, that were lower in the propofol group. Moreover, they have shown lower levels of malondialdehyde (MDA), nitrites and nitrites in the same propofol group. Peng Yang et al., have carried out a similar study regarding the inflammatory influence of sevoflurane vs. isoflurane in an experimental ischemia/reperfusion model. To quantify the impact on OS they have analysed certain biomarkers such as superoxide dismutase (SOD), MDA, nitric oxide (NO), and complement C3, C5a and C6. The study has reported lower expressions for OS in the sevoflurane group (Peng Yang).

3. Implications of genetic and epigenetic expression on inflammation and oxidative pathways

microRNA species are biosynthesized in the cell nucleus through the action of RNA polymerase II on the specific genes. The initial species that result after the first interaction are called pri-microRNAs. The chain of biochemical processes is afterwards continued by the attack of RNA polymerase III endonuclease (Drosha) on the primicroRNAs, leading to the formation of pre-microRNAs. This reaction is catalysed by DiGeorge Syndrome Critical Region 8 (DGCR8). The biosynthesis process continues in the cell cytoplasm, where pre-microRNAs are transported from the nucleus to the cytoplasm with the help of Exportin-5. The final microRNA species will result from a reaction between the pre-microRNAs and Enase III endonuclease (Dicer) and the RNA binding protein (TRBP). The newly formed epigenetic species will then be transported inside the cell as microvesicles, exosomes, ribonucleoprotein complexes and high-density lipoproteins. Recent studies have shown a series of molecular changes induces by anaesthetic drugs, being involved especially in the modulation of the inflammatory and oxidative chains. Kim et al. have studied the process and have identified a decrease in the expression of microRNA-27a, microRNA-194, microRNA-23b, microRNA-133a,

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microRNA-199a, microRNA 101, microRNA-219-5p, microRNA-30b, microRNA-92b, microRNA-127, and microRNA-204. In the same study they have reported increases in the expression of microRNA-370, microRNA-134, microRNA-302a, microRNA-107, microRNA-92a, microRNA-202, microRNA-190b, microRNA-29b, microRNA-216a, microRNA-181d and microRNA208b [119]. A similar study was carried out by Twaroski et al. showing essential changes in the expression of miRNA-21 in patients that have received propofol [120].

The brain is one of the most sensitive organs that must be protected during GA. Anaesthetic management and perioperative protocols focus especially on maintaining adequate cerebral perfusion and oxygen delivery. Pathophysiological mechanisms involved in maintaining a constant and adequate cerebral perfusion are complex and not fully understood. It is a however a known fact that cerebral autoregulation maintains a constant cerebral blood flow despite the changes in mean arterial pressure. Biological functions are extremely sensitive even at the slightest change in mean arterial pressure and therefore the cerebral autoregulation mechanisms will be activated to prevent cellular anoxia [121]. From an epigenetic point of view, scientists identified different involvement of microRNAs in the biological pathways related to cerebral ischemia and reperfusion. Gusar et al., in a study regarding the expression of microRNAs in cerebral ischemia in experimental animals have identified statistically significant changes up to 48 hours after cerebral ischemia for a series of epigenetic species such as microRNA-30c-2-3p, microRNA-125b-5p, microRNA-300-5p, microRNA-107-3p, microRNA-497-5p, microRNA-27a-3p, microRNA-30b-3p, microRNA-29c-3p, microRNA-124-3p, microRNA-330-5p, microRNA-181b-5p, microRNA-29a-3p, let-7i-3p, microRNA-22-3p, let-7i-5p, microRNA-212-3p, microRNA-26a-5p, microRNA-99a-3p, microRNA-221-3p, microRNA-27b-3p, microRNA-24-3p, microRNA-22a-5p, microRNA-29a-5p, microRNA-186-5p, microRNA-99a-5p, microRNA-128-3p, microRNA-23a-3p, microRNA-376b-5p, microRNA-30c-5p, microRNA-9a-5p, microRNA-30a-3p, let-7f-5p, microRNA-21-5p, microRNA-223-3p [122]. A molecular mechanism associated with cell survivor apoptosis is phosphatase and tensin homologus protein (PTEN) and its involvement in the biochemical activity of PI3K/AKT [123]. Wang et al., in a study on the cellular and epigenetic mechanisms involved in initiating, augmenting and maintaining cerebral ischemic injury have shown that microRNA-32-5p activity is directly proportional with the expression of PTEN/P13K/AKT that is responsible for the protection of cerebral tissue (Yao Wang). A similar study was carried out by Huang et al., as it presents the implications of microRNA-326-5P in reducing the signal transducer and activator signal of transcription-3 (STAT3) and the protection of cerebral tissue during ischemia-reperfusion syndrome [124].

Other mechanisms that are involved in cerebral injury following ischemia and reperfusion are the excessive production of free radicals, the mitochondrial disfunction, lipid degeneration, protein oxidation, DNA structure modification, and finally cerebral tissue death. Guo et al., in an experimental study have reported and described a series of neuronal protection mechanisms through the activity of microRNA-25 [125]. On the other hand, Huang et al., described that ischemia and reperfusion lead to an augmented tissue damage and accelerated cell death [126]. Zang et al., in a complex study on the protective actions of microRNA-25 in neuronal protection during cerebral ischemia have reported that increasing the expression of microRNA-25 leads to an inhibition of Fas/FasL activity and reduces apoptosis induced by ischemic injury [127]. Mao et al., reported protective effects at cerebral level when inhibiting p38 mitogen-activated protein kinases (MAPKs) activity through microRNA-128-3p. moreover, they have shown that higher levels of microRNA-128-3p are able to block the posttranscription activity of p38α and can contribute to the survival of neurons during cerebral ischemia [128].

An experimental study carried out on laboratory animals by Jian-Ping Zhang et al., investigating the expression of certain biological markers such as microRNAs-144, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and glycogen synthase kinase-3β (GSK3β) in LIRI have shown that overexpression of genes was directly proportional with the intensity of ischemic injury. Regarding the epigenetic expression of microRNA-144 the authors have identified a decrease in its concentration [129]. Li et al., have studied the expression of microRNA-146a in LIRI and have shown a decrease in the epigenetic expression in pulmonary ischemic injury. Moreover, the group has identified that microRNA-146a activity is directly proportional with the overproduction of IL-1β, IFN-γ, TGF-β1 si TNF-α [130]. On the other hand, Yan Zhou et al., have identified and increase in the expression of microRNA-155 during LIRI accompanied by aan overexpression of IL-6, IL-1β, TNF-α, 8-isoprostaglandin F2α (8-iso PGD2α) and 8-hydroxy-2- deoxyguanosine (8-OHdG) [131]. microRNA-223 is overexpressed in LIRI and is involved in the hypoxia-inducible factor-2α (HIF2α) pathway, being responsible of worsening the pro-inflammatory status in the lung [132]. Cai et al., carried out a study on the expression of microRNAs in pulmonary ischemia in laboratory animals that had undergone pulmonary transplantation, discovering increased microRNA-206 levels [133]. Another experimental study has reported decreased

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levels of microRNA-18a-5p in ischemic pulmonary tissue [134]. Qin et al., have studied the expression of microRNAs in multiorgan ischemia caused by haemorrhagic shock, and have identified an increase in the expression of microRNA-24a in the animal group that was induced haemorrhagic shock ($p<0,05$). This group has also identified a statistically positive correlation between increased microRNA-34a levels and serum malondialdehyde (MDA) [135]. Li et al., have shown in their study that the expression of micrRNA-21-5p and the IL-1β, IL-6, IL-8, IL-17 and TNF-α bioproduction by the macrophages are statistically dependent in the case of laboratory animals suffering from pulmonary ischemia [136].

During general anaesthesia one of the main pathophysiological factors that need to be considered by the anaesthetic team is the maintenance of blood pressure homeostasis in order to insure adequate oxygenation of vital organs. An important marker for the adequate perfusion of tissues is given by kidney function assessed through the excretion capacity. In many clinical scenarios, the kidneys suffer both due to tissue hypoperfusion and due to other mechanisms, such as inflammation, rhabdomyolysis, or haemorrhagic shock. One of the main causes for acute kidney injury is ischemia/reperfusion syndrome. From a pathophysiological standpoint, kidney ischemia/reperfusion syndrome is complex and multifactorial, not al causes being at this point fully elucidated. Among the causes that stay at base of kidney IR injury are destruction of renal tubular cells that finally lead to the destruction of renal tubules. Clinically, once these pathophysiological mechanisms have exerted their effects, glomerular filtration rate (GFR) has already been affected. Dixon et al., have identified a specific mechanism for the destruction of renal cells characterised by lipid peroxidation, condensation of mitochondrial membranes and iron accumulation. The process named ferroptosis has been recently identified and explained in other studies as being involved in different pathological states, including myocardial infarction [137–139]. Inside the cell there are a series of enzymes and proteins responsible for the inhibition of ferroptosis, such as glutathione peroxidases 4 (GPX4) responsible for diminishing the effects of lipid peroxidation, a fact proven by Wan Seok Yang et al., in a study regarding the ferroptosis mechanisms in cancer cells [140]. Xuexian Fang et al., have studied another mechanisms that may be responsible for ferroptosis inhibition by reducing the activity of lipid peroxidation through the transport of cystine in the cytosol and through the stimulation of GSH production through Solute carrier family 7 member 11 (SLC7A11). Another molecular and epigenetic mechanism involved in increasing renal disfunction is represented by the microRNAs [141]. Drobna et al., have identified that augmenting molecular mechanisms is possible through the action of genes and of microRNA-20b-5p si a microRNA 363-3p [142]. Ding et al., have proven in a similar study the direct involvement of microRNA- 182-5p and microRNA-378a-3p in intensifying the process of ferroptosis and deterioration of renal function due to ischemia and reperfusion [143].

Takuto Chiba et al., in an experimental study about the role of microRNAs in kidney ischemia have identified that the subjects included in the study presented high levels of microRNA-17, microRNA-18a, microRNA-19a, microRNA-20a, microRNA19b-1, and microRNA-92a-1 [144]. MicroRNA-24 was identified as a promoter of ischemic kidney injury, acting by stimulating the biological mechanisms of H2A-histone family and oxygenase 1 [145]. Wang et al., have also discovered increased expressions for microRNA-466 and microRNA- 709 in kidney disfunction induced by ischemia [146]. Furthermore, this group of authors has reported important involvement of genes Mcm5, Oip5, E2f8, Myc, E2f1, and Mdm2 in increasing the severity of ischemic injury. A similar study was carried out by Cao et al., and it identified significant implications of microRNA-125b-5p in ischemic kidney injury [147]. MicroRNA-489 was found to be a protective epigenetic species against kidney disfunction induced by ischemia through hypoxia-inducible factor-1 [148]. Other studies have found a series of microRNA species that had their expression significantly modified by acute renal injury, such as microRNA-4640, microRNA-4270, microRNA-4321, microRNA-10a-5p, microRNA-26b-5p, microRNA-16, microRNA-27a-3p, microRNA-93-3p, microRNA-29a-3p, microRNA-126-3p, microRNA-127-3p, microRNA-200c, microRNA-210-3p, microRNA-210, microRNA-423, microRNA-21, microRNA-30e, microRNA-30a [145,149–155]. Zang et al., in a study regarding microRNAs expression in septic shock patients and acute kidney injury (AKI) have identified decreased plasma and urine levels for microRNA-22-3p in patients that did not survive. The statistical analysis based on the Kaplan-Maier survival curves and Cox regression analysis has identified a statistically significant correlation between a decrease in this certain microRNA specie and 28 days mortality for patients presenting with septic shock and AKI [156]. In the case of critically ill patients, one of the most widely studied mechanism for kidney injury is the formation of oxalic acid and calcium oxalate (CaC_2O_4) that produce tubular obstruction and crystallisation in epithelial cells. Shihana et al., have identified increased expressions for microRNA-20a, microRNA-93, microRNA-92a, microRNA-195, microRNA-451 in acute kidney injury caused by oxalate [157]. Other mechanisms responsible for worsening kidney tissue injury are the activation through phosphorylation of mitogen activated protein kinase ½

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(MEK1/2). Recent studies have reported the implications of MEK1/2 in differentiation, migrations, proliferation, metabolism, and cellular death. Collier et al., have studied all these complex mechanisms and reported active involvement of microRNA-34a in decreasing MEK1/2 activity and initiating ischemic renal injury [158]. Another microRNA specie involved in the pathogenetic mechanisms is microRNA-21 [159]. Zhang et al., have also shown that microRNA-192 expression increases in patients with AKI. Moreover, it identifies an increase in the concentration at 3 hours after the ischemic event in the kidney, with a peak value at 12 hours, and a decrease in its levels during the next 24 hours. (AUC-ROC 0,673, 95% CI 0,540-0,806, p=0,014) [160]. The Wnt/β-catenin pathway is another mechanism involved in kidney ischemia and is responsible for the fibrosis happening in the kidney [161,162]. Apart from the aforementioned microRNAs, there is also a molecular complex responsible for modulating the activity of Wnt/β-catenin, that includes Dickkopf (DKK) 1, 2, 3 and 4. (DKK1, DKK2, DKK3, DKK4) [163]. Yi et al., have shown in one of their studies that microRNA-214 is directly involved in inhibiting the activity of Wnt/β by a direct blockage of β-catenin [164]. Zu et al., identified the direct molecular processes of microRNA-214 in kidney injury through the modulation of Wnt/β-catenin activity and the expression of DKK3 [165].

4. Perioperative antioxidant therapy

Numerous studies have been carried out in the last decades with the goal to reduce the pro-oxidative profile in surgical patients [166]. Different antioxidant therapies have been proposed and they targeted either the inhibition of biological processes responsible for the production of certain molecules, or the neutralization of redox activity of free radicals aiming and complexing them in molecular formulas with no chemical activity [167–169]. A widely study such molecule is hydrogen sulphite (H_2S) that due to its structural properties can easily diffuse through cell membranes and through the membrane of organelles. From a biochemical standpoint, the antioxidant activity of H_2S is represented by the inhibition of reactive oxygen species through nuclear factor erythroid 2-related factor 2 (Nrf2) activation and Kelch-like ECH-associated protein-1 (Keap1) inactivation, and by an increase in GSH and Trx expression. The main source for H_2S biosynthesis in the body is the cystathione β-synthase (CBS) that is predominantly fount in the central nervous system (CNS), and the cystathionine γ-lyase (CSE) found in the cardiovascular system (CVS). The biosynthesis mechanism is based on desulphydration of cysteine through the catalyst biological mechanisms given by the pyridoxal-5′-phosphate-dependent enzymes. Tripatara et al., carried out an experimental study on 74 lab animals (Wistar rats) on the effect of endogen and exogen H_2S on the ischemia/reperfusion syndrome in the kidney tissue. Exogen H_2S sources were represented by the administered sodium hydrosulfide that reduced the incidence and severity of tubular and glomerular dysfunction in the experimental model that undergone 45 minutes of ischemia and 6 hours of reperfusion. Histochemical analysis has shown a significant reduction in the histological score for acute tubular necrosis and important decrease in the expression of redox mechanisms [170]. Bos et al., in a similar study have reported a protective effect of H_2S for renal function, apoptosis, and kidney tissue inflammation under experimental conditions of ischemia/reperfusion injury. Moreover, they have highlighted that by inducing a hypermetabolic status through H_2S, the kidney can be protected from hypoxia [171]. The most recent studies have focused on blocking biochemical mechanisms of free radical production inside the mitochondria. In this regard, one of the most widely studied pharmacological formulas is represented by SS-31, also known as Bendavia, Elamipretide sau MTP-131. Structurally it is a synthetic tetrapeptide with the formula D-Arg-2′6′dimethylTyr-Lys-Phe-NH_2 [172]. SS-31 can selectively attack cardiolipin from inside the mitochondrial membrane and is able to block the transient mitochondrial permeability mechanism that is in action during ischemia reperfusion, therefore leading to increased ATP biosynthesis and reduced ischemic injury [173]. Szeto et al., in an experimental study have identified low levels of IL-18, IL-1β, si TGF-β in ischemic tissue. Moreover, these authors have reported a decrease in macrophage infiltration and TNF-α activity, with restoration of glomerular capillaries and podocyte structure [174]. A similar study was carried out by Birk et al. and reported the recovery of the ATP production mechanism in the mitochondria during kidney ischemia reperfusion syndrome [173]. 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl, also known as Tempol, is another compound that was investigated for reducing cellular redox activity, due to its capacity to block reactive oxygen species by reducing intracellular Fe^{2+} concentrations [175]. Chatterjee et al., in an experimental study on Wistar rats on the effects of Tempor on redox activity in the proximal renal tubules, have shown that there was a significant decrease in renal disfunction and kidney injury due to ischemia reperfusion syndrome. The mechanisms of action that were identified in this case

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are characterised by a reduction of hydrogen peroxide biosynthesis in the respiratory chain and an increase in lactate dehydrogenase (LDH) [176].

In patients undergoing surgical stress there are a series of time-related changes at a metabolic level. More et al., in their book published in 1959 described the stages of surgical stress as follows: Phase 1 - stress period that can continue for 2-4 days, Phase II – turning point – that will be followed by the anabolic phase, Phase III – regeneration of proteins and muscle that happens a few weeks after surgery, Phase IV – accumulation of fat [177] During these phases, muscular proteins are broken down to activate the gluconeogenesis, energy production, and tissue repair, that being one of the reasons for which the nutrition of the surgical patients is of utmost importance before and after surgery [178,179]. Miyachi et al., in a study on the impact of cysteine administration (700mg) and Theanine (280mg) for 4 days before surgery and 5 days after surgery, in oncological patients undergoing distal gastrectomy have shown a reduction of postoperative inflammation and faster recovery [180]. A similar, experimental study carried out by Shibakusa et al., has reported a decrease in IL-6 expression in laboratory animals that received cystine/theanine 5 days before surgery [181]. Tanaka et al., have come to similar conclusions, stating that cystine administration leads to a decrease in the concentration of IL-6 and IL-10 in lab animals with induced sepsis [182].

The most widely study molecule with antioxidant properties is vitamin C. From a chemical perspective, ascorbic acid ($AscH_2$) is a water soluble ketolactone that expresses two ionizable hydroxyl groups (Sven-Olaf Kuhn). At physiological pH, the predominant chemical type is the $AscH^-$ Anion. The redox capacity of ascorbate is given by its reduction in two consecutive steps [183–186], through donating an electron and formation of the ascorbate radical (Asc^-) and of dehydroascorbic acid (DHA) [187]. Physiologically, the concentration of ascorbate in plasma in healthy individuals is between 40 and 80 microM, a level capable of insuring an endogenous antioxidant activity. The main reactive species to which ascorbate donates an electron leading to a blockage in redox activity are alkoxyl radical (RO), thiol radical (GS), hydroxyl radical (HO), peroxyl radical (LOO), tocopheroxyl radicals (TO) [188–190]. Recent studies have demonstrated that ascorbate can inhibit lipid oxidation processes in the endothelial cells and macrophages [191]. Du et al., have shown in their experimental study the ability of vitamin C to inhibit inflammatory and pro-oxidative processes mediated by NF-κB [192]. A similar study was carried out by Brown et al., regarding the impact that vitamin E and vitamin C antioxidant therapy have in pancreatic transplantation and have shown a significant decrease in the inflammatory and oxidative expressions [193]. Moon et al., carried out a prospective, randomized study that included 132 patients scheduled for gynaecological surgery. For the statistical analysis and for underlining the antioxidant effects of vitamin C the authors have distributed the patients in 4 groups, as follows: Group 1 (n=33) that received magnesium sulphate 40 mg/kg, Group 2 (n=33) that received vitamin C 50 mg/kg, Group 3 that received magnesium sulphate 40 mg/kg and vitamin C 50 mg/kg, and Group 4 that received isotonic saline solution 40 ml. The monitored clinical effects were postoperative pain score, postoperative nausea and vomiting (PONV), and total fentanyl requirements. The study has shown significantly lower fentanyl requirements in the groups that received magnesium sulphate and vitamin C (Group 1, Group 2, Group 3). Incidence for PONV was lower in the group that received both magnesium sulphate and vitamin C [194]. Mohamed et al., studied the impact of perioperative intravenous administration of vitamin C and N-acetylcysteine on the production of malondialdehyde, IL-6 and IL-8 as markers for oxidative stress and systemic inflammation in patients needing a Tourniquet during surgery; the study included 60 patients that have undergone surgical intervention of the upper limb and that received 1 g of vitamin C and 10 mg/kg N-acetyl cysteine respectively. Following statistical analysis, the group has identified an increased expression of IL-6, IL-8 and malondialdehyde in patients that did not receive antioxidant substances [195]. Rumelin et al., studied the plasmatic concentration of vitamin C in the pre- and postoperative period, following the administration of 1 g single dose vitamin C. For the study, the authors divided the patients in two groups: one group that received 1000 mg vitamin C preoperatively and the other group that received a placebo. Vitamin C levels in plasma were determined in both groups in the first postoperative day. The study concluded that the administration of 1 g vitamin C in the preoperative period does not insure a constant increased plasma concentration [196]. Jeon et al., carried out a similar study that included 100 patients undergoing laparoscopic colectomy that received 50 mg/kg intravenous vitamin C immediately after the induction of anaesthesia. The authors wanted to monitor the postoperative morphine requirements, as well as pain scores at 2, 4 and 24 hours after surgery. They have identified a decrease in morphine requirements 2 hours after surgery in patients that received antioxidant therapy, as well as a lower pain score at 24 hours [197].

Vitamin D is a recently intensely studied antioxidant, especially due to the inflammatory mechanisms induced by the infection with the new SARS-CoV-2 coronavirus [198,199]. Recent studies have shown that decreased plasma

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concentrations for vitamin D are associated with an increase in pro-inflammatory and pro-oxidative factors, such as TNF-α, IL-6, fibrinogen and C reactive protein [200]. It was shown that the vascular and microvascular systems contain important numbers of vitamin D receptors (vitamin D), explaining its ability to modulate pro-inflammatory mechanisms at vascular level. Nieuwland et al., in an experimental study regarding the impact of vitamin D on vascular inflammation has identified a decrease in CD4+ T-helper cell count expression. Moreover, a reduction in the biosynthesis of IL-2, IL-4 and IL-10 all associated with T-cell activity was also proven [201]. Martinez-Moreno et al., in a similar study identified a decrease in pro-inflammatory cytokines such as IL-6, IL-8, IL-1β si TNF-α when human aortic smooth muscle cells are exposed to increased concentrations of vitamin D [202]. The importance of vitamin D was also noticed in the case of orthopaedic surgery. Bogunovic et al., have carried out a retrospective study that included 723 patients that had undergone orthopaedic surgery. In these patients they have determined the levels of 25-hydroxyvitamin D in the preoperative period. The prevalence for vitamin D plasma concentrations was expressed as follows: normal (≥25ng/ml), insufficient (<32ng/ml) and deficit (< 20 ng/ml). It was shown that 40% of the patients had vitamin D levels < 32ng/ml, and out of these patients, half had levels < 20 ng/ml. The authors found a statistically significant correlation between vitamin D levels in plasma and bone fractures or degeneration, underlining the importance of this vitamin in maintaining normal muscle and skeletal functions [203]. Maniar et al., have looked at the impact vitamin D has on the recovery after total knee arthroplasty. The study included 120 patients, out of which 64 had vitamin D levels <30 ng/ml preoperatively. In the postoperative period, all patients received vitamin D antioxidant therapy. Patients with vitamin D deficit before surgery presented slower recovery in comparison to the others. Analysis performed 3 months after surgery showed that functional scores were similar in the two groups [204]. Mouli et al., are carrying out a similar study, including 174 patients with vitamin D deficit (< 30ng/ml) who received antioxidant therapy with vitamin D following the protocol (1 – daily vitamin D supplementation with increasing dose between 1000 and 6000 IU, 2 – one weekly dose of 50.000 IU, administered for 4 weeks, followed by maintenance with 2000 UI daily dose). In the surgical patients included in the study the authors have recommended a vitamin D antioxidant therapy with 50.000 UI vitamin D weekly for 4 weeks, followed by a maintenance dose, as a better solution than the administration of lower, daily doses [205]. Hajimohammadebrahim- Ketabforoush et al., studied the impact of vitamin D administration in deficient patients that undergo craniectomy for brain tumour resection. The study included 2 patient groups that had lower than normal vitamin D levels < 20 ng/ml. One of the groups received intramuscular vitamin D 300.000 UI intramuscularly in the preoperative period. In the study group the vitamin D concentration increased significantly at 5 days after surgery (p<0,01). ICU admission time, as well as the duration of hospital stay in patients that received, in the preoperative period, vitamin D supplementation were also significantly shorter. The authors of the study concluded that antioxidant therapy with vitamin D in the perioperative period is beneficial in patients with brain tumours [206].

5. Conclusions

The pro-inflammatory and pro-oxidative profiles that can be identified in surgical patients undergoing general anaesthesia is similar to that of patients with sepsis or septic shock. One of the explanations is the fact that pathophysiological mechanisms are similar and are mainly represented by an increase in the inflammatory profile, as well as microvascular injury due to ischemia and reperfusion. The epigenetic analysis of the microRNA expression shows a series of molecular and cellular mechanisms responsible for either the initiation, or the augmentation of this systemic inflammatory profile. Once these pathways are identified they can be blocked and/or certain mechanisms can be minimized in order to reduce the systemic impact in the surgical patient. Moreover, through the administration of antioxidant therapies one can observe a beneficial clinical impact. The most important benefits to be considered are the reduction of postoperative adverse effects, lower opioid requirements, shorter hospital admission time, and an increase in patient safety and patient satisfaction. However, further studies are needed regarding the administration of modern antioxidant therapies, targeted to the cellular and molecular level.

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