

Propofol Cardioprotection against Myocardial Ischemia-Reperfusion Injury: A Mechanistic Review

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ABSTRACT | Reperfusion after prolonged ischemia is necessary to rescue injured hearts while it paradoxically worsens cardiac injury, a phenomenon termed myocardial ischemia-reperfusion injury (MIRI). Overproduction of reactive oxygen species, calcium overload, and inflammation contribute to the pathogenesis of MIRI. Propofol, a commonly used anesthetic with antioxidant property, has been shown to be cardioprotective in experimental studies and in some small clinical trials of cardiac surgery using cardiopulmonary bypass. However, its effectiveness of cardioprotection needs to be confirmed in large clinical trials, and the mechanisms of its action remain a focus of current research. The purpose of this review is to delineate and summarize the mechanism underlying propofol-mediated cardioprotection against MIRI.

KEYWORDS | Antioxidant; Cardioprotection; Myocardial ischemia reperfusion injury; Nitric oxide; Propofol; Protective survivor activating factor enhancement pathway; Reperfusion injury signaling kinase pathway

ABBREVIATIONS | CHD, coronary heart disease; HO-1, heme oxygenase-1; LPS, lipopolysaccharide; MIRI, myocardial ischemia-reperfusion injury; mPTP, mitochondrial permeability transition pore; NO, nitric oxide; RISK, reperfusion injury signaling kinase; NFκB, nuclear factor-kappa B; NOS, nitric oxide synthase; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; SAFE, protective survivor activating factor enhancement; TNFα, tumor necrosis factor-alpha

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1. INTRODUCTION

The increasing death rate and considerable economic burden resulting from coronary heart disease (CHD) lead to an urgent need for therapeutic strategies for CHD. Therapy targeting the initial myocardial infarction subsequent to the ischemia is a main focus during CHD treatment. Early reperfusion is an absolute prerequisite for the survival of ischemic myocardium, while reperfusion per se paradoxically worsens cardiac injury.

The hypnotic agent propofol (2,6-diisopropylphenol) is widely used during the induction and maintenance of anesthesia. It is commonly used as an intravenous anesthetic in cardiac surgery and has been shown to attenuate myocardial dysfunction [1] and reduce infarct size [2] after prolonged ischemia. However, there is no systematic discussion about the effect and mechanism of propofol-mediated protection against ischemia-reperfusion-induced injury to the heart. This review is intended to provide background information and illustration relevant to propofol with particular reference to the heart. The review focuses on discussing the pathogenesis of post-ischemia-reperfusion injury in the heart and the possible signaling pathways involved in propofol-mediated cardiac protection.

2. THE PATHOGENESIS OF MYOCARDIAL ISCHEMIA-REPERFUSION INJURY (MIRI)

Myocardial ischemia initiates a range of cellular events, causing damage to the myocardium due to blood supply cutoff. Although reperfusion is essential for the cell to survive and to restore normal function, it paradoxically causes damage to the cell, which is called “ischemia-reperfusion injury”. The pathogenesis of MIRI has been comprehensively studied, and the underlying molecular mechanism is complicated. Oxidative stress, intracellular calcium overload, mitochondrial permeability transition pore

(mPTP) opening, endoplasmic reticulum stress, and inflammation all contribute to MIRI [3–8]. Briefly, during ischemic period intracellular pH decreases due to the enhanced aerobic metabolism that also fosters the activity of the Na⁺/H⁺ exchanger and Na⁺/Ca²⁺ exchanger. During reperfusion, the Ca²⁺ overload occurs, and the excessive intracellular Ca²⁺ then subsequently causes mPTP opening, a commonly accepted pathway leading to cell apoptosis and necrosis. Moreover, reactive free radicals are abundantly generated and accumulated during ischemia-reperfusion, which can directly carboxylate protein and cause lipid peroxidation as well as DNA damage. In addition, reperfusion also triggers several pro-death kinases (e.g., c-Jun N-terminal kinases, Ca²⁺/calmodulin-dependent protein kinase, and p38 MAPK, among others) and induces inflammation [9]. The activated kinases and recruited neutrophils during inflammation also facilitate mPTP opening [10], Ca²⁺ overload, and ROS generation [11]. Thus, multiple factors along with the intimate interactions among them contribute to the pathogenesis of MIRI.

3. STRUCTURE AND FEATURES OF PROPOFOL

Propofol (structure shown in **Figure 1**), marketed as Diprivan, is a short-acting, intravenous anesthetic agent that was first introduced in the late 1980s. The currently available preparation of Diprivan contains 1% propofol, 10% soybean oil, and 1.2% purified egg phospholipid as an emulsifier, with 2.25% glycerol as a tonicity-adjusting agent, and sodium hydroxide to adjust the pH. As propofol is not soluble in water, it is formulated in an oil-in-water emulsion and is highly opaque white. A water-soluble form of propofol, namely, fospropofol, has recently been developed and approved by the United States Food and Drug Administration in 2008. Fospropofol may not produce the pain at the injection site that often occurs with the traditional form of the drug.

4. PROPOFOL'S NON-ANESTHETIC EFFECTS MAKE IT A CARDIOPROTECTIVE DRUG

Propofol has been widely used in anesthetic induction and maintenance during surgery. Propofol acts as an excellent anesthetic agent because it exhibits several advantages. For example, it is controllable during administration, has quick onset and rapid emergence from general anesthesia, and exerts minimal side effects. Aside from its anesthetic features, propofol also exhibits notable non-anesthetic effects, which can be of therapeutic importance. Propofol contains a structure similar to phenol-based free radical scavengers and resembles the structure of α -tocopherol (vitamin E), a natural antioxidant [12–15]. Propofol was reported to inhibit lipid peroxidation induced by free radicals such as hydroxyl or ferryl radicals [16] and scavenge peroxynitrite [16]. It was shown to also inhibit plasma Ca^{2+} influx [17, 18]. Propofol had a direct negative inotropic effect at a supra-clinical concentration, which was mediated by a decrease in available intracellular Ca^{2+} concentration [19]. Moreover, propofol was able to inhibit inflammatory responses of cells treated with lipopolysaccharide (LPS) [20].

As propofol is commonly used in cardiac surgery, the above mentioned non-anesthetic features suggest that propofol could be a therapeutic alternative against MIRI. Indeed, in the past 30 years researchers have investigated propofol-mediated protection against MIRI in different models. Early in the 1990s, Ko et al. started [21] and several studies followed [22, 23] to examine the effects of propofol administration on MIRI. In both isolated rat heart model and in vivo dog model, propofol appeared to be protective against MIRI in a dose-dependent manner. Propofol attenuated myocardial mechanical dysfunction, metabolic derangement, and lipid peroxidation during reperfusion [21–23].

Since 2000, studies have switched from examining the phenomenon of propofol-mediated cardioprotection to investigating the underlying mechanism. Since propofol is a free radical scavenger and a plasma membrane calcium channel inhibitor, its influence on mitochondria was extensively studied [24–27]. Most recently, Lemoine et al. reported that during early post-hypoxic re-oxygenation period, the cardiomyocyte protection by propofol was mediated by mitochondrial adenosine triphosphate-sensitive

potassium channel opening, nitric oxide synthase activation, and stimulation of mitochondrial respiratory chain complexes [28]. Propofol-mediated reduction in 15-F_{2t} -isoprostane content, a specific and reliable index of lipid peroxidation, was first discussed in 2003 by Xia et al. [29, 30]. The effects of propofol on neutrophil function [31, 32] and inflammatory response [33–35] were also studied. In the latest ten years, propofol-mediated cardioprotection in vivo [36, 37] and in clinical settings [38, 39] was extensively investigated. Furthermore, increasing studies were carried out recently regarding the comparison of propofol with other anesthetics (e.g., sevoflurane and desflurane) [35, 40] or propofol combination treatment with other drugs [41–43]. In the present review, the underlying mechanism proposed in the previous studies regarding propofol-mediated cardioprotection against MIRI along with the most updated challenges in this research area are presented.

4.1. Antioxidant Property

The antioxidant activity of propofol results partly from its phenolic chemical structure, because the hydroxyl group can release hydrogen and thereafter be converted into a less active radical by the resonance of the aromatic ring. Kokita et al. first reported in 1996 that propofol attenuated the adverse changes induced by reactive oxygen species (ROS) in the heart [1]. Then the effect was verified in both in vitro and in vivo studies in 1998 [44]. Propofol was shown to protect cells against oxidative stress and enhance the endogenous antioxidant capacity through lipid peroxidation inhibition in different models [45, 46]. In addition, propofol can react with peroxynitrite to form a phenoxyl radical, therefore demonstrating the property of peroxynitrite scavenging [47]. Peroxynitrite, a potent and unstable ROS, can damage a wide array of molecules in cells, including DNA and proteins. Acquaviva et al. demonstrated that propofol protected cultured astrocytes from peroxynitrite-mediated cytotoxicity, and the effect was partly mediated by induction of the heme oxygenase (HO)-1 pathway in a dose-dependent manner [48]. Since that, the cytoprotective effect of propofol via upregulation of HO-1 has been studied in vitro and in vivo [49, 50]. The antioxidant property of propofol is substantiated by studies in a variety of cell types or organelles, such as neurons [51, 52], astrocytes [53–55], mitochondria [12, 56], and microsomes [56].

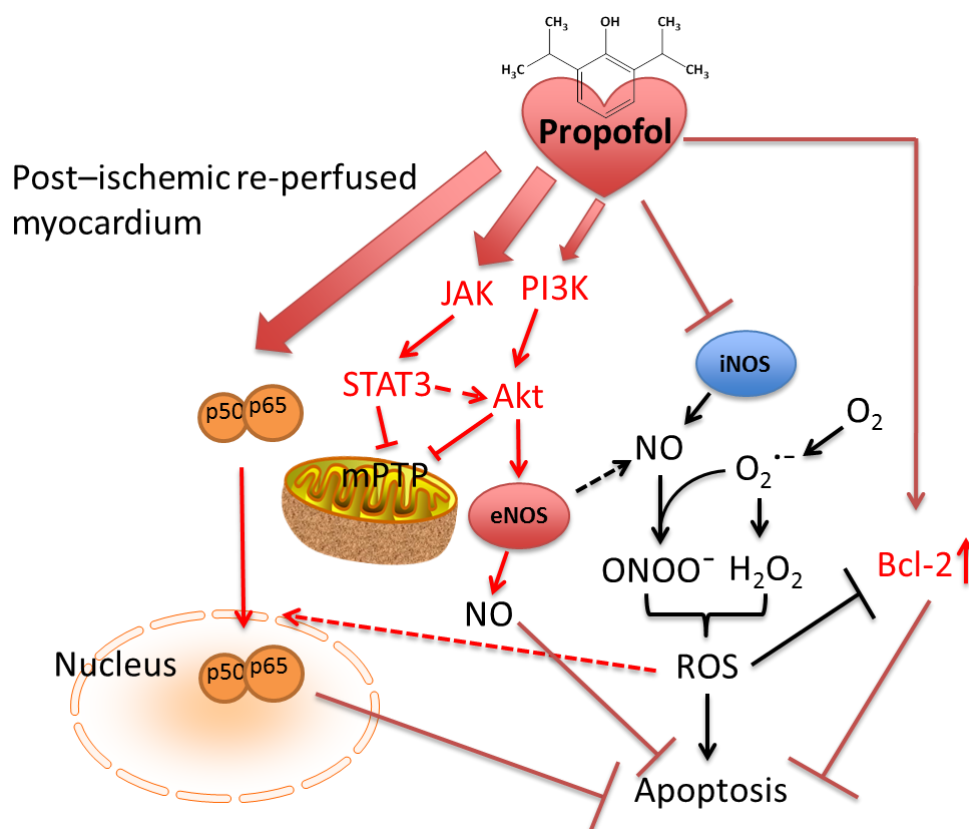


FIGURE 1. Summary of the proposed mechanism by which propofol confers cardioprotection against myocardial ischemia-reperfusion injury (MIRI). Propofol ameliorates MIRI-induced oxidative stress and enhances cardioprotective nitric oxide production by eNOS. Propofol also can activate phosphoinositide 3-kinase (PI3K)/Akt signaling pathway as well as the Janus tyrosine kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathway. Activation of JAK/STAT3 may inhibit mitochondrial permeability transition pore (mPTP) opening. Moreover, by activating NF-κB and Bcl-2 propofol reduces cardiomyocyte apoptosis. It should be noted that ROS may act as a double-edged sword. On the one side, ROS at high levels can directly cause apoptosis. On the other side, ROS at low levels may cause activation of NF-κB, leading to suppression of apoptosis. It is speculated that propofol might help control ROS at a relatively low level via its antioxidant property (not shown in the scheme) to permit NF-κB activation without directly causing apoptosis. It is also noteworthy that NO derived from eNOS is typically cardioprotective whereas NO derived from iNOS usually causes detrimental effects. Hence, the intimate interactions among the diverse factors depicted in the scheme appear to account for propofol-mediated cardioprotection in MIRI.

4.2. Nitric Oxide Induction

The cardioprotective actions of propofol may not be solely due to its antioxidant property. Nitric oxide (NO) is essentially produced by all cell types in the heart and is known to have profound effects on cardiac function. The synthesis of NO requires the par-

ticipation of nitric oxide synthases (NOS), present in three isoforms: neuronal NOS (nNOS) and endothelial NOS (eNOS), which are calcium-dependent forms, and inducible NOS (iNOS), which is expressed upon stimulation by microbial or immunological stimuli [57–59]. In general, eNOS-derived NO plays an important role in maintaining coronary

vasodilatory tone [60], inhibiting platelet aggregation [61], and the adhesion of neutrophils [62] and platelets [63, 64] under physiological conditions in the heart. Moreover, NO has negative inotropic and chronotropic effects on cardiomyocytes [65, 66]. Multiple studies demonstrated increased eNOS/NO upon propofol treatment of vascular endothelial cells [67, 68], which might account, at least partially, for propofol-mediated cardiovascular protection. On the other hand, propofol also affected NO-mediated activities under inflammation [69]. As the direct participation of NOS is a fundamental step in NO synthesis, it is suggested that propofol may modify the activity of NOS, especially iNOS [70]. Propofol increased constitutive NO production by human neutrophils, but inhibited NO production by iNOS in these cells [70]. Abnormal high concentrations of NO are generally produced by iNOS and transformed into peroxynitrite when superoxide anion radicals are present. It was further reported that propofol had a direct inhibitory effect on iNOS, especially when iNOS was induced by LPS [71]. Furthermore, it was revealed that in surgical patients treated with propofol, levels of pro-inflammatory mediators were reduced while anti-inflammatory mediators remained unchanged [70, 72–75]. Hence, propofol may have a dual effect on NO—it induces eNOS/NO, leading to cardioprotection and inhibits iNOS/NO, resulting in suppression of inflammatory injury.

4.3. Relevant Pro-Survival Signaling Pathways

4.3.1. The Reperfusion Injury Signaling Kinase (RISK) Pathway

Phosphoinositide 3-kinase (PI3K)/Akt signaling pathway is one of the key cellular pro-survival pathways central to the prevention of ischemia-reperfusion injury. A number of growth factors activate Akt through phosphorylation of its threonine-308 or serine-473 residue. Upon activation, Akt proceeds to regulate its downstream genes, such as nuclear factor- κ B (NF κ B), B-cell lymphoma-2 (Bcl-2) family, and eNOS, leading to anti-apoptotic effect [76, 77]. It was reported that propofol induced Akt and protected cardiac H9c2 cells from apoptotic injury in response to oxidative stress [78]. Also, the enhancement of the PI3K/Akt pathway played a critical role in propofol-mediated protection against myocardial toxicity from doxorubicin [79].

4.3.2. The Protective Survivor Activating Factor Enhancement (SAFE) Pathway

The activation of the Janus tyrosine kinase (JAK)–signal transducer and activator of transcription 3 (STAT3) signaling pathway plays an important role in limiting MIRI. Activation of STAT3 has been reported to limit cardiomyocyte apoptosis in rat models of myocardial infarction [80]. STAT3 also has been confirmed to exert an anti-apoptotic effect in cultured neonatal rat cardiac myocytes subjected to anoxia [81]. Propofol was shown to activate STAT3 in various models. Propofol improved cardiac function and ameliorated hyperglycemia-induced cardiomyocyte hypertrophy and apoptosis via activating HO-1/STAT3 pathway [82]. It was also suggested that propofol not only induced JAK2/STAT3, but also PI3K/Akt activation in cultured H9c2 cells in a concentration-dependent manner [83].

4.3.3. The Activation of NF κ B

NF κ B is another transcription factor involved in myocardial ischemia-reperfusion injury and cardioprotection. NF κ B is activated upon stimulation by various factors, such as tumor necrosis factor- α (TNF α), but it can in turn increase the transcriptional level of cell survival genes [84]. Thus, it is suggested that NF κ B might act differently under different conditions. It was reported that activation of NF κ B could transcriptionally induce Bcl-2 expression in pancreatic cells [85]. Propofol could induce the perinuclear translocation of NF κ B p65 subunit and enhance cell survival in cardiac H9c2 cells [83]. On the other hand, propofol could also reduce LPS-induced inflammatory responses in macrophages by inhibiting ROS-induced NF κ B activation [86]. Propofol inhibited hepatic NF κ B activation, resulting in decreased production of the pro-inflammatory cytokines TNF α and interleukin-6 [87]. The different performance of NF κ B under propofol administration may be attributed to the different roles that propofol may play in cell protection. Under normal conditions, propofol tended to induce concomitant STAT3 and NF κ B activation manifested as enhanced nuclear translocation and facilitate the crosstalk between the SAFE and the RISK pathways [83]. In contrast, when facing exacerbated inflammation, propofol conferred its anti-inflammatory effect and reduced NF κ B content [88, 89].

4.3.4. The Increase of Bcl-2 Content

Increase in the transcription of Bcl-2 helps prevent cardiomyocyte apoptosis, which is an important mechanism of many anti-MIRI therapies [90, 91]. When activated, Bcl-2 localized to the intracellular sites of ROS generation and functioned in an antioxidant pathway to prevent cell apoptosis [92]. Li et al. reported that propofol showed neuroprotective effects against neuronal apoptosis by increasing Bcl-2 expression [93]. Propofol, at concentrations $\geq 12 \mu\text{M}$, significantly and concentration-dependently ameliorated TNF α -induced Bcl-2 reduction and enhanced NO production [94]. Although propofol may regulate Bcl-2 expression through Akt, the drug may also modulate Bcl-2 gene expression through Akt-independent pathway [78].

5. SPECIFIC CHALLENGES IN DIABETES

The mortality rate of diabetic patients suffering from acute myocardial infarction after MIRI is much higher than that in patients without diabetes [95]. In addition, diabetic patients exhibit worse recovery after acute myocardial infarction [96]. The exacerbation of oxidative stress and reduction of endogenous antioxidant capacity together with the impairment of protective signaling pathways related to the activation of STAT3 and Akt contribute to the increased post-ischemic myocardial injury in diabetes after prolonged ischemic insult. The most recent study by Ansley et al. first demonstrated that propofol might be a preemptive intraoperative cardioprotectant for patients with type 2 diabetes under conditions of normothermic cardiopulmonary bypass and blood cardioplegic arrest, and the mechanism was related to Bcl-2 activation [97]. However, the detailed underlying mechanism especially whether propofol confers cardioprotection in diabetes through its antioxidant capacity remains to be further explored.

6. CONCLUSION

In summary, propofol is a short-acting intravenous anesthetic agent that causes few side effects and thus has a favorably safety profile. Propofol possesses antioxidant property and causes activation of multiple pro-survival signaling pathways. It is likely that the

non-anesthetic effects of propofol, including the signaling pathways it affects (**Figure 1**), may make the drug a potential cardioprotective agent in clinical practice. However, more investigations regarding the clinical implications and mechanism of propofol-mediated cardioprotection are needed in order to further establish its safety and efficiency.

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