Redox Disturbance and Inflammation during General Anesthesia

Subjects: Anesthesiology

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Worldwide, the prevalence of surgery under general anesthesia has significantly increased, both because of modern anesthetic and pain-control techniques and because of better diagnosis and the increased complexity of surgical techniques. Apart from developing new concepts in the surgical field, researchers and clinicians are now working on minimizing the impact of surgical trauma and offering minimal invasive procedures due to the recent discoveries in the field of cellular and molecular mechanisms that have revealed a systemic inflammatory and pro-oxidative impact not only in the perioperative period but also in the long term, contributing to more difficult recovery, increased morbidity and mortality, and a negative financial impact. Detailed molecular and cellular analysis has shown an overproduction of inflammatory and pro-oxidative species, responsible for augmenting the systemic inflammatory status and making postoperative recovery more difficult. Moreover, there are a series of changes in certain epigenetic structures, the most important being the microRNAs.

general anesthesia redox inflammation antioxidants hypermetabolism microRNAs oxidative stress

1. Introduction

Anesthesia allows the performing of surgical procedures in a rapid, safe, and pleasant manner, producing analgesia, absence of awareness, and adequate muscle relaxation when needed [1][2][3]. A critical aspect of perioperative anesthetic care is the maintenance of homeostasis, including hemodynamic stability, oxygenation, ventilation, and temperature. The World Health Organization (WHO, www.who.int/, accessed on 20 May 2022) and the World Bank (WB, www.worldbank.org, accessed on 20 May 2022) expect that by 2026, the burden of diseases requiring surgery and anesthesia will exceed that of HIV, tuberculosis, and malaria, measured in disability-adjusted life years. As anesthesia providers are an integral part of the delivery of safe and effective surgical care, it is imperative to develop the necessary tools to minimize mortality and morbidity in the perioperative period [4][5].

Surgical stress induces an immuno-inflammatory response not necessarily proportional to the degree of tissue damage. In addition to the surgical injury, other factors may be contributing to the inflammatory response in the perioperative period, including the general anesthesia itself, mechanical ventilation, the administration of blood products, and antiemetic drugs [6]. Moreover, numerous studies have highlighted a number of molecular changes

induced by anesthetic substances, involving the expression of inflammation and hypermetabolism during general anesthesia. An abnormal over- or under-expressed immuno-inflammatory response has been associated with various relevant postoperative conditions, including infections, pulmonary complications, delirium and postoperative cognitive dysfunction [7], renal injury [8], and cancer recurrence [9][10][11]. Another important molecular and cellular effect is the unbalance of the expression of antioxidants in relation to the activity of reactive oxygen and nitrogen species (ROS, RNS). This phenomenon is called oxidative stress (OS) and refers to redox activity or reduction–oxidation activity [9][10].

2. Redox Disturbance and Inflammation during General Anesthesia and Surgery Procedures

A degree of inflammation during surgery is unavoidable and represents the first necessary mechanism in wound healing. It involves complex pathways that alter endocrine, hemodynamic, metabolic, redox, and immune responses [12]. The main link between localized injury and a systemic inflammatory response is represented by the damage-associated molecular pattern (DAMP) molecules, also called alarmins [13]. These molecules have a physiological role inside the cell but acquire additional functions when 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 [14]. 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, alarmins represent a diverse and structurally different group of molecules released by damaged or dying cells [15]. Interestingly, these “danger”-sensing molecules exert their functions by interacting with specific receptors expressed on damaged or dying cells but not on apoptotic cells [16].

As the first line of defense following tissue injury, migrating macrophages and granulocytes produce a pro-inflammatory reaction at the site of injury, which stimulates the release of various pro-inflammatory cytokines [17][18][19]. This response is rapidly contained by an anti-inflammatory response that aims to fine-tune and produce a balance between the defense and healing processes [20].

From a biochemical viewpoint, oxidative stress is characterized by an imbalance between oxidant and antioxidant factors, although pro-oxidative 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 [21][22][23]. 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 of oxidant substances are nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitochondria, the endoplasmic reticulum, lysosomes, cytochrome P450, and peroxisomes [24]. The body has a series of enzymatic systems, such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT), as well as certain antioxidant molecules, such as glutathione (GSH), vitamin E, vitamin C, melatonin, uric acid, and a series of polyphenols, with important antioxidant properties. The most well-known and widely researched oxidative reduction mechanism is that of SOD, responsible for the molecular conversion of superoxide anions to hydrogen

peroxide, which leads to the formation of water through enzymatic catalyzation induced by CAT and GPX [25][26]. The reduction of oxidative species by GSH with the formation of glutathione disulfide (GSSG) is another mechanism of oxidative reduction [27]. Furthermore, reactive oxygen species help modify the cellular signaling pathways responsible for cellular proliferation, differentiation, autophagia, and apoptosis. Responsible for this is the activation of pro-inflammatory mechanisms, which leads 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) [28]. During pro-oxidative states, at a cellular level, the mitochondria are responsible for generating oxidative factors involved in the augmentation of the redox state, which has further molecular and cellular effects. The mechanism is known as mitochondrial reactive oxidative species production (mitoROS) [29][30]. In the mitochondria, complexes I, II, and III are involved in the production of reactive oxygen species. From a molecular point of view, complex I is responsible for the entrance of electrons from the NADH complex into the respiratory chain. Therefore, the interaction of flavinmononucleotides with oxygen will result in the hydroxyl anion that will afterward be released in the mitochondrial matrix [31][32][33]. Complex II helps produce 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 leads to the production of high amounts of hydrogen peroxide, which is able to diffuse in the mitochondrial matrix [34][35]. Once the biological systems responsible for the adequate functioning of the mitochondria have been pro-oxidatively damaged, increased amounts of ROS will lead to mitochondrial death and the accumulation of highly oxidative species inside the cell. Physiologically, the mechanisms responsible for inhibiting the pro-oxidative destructive mechanisms inside the cell are GSH, thioredoxin (Trx), and glutaredoxin (Grx) [36]. Recent studies have shown increased oxidative reduction activity inside the mitochondria for SOD, which functions by blocking the redox activity of oxygen ions in hydrogen peroxide. According to Ribas et al., during enzymatic antioxidant activity in the mitochondria, the most important activity is that of SOD2 (manganese-dependent superoxide dismutase, MnSOD) [37], while in the intermembrane space, it is that of SOD1 (Cu, Zn-SOD). Through the activity of the SOD molecular family, reactive oxygen species are transformed into hydrogen peroxide, which 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 reducing oxidative stress by modulating NADPH mechanisms and taking control of electron migration inside the mitochondria [38][39][40][41]. The family of Grx antioxidant enzymes includes Grx2 and Grx5, responsible for modulating molecular mechanisms that produce oxygen ions in complex I by catalyzing thiol groups in GSH [42]. An increase in the redox state at the cellular organelle level will lead to a decrease in ATP production due to the migration of electrons toward the water used in the formation of hydrogen peroxide. Other important molecular sources of oxidative species inside the cell are characterized by the interaction between reactive oxygen ions with D-aspartate oxidase, xanthine oxidase, polyamine oxidase [43][44], (ACOX), L-αhydroxyacid oxidase, D-amino acid oxidase, and L-pipecolic oxidase. Due to insufficient electrons for ATP production at the mitochondrial level, the whole cell will be affected by the so-called energy failure phenomenon, which has important implications for the whole body and will have the utmost clinical impact on critically ill patients [45][46][47][48][49].

An important goal during surgery and general anesthesia is maintaining 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 [50][51][52]. 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. Wang et al. studied the molecular effects induced by curcumin-encapsulated nanoparticles on oxidative stress in cerebral tissue that had undergone ischemia–reperfusion injury. They proved a decrease in the oxidative attachment on the endothelial tissue, as well as a decrease in the blood–brain barrier (BBB) [53][54][55].

Recent studies have discussed different theories regarding cerebral metabolism and the regional cerebral blood flow (eCBF) [56][57]. Maintaining an optimal cerebral blood flow is crucial for ensuring continuous global or regional oxygenation. Weiss et al., in an experimental study regarding cerebral oxygen consumption during ischemia and reperfusion, identified a direct correlation between O_2 supply/consumption and ischemia–reperfusion syndrome. The authors used two study groups of laboratory animals, one group (n = 9) where cerebral ischemia was induced and one group (n = 9) where reperfusion was induced. The study animals received 90% isoflurane anesthesia with a mixture of oxygen and gas through an ETT tube, with the endpoint of the partial pressure of oxygen of over 100 mmHg. To achieve cerebral ischemia, the authors blocked the medial cerebral artery for 1 h in the case of group 1, while for group 2, they reperfused the same artery for 2 h. Cerebral blood flow was determined using the C^{14}-iodoantipyrine autoradiographic technique [58].

In a study on cerebral protection bestowed by anesthetic agents, Sakai et al. reported improved neurological function after focal ischemia. During the study, the researchers induced cerebral ischemia in lab animals through the temporary occlusion of the medial cerebral artery. They proved a reduced incidence of neurological deficits in the animals that suffered from cerebral ischemia under general anesthesia with isoflurane, compared to the control group. Moreover, the authors showed that the cerebral protection induced by isoflurane persists up to eight weeks after ischemia [59].

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 interesting as they have an increased reactivity toward other molecules. A specificity of this pathway is the formation of peroxynitrite free radicals following the interaction between NO and the superoxide radical [60][61]. At the cellular level, peroxynitrite attacks the mitochondrial membrane and DNA oxidation, blocking DNA repair mechanisms and leading to cell energy failure [62][63].

Neuronal OS occurring during cerebral ischemia is divided into three major groups of nitric oxide synthases: end endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS) [64][65]. Recent studies have shown an increase in the activity of these enzymes during cerebral ischemia, with a significant increase in NO production. In a study of the expression of NO in patients suffering from Moyamoya disease who had undergone bypass surgery with a temporary occlusion of the M4 branch of the middle cerebral artery, Silver et al. showed increased

expression of mixed venous nitride (NO_2) immediately after the occlusion of the cerebral artery. The authors concluded that NO_2 expression is directly proportional to the degree of cerebral ischemia [66].

During cerebral ischemia, the released OS and the increased flow of reactive species can influence the BBB, 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 beta (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) [50][67][68][69][70]. Boutin et al. proved the destructive impact of Il-1 in ischemic brain injury. Numerous mechanisms correlate increased IL-1β production with an increase in BBB permeability [71].

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. studied the implications of CCL2 in the changes that occur at the BBB level after ischemia. Blocking CCL2 with an antibody significantly reduces the permeability of the BBB [72], together with the distribution of the tight-junction proteins. A similar study carried out by Stamatovic et al. reported that MCP-1 plays an essential role in leukocyte recruitment and in the increase in BBB permeability [73].

One of the main aspects of general anesthesia is mechanical ventilation, which has significant implications for OS expression in the surgical patient. The most common trigger for OS expression at cellular and molecular levels is lung ischemia–reperfusion injury (LIRI). By reducing or even interrupting pulmonary blood flow, the reactive oxygen species production in the endothelium will be accelerated. Another site for excessive ROS production is the alveolar macrophage. The reperfusion phase is characterized by pro-inflammatory cytokine release, the activation of NOS, and neutrophile recruitment [73][74][75][76][77][78] (**Figure 1**).

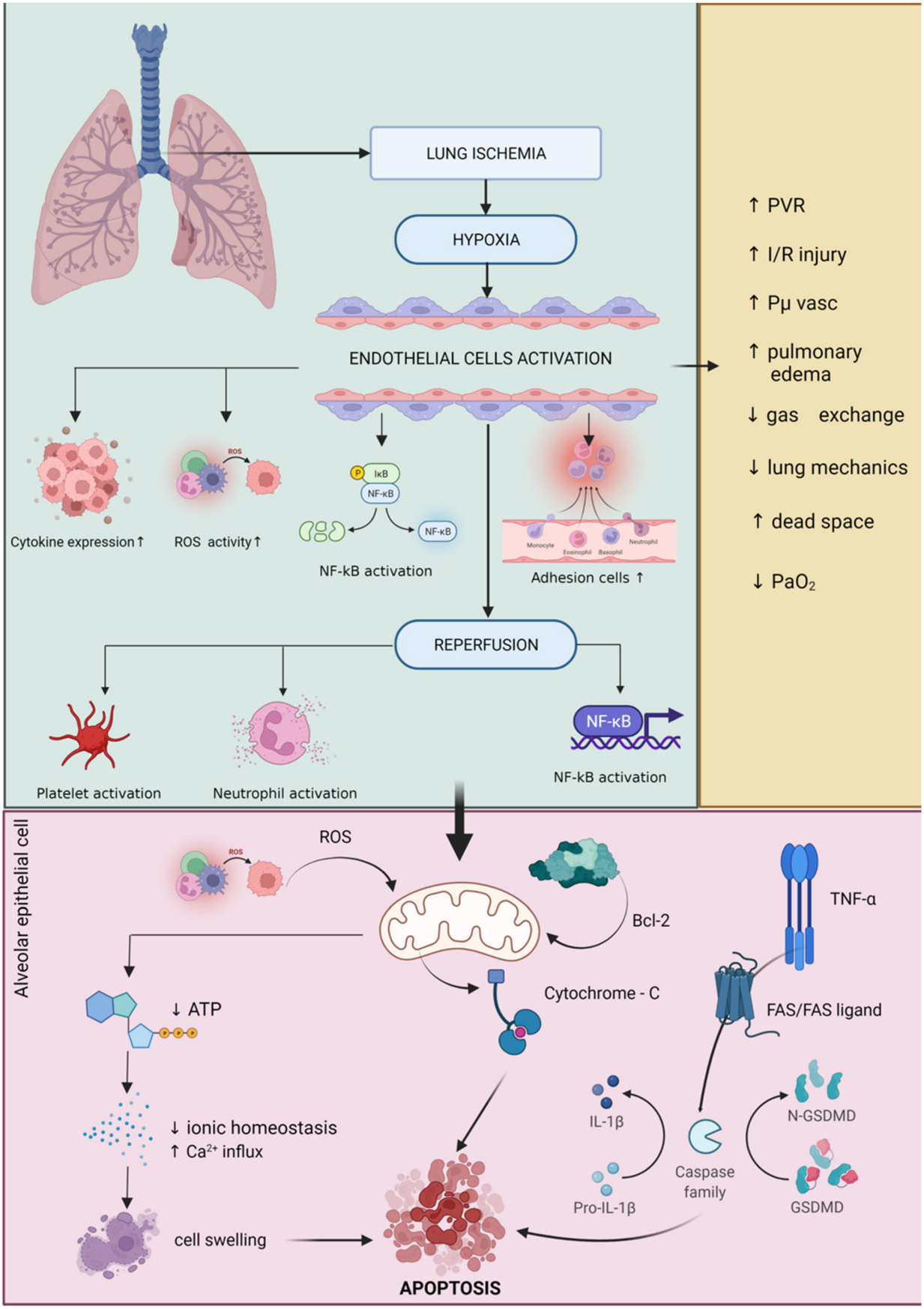

Figure 1. Schematic representation of lung ischemia–reperfusion injury. Green border: Lung ischemia causes a high degree of hypoxia that directly affects endothelial tissue with cytokine activation, increased cell adhesion

activity, NF-κB activation, and accelerated generation of reactive oxygen species (ROS). Following reperfusion, a number of other biological mechanisms responsible for increasing pro-inflammatory status (e.g., NF-κB activation), platelet activation, and neutrophil activation. Pink border: these mechanisms directly affect cellular activity by altering mitochondria-specific biochemical pathways. The direct attack of ROS on the mitochondria lowers ATP biosynthesis and affects mitochondrial electrolytic homeostasis, especially by increasing the influx of Ca^{2+} leading to cell swelling and apoptosis. Another biochemical pathway with a significant negative effect on mitochondrial activity is the activation of TNF-α, which activates caspase family via FAS/FAS-ligand and generates increased amounts of IL-1β by catalyzing pro-IL-1β factor. Another mechanism found in cellular apoptosis due to damage to alveolar epithelial cells is the direct action of bcl-2 on the mitochondria leading to cytochrome-C overexpression and finally cellular apoptosis. Yellow border: all these biochemical mechanisms that are involved in the process of mitochondrial and cellular denaturation induced by the phenomenon of ischemia–reperfusion of lung tissue lead to increased pulmonary vascular resistance (PVR), increased pulmonary edema, increased oncotic pressure of the vascular capacity, decreased lung mechanics, increased dead space and decreased adequate oxygenation. Increased expression of reactive oxygen species leads to changes in the cellular and molecular activities in lung tissue, mainly affecting the expression of calcium/calmodulin-dependent NO, nicotinamide adenine dinucleotide phosphate (NADPH), and nuclear factor kappa B (NF-κB). The acceleration of these processes inside the cell leads to pulmonary edema, resulting from 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 by up to 100%, mainly due to vasoconstriction and endothelial damage in the lung microvasculature. Increased vascular resistance, worsening pulmonary edema, and increased extravascular lung water lead to impaired gas exchange and impaired lung mechanics. All these phenomena negatively impact the clinical status of the patient through a sudden decrease in arterial partial oxygen pressure and an increase in the peak airway pressure and the alveolar–arterial oxygen gradient (A-a/DO2) [78][79]. Recent studies have shown that during pulmonary reperfusion, microvascular permeability can increase by 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 TNF-α, while the second stage is responsible for the production of activated neutrophiles and pro-oxidative factors, such as interleukin-8 (IL-8), leukocyte adhesion molecule CD18, endothelial P-selectin, and endothelial intracellular adhesion molecule-1 [74].

Changes in the redox balance represent another frequent phenomenon in the case of LIRI, as an excessive production of reactive oxygen species (ROS) occurs right after the reperfusion. In the lung, there are a series of potential ROS generators, such as activated xanthine oxidase, neutrophiles, mitochondria, the NADPH oxidase system, and NO synthase. In a study, Chen et al. showed that mitochondrial damage plays a more important role in the ischemia process than in the reperfusion process. The oxidative phenomenon is augmented by reduced oxygen delivery in the mitochondria, which leads to a decreased oxidative phosphorylation process and ATP production [80]. 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 increased destruction of certain proteins that are vital for the normal functioning of the mitochondrial system, such as cytochrome-C. Furthermore,

the release of cytochrome-C in the cytosol will lead to the activation of caspase-9 and an increase in the apoptotic process at the cellular level [81][82]. NOS found in the lung can be subdivided into four species: endothelial NOS (eNOS), inducible NOS (iNOS), neuronal NOS (nNOS), and mtNOS. Studies have shown an increased pro-inflammatory activity for mtNOS, as well as an increased anti-inflammatory activity for iNOS and eNOS [83][84][85][86].

In their study, Fischer et al. showed that apoptosis is only present after the reperfusion of lung tissue, that the activity increases dramatically, and that the peak is reached after 2 h. Apoptosis is initiated by the activation of both intrinsic and extrinsic mechanisms, with mitochondria as the modulating factor in both pathways [87]. The intrinsic pathway is also known as the mitochondrial pathway and is initiated by the action of cytokines and free radicals. It is characterized by changes in mitochondrial membrane permeability through bcl-2 proteins. The extrinsic pathway, however, is characterized by the activation of certain signaling proteins, such as the TNF receptor, angiotensin 2, and the FAS/FAS ligand [88][89].

Ischemia in the lung tissue activates caspase-8 through the FAS/FAS-ligand system. The next phase is represented by the activation of caspase-7, caspase-6, and caspase-3, leading to DNA fragmentation through the poly-ADP ribose polymerase [88]. During ischemia–reperfusion syndrome, research has 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 IL-1β, interleukin-2 (IL-2), IL-6, IL-8, interleukin-9 (IL-9), IL-10, IL-18, interferon-γ (INF-γ), and TNF-α.

The consequences of various anesthetic drugs for 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 anesthetics. Simultaneously, the cells are isolated from the whole network and interaction with other immune cells or mediators that 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 such as chemotaxis, phagocytosis, and oxidative burst. Some studies have suggested that this activity is due to the lipid solvents found in the formula. The chemotactic and phagocytic function of neutrophils may be inhibited by a decrease in intracellular calcium. The effects of propofol seem to be dose-dependent and occur at clinically relevant concentrations [90][91]. 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 and that 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 [92].

The effects of most anesthetics are at least partially mediated through GABA-A receptors. Several studies have demonstrated that these receptors can be found on the immune cell membranes and can be influenced by anesthetic drugs. GABA can activate ion channels on macrophages and monocytes and decrease cytokine

secretion and T-cell proliferation. Moreover, drugs that influence 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 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 anesthetics are also mainly inhibitory, for example, suppressed neutrophil function, altered lymphocyte proliferation, and decreased cytokine release by mononuclear cells. In contrast to halogenated inhalational anesthetics, which are known to suppress pro-inflammatory cytokines in murine pulmonary cells, volatile anesthetics induce increased gene expression of pro-inflammatory cytokines. Moreover, some studies have shown that the effects of inhalational anesthetics are dose- and time-dependent [93][94][95].

A 2013 study suggested that the NF-κB signaling pathway contributes to sevoflurane- and isoflurane-induced neuroinflammation by increasing the levels of IL-6 (isoflurane by 410% and sevoflurane by 290%) and the nuclear levels of NF-κB (isoflurane by 170% and sevoflurane by 320%). Other studies have confirmed that isoflurane can increase the levels of IL-6, which has been associated with learning and memory impairment in animals [96][97].

Several in vitro studies have reported changes in the immune and inflammatory expression of morphine and other opioids. Among the effects of morphine are altered cytokine release and lymphocyte proliferation, activated enzymes involved in macrophage and lymphocyte apoptosis, inhibition of cell adhesion, and increased secretion of stress hormones. Synthetic opioids, except for fentanyl, seem to have a less pronounced impact on the immune system, probably because they do not interact with the μ2 opioid receptors on immune-competent cells [98][99].

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 cyclo-oxygenase-2, and increasing prostaglandin E2 synthesis, which may be the cause of pain during injection [100].

Challenges in isolating various immune variables from the complex immunological network in clinical scenarios lead to far fewer in vivo than in vitro studies. Due to their volatile nature, inhalational agents are important not only to the patients but also to the personnel attending the operating theater. 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 [101]. 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, and inhibit the activation of neutrophils, leading to decreased neutrophil adhesion to human endothelial cells, decreased IL-6 and TNF-α, suppressed PMN migration and function through various pathways, altered cytokine release from macrophages, and decreased NK cytotoxic activity. A study comparing two anesthetic techniques, TIVA and balanced inhalational anesthesia, found that perioperative cell-mediated immunity was less

influenced by TIVA, suggesting that the stress response in patients undergoing anesthesia with a volatile agent is more pronounced [102][103][104][105][106][107].

A 2019 study on the effects of propofol on neutrophil function, lipid peroxidation, and the 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 in IL-6 levels and a greater decrease in 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 min 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 [108].

Potocnik et al. studied patients undergoing thoracic surgery and one-lung ventilation where either propofol or sevoflurane was used to maintain the anesthesia. They found that IL-6, IL-8, and CRP levels were higher in the propofol group, while IL-10 was higher in the sevoflurane group. The oxygenation index 6 h after the surgery was lower in the propofol group compared to the sevoflurane group ($p = 0.02$), maintained 24 h 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 [109]. In a similar manner, but on patients undergoing craniotomy, propofol proved to be less inflammatory than sevoflurane, with a lower IL-6/IL-10 concentration ratio during and at the end of surgery ($p = 0.0001$) and higher IL-10 [110].

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 anesthesia 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 [111].

The American Heart Association (AHA) recommends that patients at risk of myocardial ischemia during surgery who are hemodynamically stable should undergo general anesthesia with inhalational agents [112].

These recommendations and the benefits of these agents have been emphasized in numerous studies. A study conducted on 74 patients scheduled for coronary artery bypass graft surgery under cardioplegic arrest showed that 10 min 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 [113].

Fukazawa et al. presented extensive evidence, both in vitro and in vivo, that modern inhalational halogenated anesthetics 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 signaling molecules, such as releasing TGF-β1, activating CD73, inducing IL-11, and generating adenosine [114]. A systematic review concluded that patients undergoing cardiac surgery had a significantly lower increase in creatinine levels in the first two days after surgery and lower intensive care unit

stay and hospitalization when anesthetized with volatile anesthetics compared to TIVA propofol. However, there was no statistically significant difference in mortality between the groups [115]. Furthermore, current anesthetics seem to offer neuroprotection, sustained for 2–4 weeks, against mild or moderate ischemic injury but have no influence on severe ischemia. These effects are mediated by antagonizing postsynaptic glutamate receptors and enhancing GABA-A-mediated hyperpolarization and by inhibiting several processes that lead to neural apoptosis (increased levels of antiapoptotic proteins, such as bcl-2 and reduced cytochrome-C release) [116][117][118].

The benefits of inhalational anesthetics extend beyond the operating theater, 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). The 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 [119]. Moreover, inhalational anesthetics seem to influence glycemic control in the perioperative period. Blood glucose levels were found to be higher with volatile agents, such as sevoflurane and isoflurane, compared to propofol-maintained anesthesia. This response was attributed to impaired glucose clearance and increased glucose production and inhibition of normal insulin production.

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