

Mini-review

Cellular mechanisms against ischemia reperfusion injury induced by the use of anesthetic pharmacological agents

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ABSTRACT

Ischemia–reperfusion (IR) cycle in the myocardium is associated with activation of an injurious cascade, thus leading to new myocardial challenges, which account for up to 50% of infarct size. Some evidence implicates reactive oxygen species (ROS) as a probable cause of myocardial injury in prooxidant clinical settings. Damage occurs during both ischemia and post-ischemic reperfusion in animal and human models. The mechanisms that contribute to this damage include the increase in cellular calcium (Ca^{2+}) concentration and induction of ROS sources during reperfusion. Pharmacological preconditioning, which includes pharmacological strategies that counteract the ROS burst and Ca^{2+} overload followed to IR cycle in the myocardium, could be effective in limiting injury. Currently widespread evidence supports the use of anesthetics agents as an important cardioprotective strategy that act at various levels such as metabotropic receptors, ion channels or mitochondrial level. Their administration before a prolonged ischemic episode is known as anesthetic preconditioning, whereas when given at the very onset of reperfusion, is termed anesthetic postconditioning. Both types of anesthetic conditioning reduce, albeit not to the same degree, the extent of myocardial injury. This review focuses on cellular and pathophysiological concepts on the myocardial damage induced by IR and how anesthetic pharmacological agents commonly used could attenuate the functional and structural effects induced by oxidative stress in cardiac tissue.

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1. Introduction

There are common clinical situations in which ischemia (lack of or decreased organ blood flow and O₂ supply) occurs. Cell injury can be induced not only during the ischemic period; it may also be accentuated during the reperfusion process (ischemia–reperfusion injury, IR) [1]. Currently, mechanisms of IR have attracted great interest and are included in the pathophysiology of several clinical conditions such as myocardial infarction, stroke, major trauma, surgery, organ transplant and shock due to different sources [1,2]. Several mechanisms have been proposed as mediators of the damage induced by IR, such as complement system and leukocyte activation, increased free radical concentration, the reduction of oxidative phosphorylation, endothelial dysfunction and the activation of pathways of apoptosis, necrosis and/or autophagy [3,4]. The study of the pathophysiological mechanisms of IR has allowed the development of different experimental strategies that can lead to a reduction in organ damage due to the IR cycle and explore potential therapeutic targets.

This review includes the pathophysiological events that explain the cellular mechanisms induced by IR injury and describes the evidence regarding the protective role that several drugs commonly used in anesthesia perform against this injury.

2. Role of oxidative stress in ischemia–reperfusion injury

Oxidative stress is defined as an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense systems with the potential generation of cellular damage [5]. Reactive oxygen species concentration may increase due to a decrease in the antioxidant enzymes activities or by the depletion of antioxidants [6]. In cell metabolism, oxygen can form reactive intermediates such as superoxide, hydrogen peroxide and the hydroxyl radical before it is reduced to water. In turn, the reactive nitrogen species include mainly nitric oxide, peroxynitrite and nitrogen dioxide, formed during the homolytic decomposition of peroxynitrous acid [7].

Oxidative stress occurrence has been extensively investigated in ischemic and reperfusion (IR) injury of the myocardium [8,9]. Cellular effects of ROS are partially mediated by the activation of pro-oxidant and pro-inflammatory pathways in the myocardium, such as nuclear factor (NF)- κ B, AMPK and STAT-3 [10]. Nuclear factor- κ B exists mainly in the cytosol as a preformed trimeric complex consisting of the inhibitor protein I κ B and p50/p65 dimer protein. Reactive oxygen species induce redox changes that result in the phosphorylation of the β -subunit of I κ B, thereby activating their proteolytic digestion. Thus, p50/p65 subunits can translocate to the nucleus binding to DNA, and initiate the transcriptional process. These super families of transcription factors have been implicated in the regulation of immune cell maturation, cell survival, and inflammation in many cell types, including cardiac myocytes [11]. NF- κ B regulates the expression of cardiac genes downstream that program multiple cascades of signal transduction in a variety of physiological and pathophysiological states,

such as apoptosis, cell survival, cell growth, cell division, innate immunity, cell differentiation, and cell stress responses (hypoxia, ischemia and stretch). This evidence supports the concept that NF- κ B may be an important therapeutic target for cardiovascular diseases [12].

The pathophysiology of cardiovascular IR injury includes a pro-oxidant imbalance that does not counteract with the antioxidant defense mechanisms available. This high ROS concentration can lead to cellular damage through various mechanisms including the direct damage to biomolecules (e.g. lipids, proteins and DNA) or indirect damage through the activation of pro-apoptotic pathways. Specifically, ROS liberated during I/R promotes membrane damage through lipid peroxidation. Some of the most highly reactive aldehydes produced endogenously are 4-hydroxy-2-nonenal (4-HNE), malondialdehyde, acrolein, crotonaldehyde and methylglyoxal. Aldehydes are well-studied products of lipid peroxidation, with the α,β -unsaturated being the most cytotoxic by reacting with phospholipids, proteins and DNA. However, their effects are not only toxic but rather homeostatic as they participate in signal transduction pathways [13]. Reactive oxygen species generated during IR react with to polyunsaturated fatty acids to form aldehydes like 4-HNE, which inactivates proteins and DNA by forming hybrid covalent chemical addition compounds called adducts. The ensuing chain reaction results in cellular dysfunction and tissue damage including a wide spectrum of events ranging from electron transport chain dysfunction to apoptosis [14]. In addition, 4-HNE directly depresses contractile function, enhances ROS formation, modulates cell signaling pathways, and can contribute to many cardiovascular diseases including myocardial IR injury and arteriosclerosis [15]. Recent studies have identified that mitochondria are both a primary source and a target of lipid peroxidation products, with specific emphasis on aldehydes in cardiomyocytes and how these affect the electron transport system and Ca²⁺ balance [16]. These effects occur through a variety of mechanisms, including cross-linking of the lipid tails, which limits phospholipid mobility in the bilayer. Of singular importance, the inner mitochondrial membrane contains cardiolipin, a highly unsaturated phospholipid specifically localized to this compartment, which is particularly prone to peroxidation. The presence of cardiolipin in the inner membrane ensures the efficient function of mitochondrial components such as the electron transport chain complexes and adenine nucleotide transporter among others [17]. Acrolein, the simplest unsaturated aldehyde, has also recently been identified as a product of lipid peroxidation formed in response to increased oxidative stress [18]. Acrolein binds to cysteine and lysine residues on proteins and has been suggested to be a mediator of oxidative damage in a variety of human diseases. Despite the well-known reactivity of unsaturated aldehydes, their effects on cardiac function were only recently described. Several reports show that acrolein induces cardiac dysfunction and selective myofilament impairment, in addition to modifying proteins involved in energy metabolism, which possibly affects their function [19,20].

Although these observations do not constitute direct evidence that lipid peroxidation products are involved in the pathogenesis of these diseases, they do suggest clinical scenarios by which these

compounds should be investigated for evidence that they directly mediate the pathophysiology of disease.

Therefore, it is important to analyze the mechanisms that occur in an event of myocardial ischemia and subsequent reperfusion.

2.1. Ischemia–reperfusion injury

Cardiac ischemia followed by reperfusion is often associated with the activation of a prooxidant and inflammatory cascade and in the cell. These events are harmful for cardiomyocytes and tissue viability. There is considerable evidence implicating ROS in clinical conditions associated with the occurrence of oxidative stress in the myocardium [21,22]. Reactive oxygen species can be produced from various sources in cardiac tissue, with the mitochondrial transport chain being the main source [4]. During electron transfer, a number of electrons “leak” prematurely before being captured by oxygen (O_2), the final acceptor in the mitochondrial transport chain. These particles can participate in a one-electron reduction of O_2 , producing superoxide (O_2^-), the initial event in the formation of ROS [23]. It is estimated that up to 1–2% of mitochondrial O_2 consumption is used for ROS generation. However, this estimation was obtained under artificial, non-physiological conditions. In healthy tissues, mitochondrial ROS production might account for a lower fraction of oxygen consumption. Despite this consideration, mitochondria are a major source of superoxide (O_2^-) production. Different enzymes are involved in mitochondrial ROS production, including complexes I, II and III [24]. Another source of ROS, are the phagocyte NADPH oxidase and cardiac xanthine oxidoreductase, which are activated during the IR cycle. After ischemia, with the reintroduction of oxygen, there is an early increase in ROS concentration. Moreover, there is growing awareness that these sources also participate in endothelial dysfunction, hypertension and heart failure [25]. However, the blockade or inhibition of enzymatic sources has not led to a substantial structural or functional improvement in the heart. Therefore, more mechanistic studies are needed in models of IR.

2.1.1. Mitochondria and IR injury

The proton-translocating ATP synthase, which normally produces ATP, switches into reverse mode, i.e., becomes an ATPase, and consumes ATP to pump protons from the matrix into the intermembrane space [26]. In prolonged ischemia, Na^+/K^+ ATPase is inhibited due to the drop in ATP levels, and the intracellular acidification activates the Na^+/H^+ exchanger, i.e., the cell tries to restore the intracellular pH. The resulting increase in intracellular Na^+ concentration activates the Na^+-Ca^{2+} exchanger, which leads to Ca^{2+} overload. Elevated cytosolic Ca^{2+} concentrations may contribute to cellular damage by the activation of degrading enzymes such as nucleases, phospholipases and proteases, culminating in the destruction of the membrane integrity and leading to cell death if the ischemic period is of sufficient duration [27]. At reperfusion, the recovery of pH, oxidative stress and Ca^{2+} overload can induce the abrupt opening of the mitochondrial permeability transition pore (mPTP), a large conductance pore in the inner mitochondrial membrane, which strongly contributes to cardiomyocyte hypercontracture, apoptosis and necrosis [22,4].

The opening of mPTP is the pivotal event in reperfusion injury. Studies have indicated an important contribution of the mPTP opening and have correlated cell death with the release of cytochrome c after Bax and an increase in ROS levels [25,28,29]. Different energetic conditions are created depending on whether the mitochondrial membrane potential rapidly recovers. In the case of energized respiring mitochondria, a low pH can stimulate Pi uptake, increasing its intra-mitochondrial content and thus acting as an mPTP opener [30,31]. In contrast, in the presence of mitochondrial membrane depolarization, the long-lasting opening

of the mPTP takes place when rapid normalization of tissue pH occurs in the presence of Ca^{2+} overload, Pi, ROS formation, and/or lower levels of NO^- [32,33]. This latter condition is the more common event upon abrupt reperfusion. In fact, the probability of this pore being open is facilitated by several factors including high pH, Ca^{2+} overload, and burst of ROS at the onset of reperfusion [34].

2.1.2. Myocardial stunning

Different events are included in this type of reperfusion injury, in which the time of ischemia and reperfusion are an important aspect that determines the main changes in the myocardium. Myocardial stunning is defined as a reversible deficit in myocardial function on reperfusion that resolves during an extended period (days) assuming no ischemic effective insult [35]. The mechanism of stunning implicates alterations in excitation–contraction efficiency and the Ca^{2+} mobilization of intracellular sources. It is important to note that no significant amount of cell death is associated with stunning [36]. The duration of the ischemic insult is important in determining the outcome of an episode of ischemia followed by reperfusion. When the duration of the ischemic episode lasts more than 15 and ≤ 60 min, the restoration of arterial blood flow is associated with structural changes in subendocardial myocytes documented by electron microscopy: cellular swelling, myofilament hypercontracture, areas of membrane disruption and calcification of the mitochondria. These changes are associated with cell death, such as apoptosis or necrosis, and are defined as irreversible injury because the restoration of blood flow does not result in salvage of the tissue but rather accelerates cellular disintegration [37].

2.2. Cell death under ischemia and reperfusion condition

A more important form of reperfusion injury has been called lethal reperfusion injury. This occurs when the occluded artery is acutely opened and the abrupt restoration of blood flow causes additional cell death above and beyond that predicted to result from the preceding period of ischemia. Different types of cell damage and non-adaptive changes occur, leading to cell death by apoptosis, necrosis or autophagy. The apoptotic process involves two pathways, the extrinsic and intrinsic pathway [38]. The extrinsic pathway involves FasL (Fas ligand) and TNF- α , which binds and activates death receptors on the cell surface. Instead, in the intrinsic pathway multiple stimuli converge on mitochondria and form pores that trigger the release of cytochrome c, which leads to the formation of the complex “apoptosome” that determines the activation of caspases. This event produces a decrease in vital cell substrates such as actin, actinin, myosin heavy chain, light chain myosin, tropomyosin and cardiac troponin, which leads to cell damage [39].

Necrosis triggers distinct changes in cell morphology that uniquely distinguishes it from apoptotic cell death. A key primary event that distinguishes necrosis from apoptosis is the change in the permeability of the internal mitochondrial membrane resulting in the formation and opening of the mitochondrial permeability transition pore (mPTP). Transition pore opening may activate apoptosis even when ATP levels are maintained. Instead, a sudden or severe decline in ATP beyond a certain threshold, such as the one seen during acute ischemia or myocardial infarction [40], may trigger necrosis. These events lead to swelling of the internal mitochondrial membrane, releasing mitochondrial proteases into the cytoplasm. The subsequent rupture of the plasma membrane will release cytoplasmic proteins, including lactate dehydrogenase and troponin-T, at the site of necrotic injury [41]. The release of intracellular constituents, including proteins and enzymes, trigger

an overt inflammatory response induced by neighboring cells, a key distinctive feature of necrosis from apoptosis.

Autophagy is a highly regulated process that becomes activated by cellular stress such as nutrient deprivation or metabolic crisis [42]. The vesicular-lysosomal pathway degrades damaged organelles such as mitochondria or macromolecular proteins. In the context of mitophagy, a double membrane-bound vesicle called an autophagosome engulfs damaged mitochondria. The autophagosome fuses with a lysosome and forms an autophagolysosome [43], resulting in the lysosomal hydrolytic degradation of the engulfed contents. Basal autophagy maintains cellular homeostasis by removing damaged organelles while providing metabolic requirements for ATP synthesis. Evidence obtained in multiple models and in multiple tissues (including heart) has established that the up-regulation of autophagy is a highly conserved mechanism to promote cell survival under conditions of energy deprivation and metabolic stress [44]. Autophagy is, however, tightly associated with apoptosis and, under certain conditions, functions as a destructive (rather than adaptive) pathway: i.e., autophagic-programmed cell death. Indeed, it is this pivotal “life-or-death” pathophysiological role of autophagy that has prompted investigators to interrogate its involvement in the stressful circumstances of myocardial IR injury [45].

2.3. Inflammation process and ROS damage

The increase of ROS concentration in ischemia and subsequent reperfusion induces an inflammatory response that leads to the release of highly toxic products that may reduce cell viability in the first few minutes of reperfusion. After a cycle of IR, the endothelial cells are activated to initiate an inflammatory response through cytokine release, highly active molecules such as platelet activating factor and the expression of adhesion molecules [46]. A number of inflammatory mediators recruit blood leukocytes into tissues and thereby cause inflammation among the resident tissue cells. The local activation of phospholipase A2 results into elevated arachidonic acid, which is metabolized into prostaglandins, eicosanoids, or leukotrienes. Additionally, IR injury-induced ROS can cause the release of proteases, danger-associated molecular patterns, and tumor necrosis factor (TNF) and others cytokines [47]. The activation of these cytokines during the ischemic period is early and transient. However, the induction of a second much more persistent inflammatory response mediated by two other cytokines, interleukin 6 (IL-6) and interleukin 8 (IL-8) leads to diverse cellular events. Specifically, IL-8 appears to play a fundamental role in regulating the localization of the neutrophil in ischemic myocardium [48]. Chemotactic response in ischemic tissues can be induced by several factors, including ROS, cytokines (TNF- α), and the complement activation of NF- κ B. NF- κ B is activated by cytokines released by macrophages and T-cells, exerting its action on cardiomyocytes and fibroblasts. NF- κ B signaling can either be beneficial [49] or deleterious [50] and can contribute to the survival of cardiomyocytes by reducing apoptosis caused by hypoxic or ischemic injury [51]. NF- κ B activation may induce the expression of pro-inflammatory cytokines and adhesion molecules, all of which combine to produce inflammatory responses. These responses, in turn, trigger the infiltration of neutrophils, monocytes, and lymphocytes into the damaged sites where adjacent tissues interact with one another for persistent inflammation [52]. Selectins, members of the immunoglobulin superfamily, are glycoproteins that contribute to the initial interaction between leukocytes and endothelial cells in the periphery of the infarction. Its action is transient and reversible and leads to other secondary cell interactions mediated by other groups of adhesins. The integrins are also involved in intracellular adhesion as well as the interaction of these cells with components of the extracellular matrix. Integrins are activated by

IL-8 (as opposed to the selectins and immunoglobulin superfamily that are activated by IL-6), and their action is much later [53]. Following activation, adhesins allows leukocyte recruitment and subsequently their aggregation and adhesion to the vessel wall. These changes are responsible for the obstruction of the microvasculature and the phenomenon of “no-reflow”. Further, conversion of the endothelium in a prothrombotic state and increased vascular permeability are other factors involved in cell damage mediated inflammation [54].

Recently, it has been demonstrated that certain metalloproteinases matrix (MMPs) are involved in post ischemic tissue injury. Metalloproteinases are a family of proteolytic enzymes that are responsible for the remodeling of the extracellular matrix and which, together, can degrade all of the matrix compounds [55]. The relationship between inflammatory response and the expression of MMPs is known to be increased for some proinflammatory cytokines such as IL-1, IL-6 and TNF stimulate transcription of MMPs, especially of the “gelatinases” group represented by MMPs-2 and MMP-9 [56]. Both extracellular and intracellular proteolytic activities appear to be imperative in determining the true extent of IR injury and their inhibition seems to be of critical importance for improving the recovery of cardiac function. Thus, both extracellular and intracellular proteases may serve as potential targets for the development of cardioprotective interventions by reducing damage to the heart and retarding the development of contractile dysfunction caused by IR injury [57].

Cellular mechanisms induced by IR injury are show in Fig. 1.

3. Strategies in cardioprotection

3.1. Preconditioning

Cardiac ischemic preconditioning was first described in 1986 in dogs subjected to brief, intermittent episodes of ischemia. These episodes caused a protective effect on the myocardium that was later subjected to a sustained ischemia cycle [58]. This protocol revealed that infarct size was reduced by 75% in dogs exposed to intermittent occlusion of 4–5 min of the circumflex artery followed by 40 min of total occlusion. Accordingly, brief ischemia of the myocardium initiates a cascade of biochemical events in cardiomyocytes that protects the heart muscle during subsequent ischemic insults [59]. The mechanisms underlying these endogenous cardioprotective phenomena are complex in nature and are conventionally divided into triggers, mediators and effectors. Signaling pathways involve surface receptors such as adenosine, bradykinin and opioids signaling kinases (PI3K-Akt-eNOS, Erk1/2, p38, JNK MAPKs, JAK-STAT3, PKC and PKG) and the mitochondrial components (mitochondrial potassium channel dependent on ATP [mKATP], the mPTP and protein kinase C) [60]. The cellular and paracrine effects of preconditioning in cardiomyocytes include the induction of angiogenesis and progenitors, stem cell activation and the attenuation of cell death, inflammation and adverse remodeling [61]. Because classic preconditioning is required to be implemented before the onset of severe myocardial ischemia, its clinical use is largely restricted to specific situations, such as cardiac surgery, in which the ischemic injury can be anticipated. The non-genetic approach of ischemic preconditioning to enhance cell- and tissue-based therapies has received much attention in recent years due to its non-invasive, drug-free application. Therefore, the use of pharmacological preconditioning strategies to obtain cardioprotection through classical cellular targets and studies on new targets are actually developing. Clinical use of ischemic approach has until now been controversial. However, the current design of a reperfusion intervention has provided the basis for new therapy in cardiovascular pharmacology against IR injury.

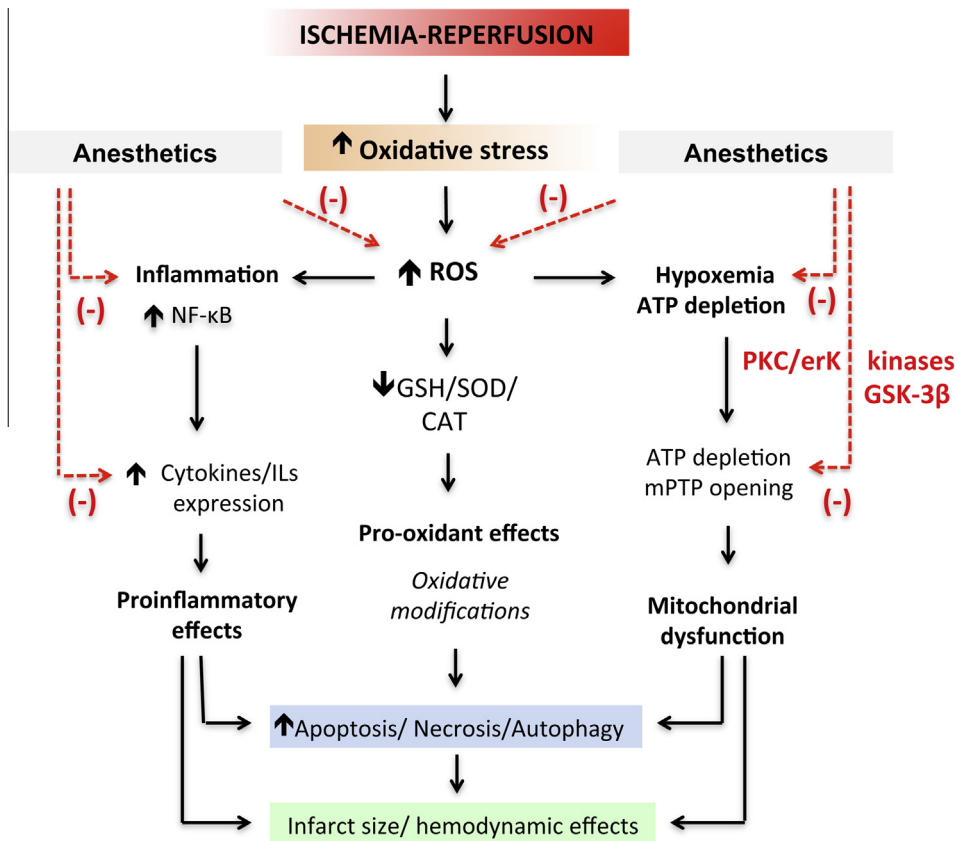


Fig. 1. Cellular mechanisms induced by ischemia–reperfusion injury. It is included the activation of three pathways: proinflammatory, nuclear factor (NF)-kappaB activation, prooxidant state (depletion of antioxidant defense system) and production of the mitochondrial dysfunction. These processes induce structural and functional effects in myocardium and hemodynamic effects. ROS, reactive oxygen species; CAT, catalase; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; ATP, adenosine triphosphate; mPTP, mitochondrial permeability transition pore; PKC, protein kinase C; ERK, extracellular-signal-regulated kinases; GSK-3 β , glycogen synthase kinase 3 beta.

3.2. Postconditioning

Studies published in the mid-1980s established that myocardial ischemic injury could be reduced if reperfusion time was gradually modified in certain myocardial zones [62]. However, this concept has not been as successful as ischemic preconditioning.

Vinten-Johansen's laboratory was the first to establish a postconditioning protocol. The researchers interrupted myocardial reperfusion with three cycles of 30 s followed by re-occlusion of the dominant coronary artery, describing several beneficial effects, including the reduction of infarct size, myocardial edema, neutrophil accumulation, apoptotic cell death and improved endothelial function [63]. Since its initial description, the underlying mechanisms of postconditioning have been intensively investigated, and data suggest a transduction pathway similar to preconditioning. Similar signaling pathways include those that comprise cell surface receptors, kinases, the preservation of mitochondrial function, and most outstandingly the attenuation of opening of the mPTP. Consequently, a number of pharmacological agents including volatile anesthetics, G-protein coupled ligands such as opioids, adenosine and bradykinin, growth factors such as insulin and erythropoietin, natriuretic peptides, receptor adipocytokines and statins have been studied [64]. The extent of protection by ischemic postconditioning is dependent on the duration of ischemia and the postconditioning protocol used. Species- and inter-individual variations are obvious. Whether the same is true for pharmacological postconditioning is unknown. The evidence remains, however, insufficient to recommend the widespread clinical use of ischemic or pharmacological postconditioning to reduce the infarct size in clinical practice, and enthusiasm arising from these

encouraging basic research studies must be tempered by the need to demonstrate an actual benefit in larger scale clinical studies [65].

4. Role of anesthetic agents in the protective mechanism against IR injury

A large number of anesthetic agents have been implicated in the protection against IR injury. Several mechanisms have been proposed to explain its protective action, including preconditioning, antioxidant and anti-inflammatory activities.

The following are several commonly used drugs in anesthesiology and their possible protective role in IR injury.

4.1. Propofol

Propofol (2,6-diisopropylphenol) is a general anesthetic used extensively for the induction and maintenance of cardiac anesthesia. It has also been used for sedation in procedures and critical care units. Propofol has a rapid onset after infusion or bolus injection plus a very short recovery period of a couple of minutes. It has been shown to protect the heart against insults in a variety of experimental models. Propofol has free radical scavenging properties during ischemia and reperfusion that may be beneficial. It has a chemical structure similar to phenol-based free radical scavengers such as vitamin E, which confer an important antioxidant activity against damage induced by ROS on lipids in the membrane cell [66,67]. Cheng et al. showed that a small-dose of propofol infusion (2 mg/kg/h) reduced ROS production after tourniquet-induced IR

injury [68]. Recently, it was demonstrated that propofol infusion could attenuate the MDA production after IR in liver transplant recipients [69]. *In vivo/in vitro* studies have suggested that propofol, when administered before the ischemic period, has cardioprotective effects [67,70]. Various mechanisms support these findings. Propofol acts as a calcium antagonist thus preventing intracellular Ca^{2+} overload that can cause myocardial injury [71]. With the widespread use of propofol in cardiac surgery, the cardioprotective effect of propofol has been increasingly recognized. It has been shown that propofol can improve the functional recovery of the myocardium and reduce myocardial necrosis in ischemic reperfused hearts [66]. Furthermore, it increases the activity of nitric oxide synthase improving cardiac function [72]. Existing evidence that the probable mechanism associated with propofol administration is the myocardial protection through the mitochondrial ATP-sensitive potassium channel opener. Propofol mimics the effects of ischemic preconditioning to reduce cardiomyocyte cytotoxicity and reduce infarct size [73]. The role of the mK-ATP during IR injury is known to optimize mitochondrial ATP production and reduce the Ca^{2+} overload. Indeed, propofol may control by switching the level of gene expression of the K-ATP ion channel according to its dosage [74].

In samples of human skeletal muscle, propofol increases the activity of antioxidant enzymes and attenuates lipid peroxidation induced by IR in patients undergoing orthopedic surgery with an upper extremity tourniquet. In a similar research, the authors showed that the induction and maintenance of anesthesia with propofol was associated with a decrease in the damage by lipid peroxidation in both plasma and skeletal muscle [75,76].

Previous studies have shown that propofol can increase the antioxidant capacity of red blood cells of pigs and humans *in vivo* [77]. This effect has been confirmed also under clinical cardiopulmonary bypass. Another study investigated the neuroprotective effects of anesthetic drugs in a fetal rat brain IR model. The authors concluded that propofol showed lower levels of lipid peroxidation than other anesthetics in intrauterine brain rats subjected to IR [78].

In humans receiving an infusion of propofol while undergoing coronary artery bypass surgery, a study of atrial tissue biopsies demonstrated a reduction in lipid peroxidation compared with a group that received fentanyl [79]. Indeed, lipid peroxidation in the fentanyl group increased significantly during cardiopulmonary bypass.

4.2. Opioid

Opioids have been widely used as analgesics and anesthetic pharmacologic adjuvants. The pharmacological activity of these compounds may be related to its antioxidant activity. *In vitro* studies show that morphine had powerful antioxidant capacity [80]. The possible mechanism of antioxidant activity of morphine includes reductive ability, metal chelator, hydrogen donating ability and scavengers of hydrogen peroxide, superoxide and free radicals [81]. With respect to administration during anesthetics procedures, it has been well known that the activation of opioid receptors by ischemic preconditioning or opioid-induced pharmacological pretreatment provides cardioprotection against myocardial ischemic-reperfusion injury.

Investigators have demonstrated that opioid receptors are involved in the mechanism of ischemic preconditioning-induced cardioprotection. Schultz et al. [82] reported that opioid receptors play an important role in ischemic preconditioning-induced in rat hearts. The infarct reducing effect of ischemic preconditioning-induced by three cycles of 5-min occlusion and reperfusion before 30 min ischemia was completely blocked by the nonselective opioid receptor antagonist naloxone. One year later, these authors

demonstrated that infarct limiting effect secondary to ischemic preconditioning was blocked by naloxone hydrochloride administered 25 min before ischemia in open-chest rabbits. In addition, other authors proposed that the cardioprotective effect by ischemic preconditioning was mediated by peripheral opioid receptors [83]. In open-chest rat hearts, a high dose of naloxone methiodide that does not cross the blood–brain barrier antagonized the infarct sparing effect by ischemic preconditioning. Taken together, these results strongly suggest that ischemic preconditioning-induced cardioprotection is likely to be opioid receptor mediated [84,85].

Multiple animal studies have demonstrated the mechanism by which opioid receptor agonists exert their protective effect against IR. Fentanyl protected the heart against post-ischemic injury by a mechanism that involved blockage by opioid, adenosine A1 receptor and K-ATP channel antagonists [86]. It has been shown that the administration of morphine and remifentanyl could have a similar effect to ischemic preconditioning, limiting infarct size in rat hearts [87]. Reports of ischemic postconditioning in animals were encouraging. Although ischemic postconditioning possessed a wide prospect in clinical application, debates on what precise ischemic postconditioning algorithm to use in clinical settings were ongoing. Consequently, pharmacological strategies are possible alternative methods. Accumulating data demonstrates that pharmacological postconditioning with morphine confers cardioprotection in animals. From a clinical point of view, in humans, postconditioning cardioprotection has been shown with morphine in Tretralogy of Fallot correction surgery [88].

With respect to molecular mechanism, the ischemic- and morphine-induced post-conditioning is mediated by the activation of mitochondrial calcium-sensitive potassium channels. Additionally, it has been shown that morphine upregulates Akt activity by inactivating protein Ser/Thr phosphatases via ROS, which may contribute to the cardioprotective effect [89]. Moreover, preconditioning by morphine may activate opioid receptors, which in turn increase the release of calmodulin, which in turn increases the release of calcitonin gene-related peptide probably via the nitric oxide pathway, thus conferring cardioprotection [90]. With respect to antioxidant/prooxidant conditions, the $\mu 3$ -opioid receptor is coupled to cellular nitric oxide synthase, resulting in nitric oxide production and release [91]. This finding is relevant in prooxidant conditions, such as early reperfusion, because the nitric oxide pathway can lead to the generation of peroxynitrite and nitrosative stress.

4.3. Volatile anesthetics

Volatile anesthetics present indirect protective effects when given continuously through surgery influencing the myocardial oxygen-supply demand balance. They produce coronary vasodilatation and increase in collateral blood flow to the ischemic area, negative inotropic and chronotropic effects and the maintenance of myocardial energy stores. In addition, volatile anesthetics demonstrated anti-inflammatory properties via the inhibition of neutrophil activity, the suppression of pro-inflammatory cytokines and the decreased expression of adhesion molecules [92]. Nevertheless, when given intermittently, prior to or after an ischemic episode, they induce powerful cardioprotection similar to that seen with ischemic pre- and post-conditioning.

All commercially used volatile anesthetics used today have been shown to have beneficial effects on myocardial stunning [93–95]. In addition to reducing the effects of ischemia on contractility, anesthetic preconditioning also decreases the area of the myocardium that may be affected during ischemia [93]. Anesthetic preconditioning has also been shown to reduce reperfusion dysrhythmias, endothelial dysfunction and protect other organs such as the brain, kidney, and liver [96].

4.3.1. Isoflurane

The most widely used volatile anesthetic is isoflurane. Several characteristics support its popularity: it is stable, has almost null metabolism, is non-explosive, and is commonly used for maintenance in anesthesia. Formerly, it was thought to be a potent coronary vasodilator that could produce the coronary “steal” phenomenon, causing secondary myocardial ischemia. Nevertheless, it was discovered that although it acts as a coronary artery vasodilator, isoflurane’s action is relatively mild and could be beneficial for myocardial perfusion. In 1988, Warltier et al. [97] demonstrated that volatile anesthetics, including isoflurane, protected the heart against ischemic injury and enhanced the recovery of stunned myocardium. In 1997, Cason et al. [98] showed in rabbits that short exposure to isoflurane before ischemia triggers a signal that protects the myocardium, introducing the concept of anesthetic preconditioning. Previous exposure to a volatile anesthetic could provide lasting myocardial protection (preconditioning). Since then, different groups have examined the mechanisms responsible for this anesthetic myocardial protection. Different signal transduction cascades have been involved in this phenomenon. Among these, Kersten et al. [99] demonstrated that isoflurane mimics preconditioning by the activation of K-ATP channels, producing a reduction in infarct size with an acute memory phase. This effect was blocked by K-ATP antagonists such as sulfonylureas (e.g., glyburide-glybenclamide). Indeed, Kowalski et al. [100] described an indirect effect of volatile anesthetics in the modulation of neutrophil-mediated damage, a pivotal event in reperfusion injury. Additionally, the involvement of PKC, mitogen activated protein kinases, ERK, heat shock proteins and eNOS have been described [96]. During the last several years, the inhibition of glycogen synthase kinase 3beta (GSK-3 β) and the inhibition of the opening of the mPTP have been shown to play a critical role as mechanisms modulating preconditioning [101,92]. The activation of the mK-ATP channel is an important signaling step in a trigger phase of preconditioning, which ultimately enhances GSK-3 β phosphorylation upon reperfusion, and this channel functions as a mediator of cytoprotection as well. The contribution of GSK-3 β to IR injury has recently received attention because GSK-3 β was found phosphorylated by multiple pro-survival signaling pathways [102].

Regarding isoflurane postconditioning, it was discovered that this volatile anesthetic protected the heart against IR injury also when administered after a period of myocardial ischemia (postconditioning) [103]. The mechanisms involved in this protection are similar to that involved in preconditioning and includes extracellular signal-regulated kinase (ERK) 1/2, eNOS and p70s6K [104], phosphatidylinositol-3-kinase [105], mitochondrial ATP-dependent potassium channel [106], inhibition of GSK-3 β [107], and the inhibition of mPTP [108].

4.3.2. Sevoflurane

This inhalational anesthetic also has an extended use and is indicated for inhalational induction because it is free of respiratory irritation. It is characterized by a lower solubility and potency than isoflurane. Similar to other volatile anesthetics, it presents cardioprotective properties in preconditioning and postconditioning. Sevoflurane has been demonstrated to present beneficial effects on myocardial stunning and infarct size in animals with preconditioning and postconditioning protocols [109].

In a clinical study comparing the use of sevoflurane instead of TIVA (total intravenous anesthesia), this volatile anesthetic was associated with the preservation of global hemodynamic and left ventricular function, as well as significantly reduced the postoperative release of cardiac troponin I, a marker of myocardial injury [110]. It has also shown a reduction in perioperative myocardial infarction and death in patients randomly assigned to receive

desflurane or sevoflurane versus TIVA in cardiac surgery [111]. For this reason, the American College of Cardiology/ American Heart Association Guidelines recommend the use of volatile anesthetic agents, including sevoflurane, during non-cardiac surgery for the maintenance of general anesthesia in patients at risk for myocardial infarction [112].

The mechanisms involved in the cardioprotective properties or sevoflurane are similar to those described for other halogenated anesthetics: a decrease in reactive oxygen species, the inhibition of the apoptotic cascade, a reduction in the Ca²⁺ intracellular overload, and neutrophil/platelet adhesion to the vascular wall after ischemia [113]. Recently, Quiao et al. postulated that anesthetic preconditioning initiated delayed cardioprotection against IR injury via the activation of NF- κ B and upregulation of autophagy, while suppressing expression of TNF- α , IL-1 β , and caspase-3 [114]. These results correspond to the delayed phase called the second window of cardioprotection. Nuclear factor- κ B (NF- κ B) is involved in the myocardial protection conferred by preconditioning in the acute phase; autophagy has been reported to confer apoptosis inhibition and infarction reduction. Recently, Zhao et al. [115], demonstrated that anesthetic preconditioning with sevoflurane mediates protection against IR injury via caveolin-3-dependent cyclooxygenase-2 inhibition and antioxidative effects.

4.3.3. Desflurane

This volatile anesthetic is chemically similar to isoflurane. It presents lower solubility, achieving faster titration of anesthetic depth and recovery. For this reason, it has been increasingly used as an anesthetic for day case surgery. The lack of appreciable metabolism and is less potent than isoflurane and sevoflurane. Desflurane is not suitable for inhalational induction because it is an irritant to the respiratory tract and can lead to coughing and broncospasm.

Desflurane, similar to isoflurane and sevoflurane, has been implicated in anesthetic preconditioning [116] and postconditioning [117]. The mechanisms involved in these events are similar to those described in ischemic pre-postconditioning: the modulation of mitochondrial ATP-dependent potassium channels, the reduction of Ca²⁺ intracellular overload and nitric oxide and reactive oxygen radicals [118,119].

Controversy exists concerning whether the application of ischemic preconditioning under general anesthesia is an ineffective way to achieve cardiac protection because anesthetics administration could mitigate the ischemic response in the human body necessary to elicit the preconditioned state. Vianna et al. [120] demonstrated that ischemic preconditioning, when applied during isoflurane anesthesia, completely abolished its renal protection compared to isoflurane anesthesia alone. Conversely, Toller et al. [121] reported in a dog model of coronary artery occlusion synergistic effects of ischemic preconditioning and sevoflurane if administered sequentially and not concomitantly. These studies provide evidence of antagonism rather than lack of synergy between different types of preconditioning, i.e., ischemic and pharmacologic preconditioning, and suggest that anesthetics attenuate or even abolish ischemic preconditioning when administered concomitantly (see Table 1).

Volatile anesthetics have been shown to protect against cardiac IR injury via mechanisms that are apparently independent of their effects to cause coronary vasodilation or to depress cardiac contractility. The specific mechanism of this decrease in ROS formation is unclear but likely results from the initiation of an intrinsic protective effect. Reactive oxygen species appear to play a dual, and apparently paradoxical, role in anesthetic preconditioning as the formation of a small quantity of ROS is required to trigger preconditioning, for example the generation of ROS at corresponding mitochondrial electron transport chain complexes [122,123]. The

Table 1
Anesthetics drugs and their action mechanism in cardiac IR.

Drug	Pharmacological classification	Classical action mechanism	Mechanism in ischemia reperfusion
Propofol	Anesthetic inductor	Unknown Potentiates action of GABA	Calcium antagonist Antioxidants
Opioids	Analgesia Anesthetic inductor Sedation	Opioid receptor antagonists-agonists	Preconditioning: Attenuate myocardial apoptosis
Isoflurane Desflurane Sevoflurane	Halogenated volatile anesthetics	Unknown. Stimulate postsynaptic inhibitory currents Potentiates action of GABA Inhibition of calcium channels	Preconditioning: Activation of K-ATP channels Postconditioning: Inhibition of GSK3 β and mPTP Antioxidant

GABA, gamma-aminobutyric acid; K-ATP, ATP-sensitive potassium channels; GSK3 β , glycogen synthase kinase 3 beta; mPTP, mitochondrial permeability transition pore.

attenuation of ROS formation during subsequent ischemia and reperfusion may underlie, at least in part, the functional and structural conservation. ROS could interact with each other and with endogenous antioxidant systems. It is the balance of all of these constituents that determines their beneficial versus deleterious effects [124].

5. Concluding remarks

Extensive experimental research carried over the past two decades to elucidate the complex signaling pathways underlying the cardioprotective effects of ‘conditioning’ therapies have led to the discovery of several pharmacological agents able to recapitulate the benefits of these mechanical procedures; hence, the terms pharmacological pre- and postconditioning have been introduced. In this respect, anesthetics drugs have been shown to possess such properties and, therefore, allowed for anesthetic preconditioning and postconditioning terms, respectively. These denominations refer to cardioprotection triggered by anesthetics administered in either setting (i.e., before and after a prolonged ischaemia). In the case of the volatile anesthetic conditioning is considered less risky and safer in clinical application as compared to its ischemic counterparts, particularly in the diseased myocardium because it does not require the direct administration of the therapeutic agent into the coronary artery and moreover, after inhalation, provides systemic protection. In this context, the protection of the myocardium, nervous system, gut and kidney beyond the duration of exposure to volatile agent, anesthetic conditioning may offer additional benefits during the critical postoperative period and may also have a direct impact on long-term prognosis and clinical outcome.

Endogenous opioid peptides and their receptors play an important role in the pathophysiology of IR injury and in the adaptive phenomenon in the heart and other organs. Of interest for therapeutic developments, opioid receptor agonists have been administered successfully to improve tolerance against experimental IR in various tissues. Recent human studies now raise the possibility to exploit this opioid-induced protection in clinical cardiac ischemia.

Finally, cardioprotective effects of anesthetic agents depend on the interaction of various factors such as administration protocols, choice of specific agents, concomitant use of other drugs, and the variables used to assess myocardial function. Many reasons act as confounding factors that limit applicability of anesthetic conditioning in humans. Some issues to be resolved by future experimental studies are: gender differences, maximal duration of index ischemia, optimal duration and concentration of halogenated drug, potential interactions with other drugs, differences among volatile anesthetics.

Randomized, placebo-controlled, prospective clinical trials in both cardiac surgery patients and noncardiac surgery populations at risk of ischemic events are required to definitively establish a clear cause–effect relationship for the anesthetic pre- and postconditioning-associated cardioprotection on clinical outcomes.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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