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Review

Cellular Mechanisms in Sevoflurane-Induced Myocardial Protection Against Ischemia–Reperfusion Injury

Alex Bui [1], Garrison Peck [2], Nathan Burnham [2], Khushi Urs [3] and Siddharth Dave [1,4,*]

[1] Department of Anesthesiology and Perioperative Medicine, Creighton University-Phoenix, Phoenix, AZ 85012, USA
[2] School of Medicine, Creighton University-Phoenix, Phoenix, AZ 85012, USA
[3] College of Liberal Arts and Social Sciences, University of North Texas, Denton, TX 76203, USA
[4] Valleywise Health Medical Center, Phoenix, AZ 85008, USA
* Correspondence: siddharthdave@creighton.edu

Highlights

What are the main findings?

- Ischemia–reperfusion injury is a common cause of significant morbidity in the setting of myocardial ischemia.
- Sevoflurane has been demonstrated to provide a protective effect against myocardial ischemia–reperfusion via a variety of cellular mechanisms.

What are the implications of these findings?

- Sevoflurane is a commonly used anesthetic whose use may be expanded to patients experiencing myocardial ischemia.
- There is a need for further human research to expand our understanding of the role of sevoflurane in myocardial ischemia–reperfusion outside the setting of cardiac surgery.

Abstract

Ischemia–reperfusion injury is a significant contributor to myocardial injury following periods of hypoperfusion. Sevoflurane demonstrates a cardioprotective effect against ischemia-reperfusion through a variety of mechanisms. Here, we provide a narrative review of the current literature surrounding sevoflurane's effects on ischemia–reperfusion, with a focus on cellular and molecular mechanisms. We conclude with a discussion on clinical implications, and directions for future research.

Keywords: reperfusion injury; sevoflurane; myocardial ischemia

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Academic Editor: Lei Ye

Received: 30 October 2026
Revised: 11 November 2026
Accepted: 16 November 2026
Published: 18 November 2026

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1. Introduction

1.1. Role of Blood Flow in Myocardial Function

Continuous tissue perfusion provides the oxygen and metabolic substrates required for cellular function while facilitating the removal of carbon dioxide, hydrogen ions, and other metabolic products. The myocardium is particularly dependent on uninterrupted perfusion because aerobic ATP production must continuously support excitation–contraction coupling, calcium handling, transmembrane ionic gradients, and myocardial relaxation. At rest, left ventricular blood flow is approximately 0.7–1.0 mL·min^{-1}·g^{-1}, with regional flow changing in response to myocardial workload, coronary perfusion pressure, vascular resistance, and wall stress [1,2].

The metabolic demand of the myocardium is high relative to most other tissues. Resting myocardial oxygen consumption is approximately 5–10 mL $O_2 \cdot min^{-1} \cdot 100\ g^{-1}$, reflecting the continuous energetic requirements of contraction, relaxation, calcium cycling, and membrane ion transport [2]. Consequently, coronary oxygen delivery must remain closely matched to myocardial oxygen consumption.

The myocardium extracts approximately 70–80% of the oxygen delivered through the coronary circulation under resting conditions [1,2]. Because extraction is already high at baseline, increases in myocardial metabolic demand are accommodated predominantly by increasing coronary blood flow rather than by markedly increasing oxygen extraction. During heavy exercise, for example, left ventricular oxygen demand may rise approximately sixfold while coronary blood flow increases approximately fivefold [1].

Delivery of oxygen to the cardiomyocyte also depends on maintaining an adequate diffusion gradient between the coronary capillary and the intracellular environment. Oxygen released from hemoglobin must traverse the microvascular wall and interstitial space before reaching the mitochondria, where it serves as the terminal electron acceptor for oxidative phosphorylation. Coronary perfusion pressure, microvascular resistance, arterial oxygen content, capillary density, and diffusion distance therefore collectively influence myocardial oxygen availability [2].

This combination of high metabolic activity and high baseline oxygen extraction leaves the myocardium particularly sensitive to reductions in coronary perfusion. A substantial decrease in coronary flow therefore produces metabolic and mechanical consequences soon after the onset of ischemia [1,2].

1.2. Reduced Function with Low Flow

Myocardial ischemia occurs when coronary oxygen and substrate delivery become insufficient to meet the myocardial metabolic requirements (Figure 1). With acute coronary occlusion, aerobic ATP production declines and anaerobic glycolysis assumes a greater role in energy production. The limited ATP yield of glycolysis cannot fully replace mitochondrial oxidative phosphorylation, resulting in progressive depletion of high-energy phosphates and accumulation of lactate and hydrogen ions [3,4].

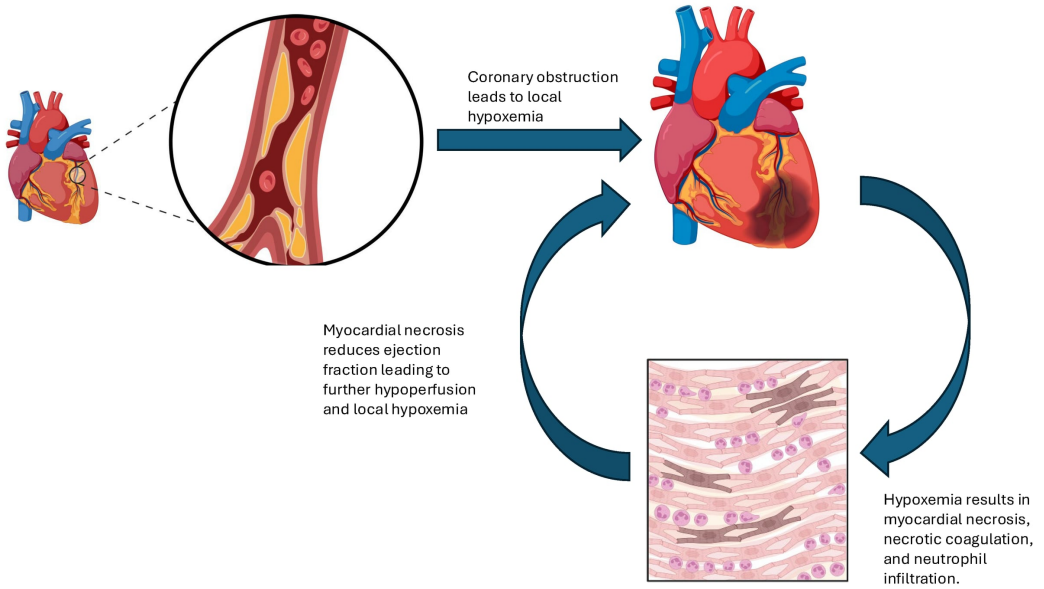


Figure 1. Reduced coronary blood flow leads to reductions in oxygen availability as myocardial cells are unable to increase oxygen extraction.

Intracellular acidification develops progressively during severe ischemia. Cardiomyocyte intracellular pH is approximately 7.15–7.20 under normal conditions but falls substantially when coronary flow is interrupted. Experimental models of total ischemia have demonstrated intracellular pH values near 6.5 after approximately 4 min and values approaching 6.2–6.0 after 10–20 min [3]. The rate of this decline varies with residual perfusion, temperature, species, ischemic duration, and experimental conditions.

Mechanical dysfunction develops alongside these metabolic changes. Decreasing ATP availability compromises energy-dependent calcium handling and membrane transport, while acidosis reduces the calcium sensitivity of the contractile apparatus. Impaired myocardial relaxation and diastolic dysfunction therefore appear early, followed by the progressive deterioration of systolic contraction as ischemia continues [3,4].

Prolonged ischemia further disrupts ionic homeostasis. Reduced Na^+/K^+-ATPase activity and alterations in sodium and hydrogen exchange promote intracellular sodium accumulation, which contributes to secondary calcium loading [3] (Figure 2). During ischemic reperfusion stress, calcium enters the mitochondrial matrix through the mitochondrial calcium uniporter, driven by the mitochondrial membrane potential. Intramitochondrial calcium accumulation, alongside ROS and ATP depletion, triggers mitochondrial permeability transposition pore (MPTP) formation and opening [5]. Once open, the MPTP acts as a non-selective channel that causes the efflux of calcium and pro-apoptotic proteins from the matrix into the cytosol, driving membrane collapse and cell death (Figure 3).

The functional consequences of ischemia depend strongly on its duration and severity. Short periods of ischemia may leave the myocardium viable despite substantial contractile impairment. When impaired contraction persists after coronary flow has been restored despite the absence of irreversible myocardial necrosis, the phenomenon is described as myocardial stunning [6]. More prolonged ischemia progressively increases the likelihood of irreversible cardiomyocyte injury and infarction.

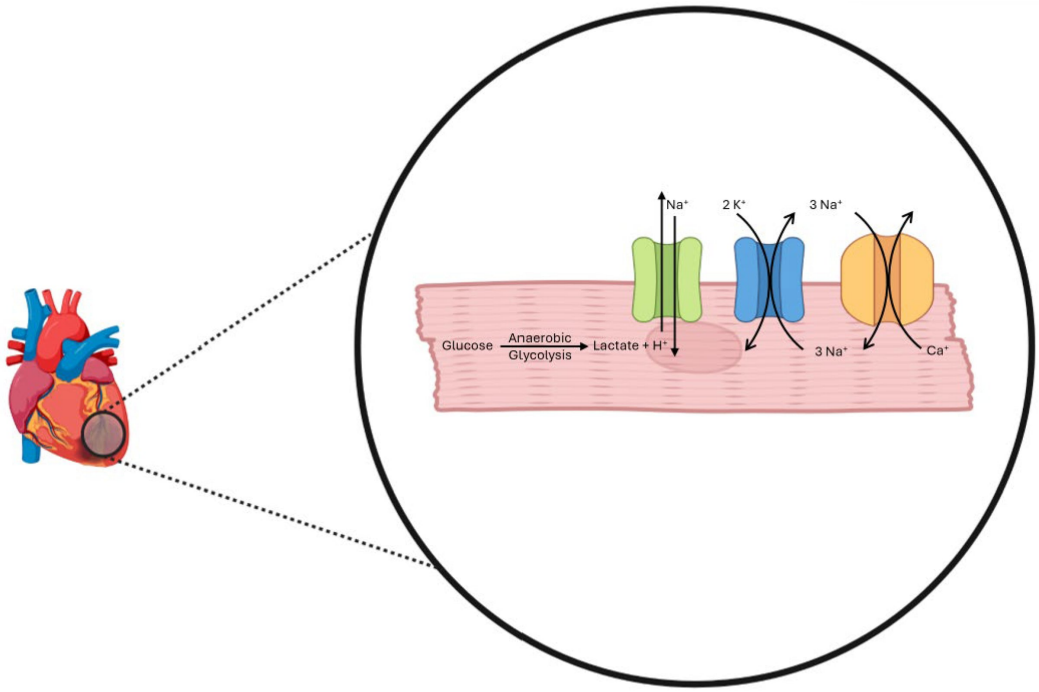


Figure 2. Myocardial ischemia results in cellular acidosis and dysfunction of the Na/K pump. Efflux of protons leads to intracellular Na accumulation and impaired calcium excretion and intracellular hypercalcemia.

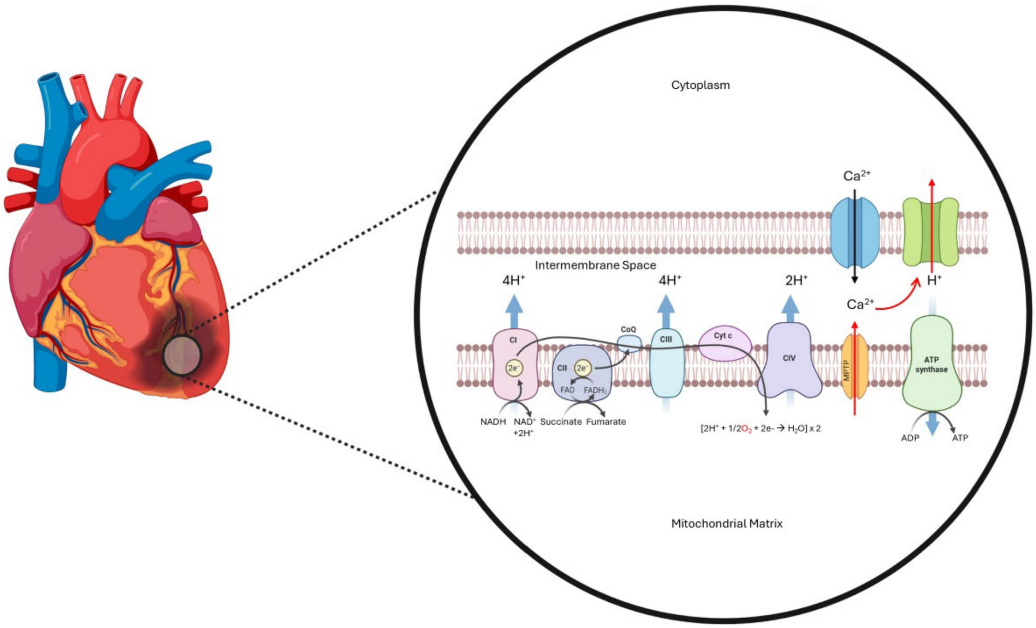


Figure 3. Hypoxemia inhibits oxygen-dependent electron transport at the inner mitochondrial membrane. Increased intracellular calcium leaks into the mitochondrial matrix, triggering increased mitochondrial permeability, membrane collapse, and cell death.

1.3. Definition of Myocardial Ischemia–Reperfusion Injury

Re-establishing coronary perfusion is necessary to rescue ischemic myocardium, but restoration of blood flow also initiates a distinct series of cellular stresses. Injury attributable to the combined ischemia and reperfusion phases is termed myocardial ischemia–reperfusion injury (MIRI). Within this broader process, lethal reperfusion injury describes cardiomyocyte death associated with mechanisms activated during the reperfusion period [7,8].

The transition from ischemia to reperfusion abruptly exposes an acidic, oxygen-deprived myocardium to oxygenated blood and restoration of extracellular physiological conditions. This transition produces rapid changes in cellular redox state and is accompanied by reactive oxygen species generation, calcium overload, inflammatory activation, and mitochondrial permeability transition [7–9]. These processes may disrupt mitochondrial function and contribute to cardiomyocyte death during early reperfusion.

Reperfusion injury is not restricted to cardiomyocytes. The coronary microcirculation may also be affected by endothelial dysfunction, inflammatory-cell recruitment, platelet activation, tissue edema, and microvascular damage [7–9]. Consequently, restoration of epicardial coronary patency does not invariably restore normal tissue-level perfusion. Persistent impairment of the myocardial microcirculation after reopening of the supplying coronary artery constitutes the no-reflow phenomenon and may involve endothelial swelling, capillary obstruction, interstitial edema, and intramyocardial hemorrhage [7,9].

Some experimental models have attributed approximately 40–50% of final infarct size to injury developing during reperfusion [10]. This value is best regarded as an experimental estimate rather than a fixed proportion applicable to individual patients. Ischemic injury and reperfusion injury are biologically interconnected, and their relative contributions vary with ischemic duration, collateral perfusion, metabolic state, species, and experimental conditions [7,8,10]. Accordingly, the extent of myocardial injury observed after reperfusion reflects processes initiated both during the preceding ischemic interval and during restoration of coronary flow.

1.4. Introduction to Sevoflurane

Sevoflurane is a fluorinated volatile ether commonly used for maintenance of general anesthesia [11]. Although its anesthetic effects arise primarily through actions within the central nervous system, experimental studies have identified additional effects on mitochondrial function, ion channels, intracellular signaling, and cellular responses to oxidative stress [12,13]. These observations led to investigation of volatile anesthetics as pharmacological modifiers of MIRI.

Evidence that volatile anesthetics could influence the myocardial response to ischemia appeared before the modern concept of anesthetic conditioning was established. In 1976, Bland and Lowenstein reported attenuation of electrocardiographic manifestations of myocardial ischemia with halothane in a canine coronary-occlusion model [14]. Subsequent studies shifted attention from the hemodynamic effects of volatile anesthetics toward cellular responses that persisted beyond the period of anesthetic exposure.

Cason and colleagues provided an important demonstration of this phenomenon in 1997 using a rabbit infarction model. Isoflurane administered before coronary occlusion produced an infarct occupying 23.4 ± 8.5% of the ischemic area at risk, compared with 33.1 ± 13.3% in untreated controls. For comparison, infarct size in an ischemic-preconditioning group was 8.7 ± 6.2% [15]. These observations helped establish the concept that exposure to a volatile anesthetic could serve as a pharmacological conditioning stimulus.

Anesthetic preconditioning describes exposure to a volatile anesthetic before a subsequent ischemic event, whereas anesthetic postconditioning involves administration during late ischemia or around the onset of reperfusion. Experimental work with sevoflurane and other volatile anesthetics has implicated several pathways in these responses, including mitochondrial ATP-sensitive potassium channels, protein kinase C, redox-sensitive signaling, prosurvival kinase cascades, regulation of intracellular calcium, maintenance of mitochondrial membrane function, and modulation of mitochondrial permeability transition [12,13].

2. Mechanisms of MIRI

2.1. Reactive Oxygen Species

At reperfusion, oxygen reintroduction triggers the production of reactive oxygen species (ROS) via several mechanisms: xanthine oxidase reacts with accumulated hypoxanthine/xanthine to release superoxide and hydrogen peroxide, while the electron transport chain leaks electrons at an increased rate, fueled further by calcium re-entry as membrane potential is restored; uncoupled NOS and NADPH oxidase add to this pool [16] (Figure 4).

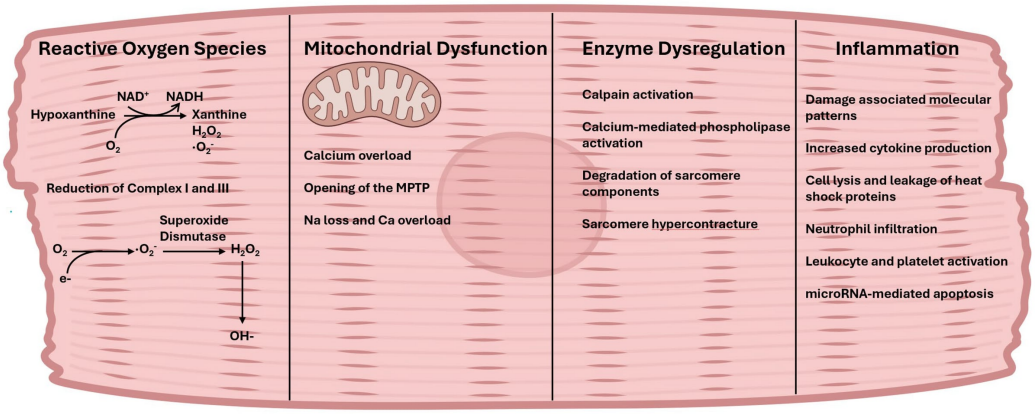


Figure 4. Myocardial ischemia–reperfusion injury occurs via generation of reactive oxygen species, mitochondrial dysfunction, abnormal enzyme function, and inflammatory pathways.

Combined with calcium overload and rapid pH normalization, this surge forces open the mitochondrial permeability transition pore, collapsing membrane potential and provoking further ROS release in a self-perpetuating loop. The resulting oxidative wave peroxidizes membrane lipids, damages DNA and proteins, triggers apoptosis and pyroptosis, while also priming the NLRP3 inflammasome to release IL-1 and IL-18 [16].

Ischemia halts electron flow, leaving complex I and III hyper-reduced with elevated $NADH/NAD^+$. When O_2 returns during reperfusion, these saturated, complex I-impaired complexes transfer single electrons directly to O_2 instead of the regulated chain, forming superoxide [16,17]. This initial leak, amplified by Ca^{2+}-triggered mitochondrial permeability transition port (mPTP) opening and membrane potential collapse, drives a self-propagating cycle of further electron leak—ROS-induced ROS release [16,18].

Reperfusion triggers a burst of mitochondrial electron leakage, generating superoxide anion ($O_2 \cdot -$), which is converted by superoxide dismutase into hydrogen peroxide (H_2O_2) and further reacts to form the highly reactive hydroxyl radical ($\cdot OH$) [16]. These species overwhelm cellular antioxidant defenses, producing oxidative stress that attacks the polyunsaturated fatty acids of the sarcolemmal membrane [18]. Through lipid peroxidation, radicals strip hydrogen atoms from membrane lipids in a self-propagating chain reaction, disrupting membrane integrity and increasing permeability. This allows uncontrolled calcium influx, driving hypercontracture, further mitochondrial damage and cardiomyocyte necrosis [18].

2.2. Mitochondrial Dysfunction

2.2.1. Calcium Overload

During early reperfusion, restored extracellular pH activates the sodium–hydrogen exchanger, which corrects intracellular acidity but floods the cell with Na^+. Because ATP-dependent Na^+/K^+ ATPase remains dysfunctional from ischemia, this Na^+ surge cannot be cleared normally, forcing the sodium–calcium exchanger into reverse mode—expelling Na^+ while pulling Ca^{2+} into the cytosol [16]. Simultaneously, reperfusion restores the mitochondrial membrane potential, powering the Ca^{2+} uniporter to rapidly draw this cytosolic calcium into the mitochondrial matrix. This pH-correction-driven Ca^{2+} overload combines with the ROS burst to trigger mPTP opening and mitochondrial collapse [17].

2.2.2. Mitochondrial Permeability Transition Pore

mPTP opening is structurally linked to F-ATP synthase, which may form the pore itself, and is regulated by Cyclophilin D, a matrix protein essential for pore activation during necrotic cell death [18]. Pore opening is tightly controlled by the cell's chemical environment: acidic pH keeps it inhibited during ischemia, while reperfusion-driven normalization of pH, calcium overload, ROS bursts, and accumulated inorganic phosphate together trigger its opening [16]. Once open, the mPTP collapses membrane potential, halts ATP production, and causes mitochondrial swelling and rupture, releasing pro-apoptotic factors like cytochrome c [16,18].

2.3. Enzyme-Dysregulation

2.3.1. Calpain

Reperfusion-driven calcium overload triggers calpain activation, where these non-lysosomal cysteine proteases initiate calcium-dependent proteolysis of the cardiomyocyte's internal architecture [19]. Calpains drive sarcomeric degradation by cleaving troponin I, titin, and desmin, desensitizing myofilaments to calcium and collapsing the sarcomere's structural and elastic integrity [17]. Simultaneously, degradation of cytoskeletal-anchoring proteins like vinculin and dystrophin severs the connection between the internal cytoskele-

ton and the sarcolemma. With anchoring lost but the contractile apparatus reactivated by restored oxygen and persistently high Ca^{2+}, cells undergo hypercontracture, an uncontrolled sustained shortening [17]. At the gross/tissue level, this widespread contracture produces "stone-heart" stiffness, impairing ventricular filling and compressing coronary vessels to worsen the no-reflow phenomenon [19].

2.3.2. Phospholipases

Elevated intracellular calcium activates cPLA2, which hydrolyzes phosphatidylcholine into lysophospholipids and free fatty acids like arachidonic acid [20]. These act as endogenous detergents, reducing membrane rigidity and inducing curvature stress that destabilizes the bilayer, with shorter-chain lysolipids causing disproportionately large disruption. This progressively increases membrane permeability and lowers lysis tension, ultimately driving full solubilization into micelles. In effect, calcium-triggered phospholipase activity turns the cell's own lipids into agents of self-destruction, fueling reperfusion-induced necrosis.

2.4. Inflammatory Pathways

2.4.1. Damage-Associated Molecular Patterns

When cardiomyocytes lyse during ischemia–reperfusion injury, they release intracellular alarmins—including High Mobility Group Box 1 and mitochondrial DNA (mtDNA)—into the extracellular space, where they act as damage-associated molecular patterns (DAMP), signaling tissue injury without infection [17,21]. These molecules bind pattern recognition receptors on nearby cells, particularly Toll-like receptor 4 (TLR4), triggering TLR4 activation despite the receptor's typical role in detecting bacterial pathogens. This receptor engagement initiates a signaling cascade through adaptor proteins like MyD88, culminating in NF-κB nuclear translocation, where the transcription factor moves into the nucleus to activate pro-inflammatory genes.

The resulting cytokine production (IL-6, IL-1β, TNF-α) recruits immune cells such as neutrophils to the injury site, constituting sterile inflammation—an immune response to internal damage rather than pathogens. Though meant to promote healing, this response can become excessive, causing additional tissue damage and contributing to adverse cardiac remodeling [21].

Beyond HMGB1 and mtDNA, additional DAMPs include N-formyl peptides, succinate, and TFAM, with mitochondria's high volume fraction in cardiomyocytes amplifying their release. How these molecules escape the cell depends on death mode: necrosis causes uncontrolled lysis releasing all DAMPs, apoptosis normally sequesters contents in apoptotic bodies unless clearance is delayed, and pyroptosis releases DAMPs through Gasdermin D pores before eventual lysis [18,21]. HMGB1 can also bind RAGE in addition to TLR4, and the downstream cascade specifically proceeds through TRAF6 to activate the IKK complex, which phosphorylates IκB to permit NF-κB release.

2.4.2. Heat-Shock Proteins

Inside the cell, HSP60 and HSP70 act as protective intracellular molecular chaperones that assist protein folding and even suppress NF-κB activation to limit internal inflammation. Once cells rupture during necrosis or pyroptosis, these same proteins spill into the interstitium, where their conserved structures are instead recognized by the immune system as danger signals. As extracellular molecular chaperones, they function as pattern recognition receptor ligands for TLR2 and TLR4, binding endothelial cells to trigger NF-κB translocation and cytokine release (IL-1β, IL-6, TNF-α). This upregulates adhesion molecules like ICAM-1, promoting neutrophil and monocyte infiltration and amplifying local tissue inflammation [21,22].

2.4.3. Lymphocyte Activation

Cytokines from injured cardiomyocytes activate NF-κB in endothelial cells, upregulating adhesion molecules ICAM-1 and VCAM-1 while a chemokine gradient (IL-8, MCP-1, mitochondrial N-formyl peptides) guides circulating leukocytes to the infarct zone [21]. This drives rapid neutrophil infiltration, peaking 6–24 h post-injury, as activated neutrophils—larger and stiffer than red blood cells—adhere to the sticky endothelium and physically plug capillary lumens. During this time, leukocytes and platelets form microthrombi via NETs and pro-thrombotic factors, while inflammation causes endothelial swelling that further narrows vessels [23].

Together with ROS-mediated glycocalyx damage, loss of nitric oxide-driven vasodilation, and interstitial edema compressing capillaries externally, these mechanisms produce microvascular no-reflow [23].

2.5. microRNA

MicroRNAs are short, noncoding RNA molecules that bind to the 3′-untranslated region of messenger RNA (mRNA) and reduce translation or promote mRNA degradation [24]. Multiple miRNAs have been implicated in the development of MIRI via different mechanisms, of which our understanding continues to evolve. miRNA-663b and miRNA-184 were shown to inhibit BCL2L1, an antiapoptotic protein, resulting in cardiomyocyte apoptosis [25]. In a mouse model of MIRI, miRNA-802-5p expression reduces expression of PTCH1, a receptor for the antiapoptotic sonic hedgehog signaling pathway [26].

3. Effects of Sevoflurane on MIRI

3.1. Micro-RNA/BRD4

In a mouse model of MIRI, sevoflurane increased the expression of miRNA-99a, which binds bromodomain-containing protein 4 (BRD4) mRNA and decreases BRD4 protein production [27]. BRD4 is an epigenetic "reader" protein that recognizes acetylated lysine residues on histones and transcription factors. After binding these acetylated sites, BRD4 recruits transcriptional machinery which allows RNA polymerase II to efficiently transcribe inflammatory genes IL-1β, IL-6, and TNF-α [28]. Sevoflurane-induced suppression of BRD4 limits the transcription of these mediators, which reduces inflammation, oxidative stress, and apoptosis.

3.2. Mitochondrial Impairment

Sevoflurane plays an important role in maintaining mitochondrial structure in MIRI. In a murine model of MIRI, it was found that sevoflurane-treated hearts displayed relatively intact mitochondria with preserved cristae and less swelling and vacuolation than untreated hearts; these structural improvements were accompanied by substantially higher myocardial ATP content [29]. One proposed upstream mechanism is the sevoflurane-induced activation of mitochondrial ATP-sensitive potassium channels (mitoKATP). The opening of mitoKATP channels permits a limited influx of K^+ into the mitochondrial matrix, followed by osmotically coupled water movement that produces more mild matrix swelling and regulates mitochondrial volume. This smaller change reduces overload and reactive oxygen species generation [30]. It has also been found that pharmacologically inhibiting mitoKATP channels with agents such as 5-hydroxydecanoate or glibenclamide reduces the cardioprotective effects of sevoflurane [31]. This supports a protective role for these channels, and sevoflurane, in MIRI.

3.3. ROS

A controlled reduction in mitochondrial membrane potential (ΔΨm) can limit oxidative injury by decreasing the thermodynamic conditions that favor electron leakage from the electron transport chain. Under normal conditions, electron transport through complexes I–IV pumps protons across the inner mitochondrial membrane, generating ΔΨm as a major component of the proton-motive force used by ATP synthase. When ΔΨm becomes excessively high, however, further proton pumping is energetically opposed, respiratory-chain carriers remain highly reduced, and electrons are more likely to be transferred prematurely to molecular oxygen, generating superoxide. This process becomes particularly important during early reperfusion, when succinate accumulated during ischemia is rapidly oxidized by complex II. The resulting reduction in the coenzyme Q pool, together with rapid restoration of the proton-motive force, can drive electrons backward through complex I by reverse electron transport, producing a concentrated burst of mitochondrial reactive oxygen species [32].

Sevoflurane may induce a more mild, transient depolarization of the mitochondrial membrane potential (ΔΨm) through activation of mitoKATP channels. Potassium entry into the mitochondrial matrix via mitoKATP channels partially dissipates the electrical gradient across the inner membrane. This controlled change in ΔΨm may be particularly beneficial when sevoflurane is administered at the onset of reperfusion, because it can restrain rapid mitochondrial re-energization and reduce the magnitude of the pathological ROS burst. It is important to note that sevoflurane does not eliminate ROS production entirely. Rather, it induces a small, transient ROS signal during conditioning which may activate protective kinase pathways. This also attenuates the big damaging ROS burst during reperfusion.

Sevoflurane also appears to establish a slower and more sustained antioxidant response that complements this immediate bioenergetic effect. In a rat MIRI model, sevoflurane preconditioning increased expression of antioxidant enzymes superoxide dismutase-2 (SOD2) and catalase. This resulted in increased respiratory-chain activity and ATP production [33]. Upregulating the SOD2 and catalase enzymes complements the immediate effects of mild depolarization by detoxifying residual superoxide and hydrogen peroxide.

3.4. Rescuing Autophagic Clearance

Autophagic flux refers to the complete process of autophagy, including the formation, degradation, and recycling of cellular components through the lysosomal pathway. Although ischemia activates autophagosome formation as an adaptive response to nutrient and ATP depletion, reperfusion can impair the terminal degradative phase of this pathway. It has been suggested that reactive oxygen species created during reperfusion reduce lysosome-associated membrane protein 2 (LAMP2), a protein required for efficient autophagosome–lysosome fusion [29,34].

Sevoflurane appears to protect the reperfused myocardium by normalizing autophagy. MIRI models found that sevoflurane reduced autophagosome accumulation, restored LAMP2 expression and lysosomal cathepsin activity, and improved the clearance of sequestered cellular material [29,35]. Restoration of autophagosome–lysosome processing facilitates the lysosomal clearance of damaged cellular components, including dysfunctional mitochondria targeted for mitophagy. By improving the removal of compromised mitochondria, sevoflurane may reduce the persistence of organelles capable of generating ROS, releasing cytochrome *c*, and activating the intrinsic apoptotic cascade.

Another important marker of autophagic flux is p62/sequestosome-1 (p62/SQSTM1), a selective autophagy receptor that facilitates the delivery of damaged cellular material to autophagosomes. p62 contains a ubiquitin-associated domain that recognizes ubiquitinated cargo and an LC3-interacting region that binds LC3 on the developing autophagosomal

membrane, thereby physically linking material targeted for degradation to the autophagic machinery [36]. In myocardial ischemia–reperfusion, increased LC3-II is accompanied by accumulation of p62, indicating that autophagosomes are being generated but their contents are not efficiently cleared. Sevoflurane postconditioning reverses this pattern, decreasing both LC3-II and p62 while improving lysosomal cathepsin activity, consistent with restoration of autophagosome clearance rather than inhibition of autophagosome formation [35]. Thus, the reduction in p62 following sevoflurane exposure provides evidence that previously sequestered cargo is progressing through the autophagosome–lysosome pathway to degradation, facilitating the removal of damaged proteins and organelles that would otherwise contribute to continued mitochondrial dysfunction and cardiomyocyte injury.

3.5. SIRT

Sevoflurane appears to alter the cell's internal free-radical scavenging capacity through coordinated activation of the NAD^+-dependent sirtuin pathways, particularly SIRT1 and SIRT3. In myocardial ischemia–reperfusion, SIRT1 expression is reduced. Sevoflurane treatment has been shown to suppress miR-155, a negative regulator of SIRT1, thereby restoring myocardial SIRT1 expression [37]. SIRT1 is predominantly nuclear and cytosolic and therefore influences mitochondrial antioxidant capacity largely through transcriptional regulation rather than through the direct modification of mitochondrial enzymes. For example, SIRT1 deacetylates forkhead box O (FoxO) transcription factors, shifting their activity toward cellular stress resistance. In MIRI specifically, SIRT1-dependent activation of FoxO1 increases expression of manganese superoxide dismutase (MnSOD/SOD2) and thioredoxin-1, thereby increasing the capacity of cardiomyocytes to neutralize ROS [38].

SIRT3 is an important deacetylase that has also been demonstrated to have a scavenging effect on ROS. SIRT3 provides a more direct link between sevoflurane and mitochondrial redox control because it is localized predominantly within mitochondria, placing it in the same compartment in which a large proportion of reperfusion-associated ROS are generated [38]. In rats subjected to MIRI, sevoflurane preconditioning increased myocardial NAD^+ content and SIRT3 expression while increasing SOD2 and catalase expression, mitochondrial complex I, II, and IV activities, and ATP content; inhibition of SIRT3 with 3-TYP substantially reversed these effects. Mechanistically, increased levels of SIRT directly deacetylates mnSOD at lysine residues that regulate its enzymatic activity, which increases conversion of mitochondrial superoxide (ROS) to hydrogen peroxide [39]. Combined, sevoflurane's effects on SIRT1 and SIRT2 demonstrate a cardioprotective effect in reperfused myocardium.

3.6. JAK/STAT

The survivor activating factor enhancement (SAFE) and reperfusion injury salvage kinase (RISK) pathways are two major prosurvival signaling pathways that help protect cardiomyocytes during reperfusion. The SAFE pathway is commonly initiated by cytokine signaling, particularly through tumor necrosis factor-α (TNF-α) and TNF receptor 2 (TNFR2). This signaling promotes phosphorylation of Janus kinase 2 (JAK2), which then phosphorylates signal transducer and activator of transcription 3 (STAT3). Once phosphorylated, STAT3 forms dimers and translocates into the nucleus, where it regulates transcription of genes involved in cell survival [40]. In sevoflurane postconditioning, activation of the JAK2/STAT3 pathway has been associated with increased expression of the antiapoptotic protein Bcl-2 and decreased expression of the pro-apoptotic protein Bax [41]. Increasing the Bcl-2/Bax ratio helps stabilize the mitochondrial outer membrane, reducing cytochrome *c* release and subsequent activation of caspase-mediated apoptosis.

In parallel, sevoflurane activates the RISK pathway through phosphoinositide 3-kinase (PI3K) and Akt. Activation of PI3K leads to phosphorylation of Akt, which then regulates several downstream targets, including glycogen synthase kinase-3β (GSK3β). Phosphorylation of GSK3β reduces its pro-death activity and decreases the likelihood of mPTP opening during reperfusion.

SAFE and RISK should not be viewed as a single linear pathway; rather, they operate in parallel. SAFE signaling increases STAT3-dependent survival signaling and the Bcl-2/Bax ratio, while RISK signaling activates Akt and inhibits GSK3β-dependent pro-death signaling. Sevoflurane has been demonstrated to positively modulate both of these pathways.

Importantly, the JAK/STAT and SIRT pathways share multiple points of intersection where regulatory interactions serve not only regulatory functions but may provide potential therapeutic targets (Figure 5). Thomas et al. showed that a rat model of SIRT1 activation reduced JAK/STAT-mediated inflammation via reductions in several pro-inflammatory mediators such as IL-15, IL-22, Socs2, and Socs 5 [42]. Acetylation of the p65 subunit of NF-κB regulates transcription of genes for Socs1 and Socs3, which are important antagonists of the JAK/STAT pathway [43].

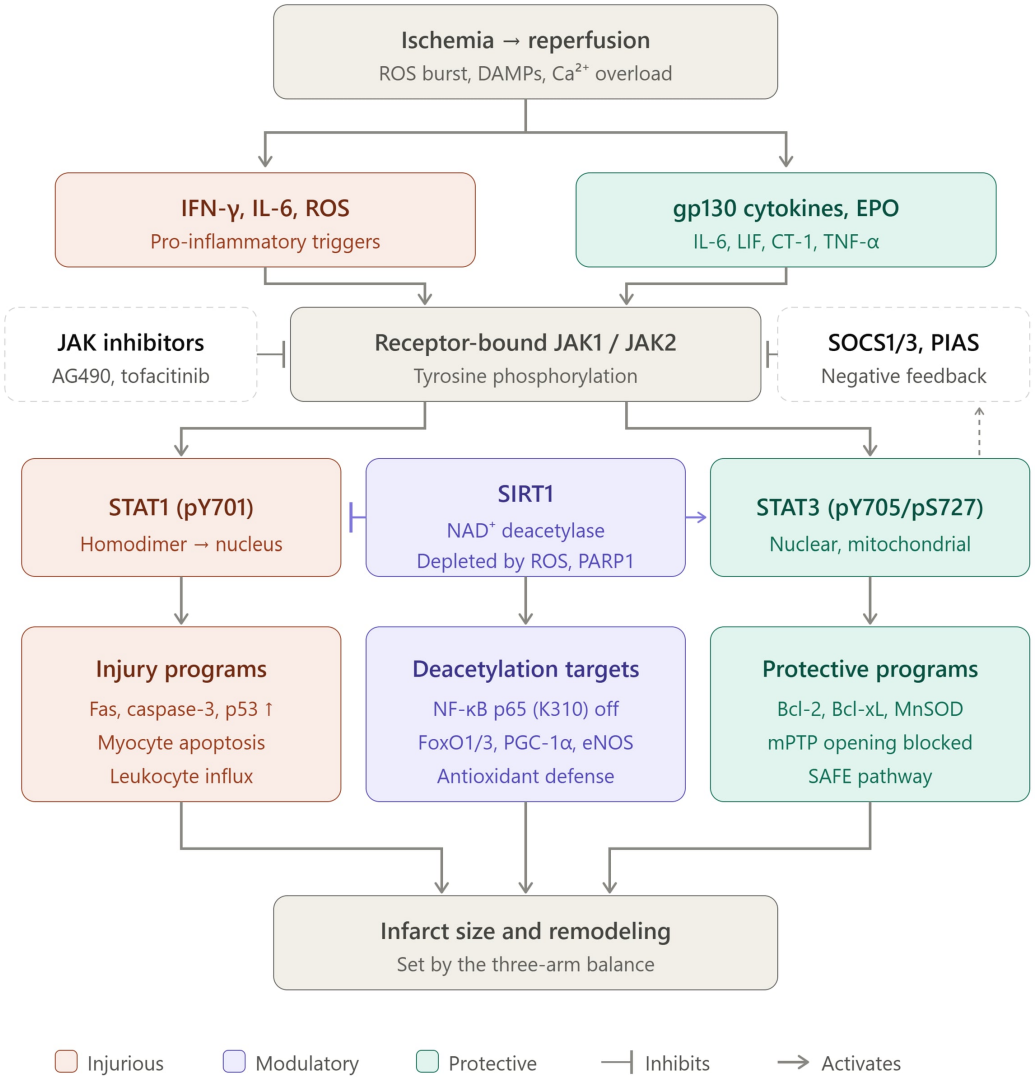


Figure 5. SIRT1 provides multiple important regulatory functions on JAK/STAT-mediated inflammatory pathways. AG490, tyrphostin B42 (JAK2 inhibitor); Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma–extra large; Ca^{2+}, calcium ion; caspase-3, cysteine-aspartate protease 3; CT-1, cardiotrophin-1; DAMPs, damage-associated molecular patterns; eNOS, endothelial nitric oxide

synthase; EPO, erythropoietin; Fas, Fas cell surface death receptor (CD95/APO-1); FoxO1/3, forkhead box O1 and O3; gp130, glycoprotein 130 (shared IL-6-family receptor subunit); IFN-γ, interferon gamma; IL-6, interleukin-6; JAK1/JAK2, Janus kinase 1 and 2; K310, lysine 310; LIF, leukemia inhibitory factor; MnSOD, manganese superoxide dismutase (SOD2); mPTP, mitochondrial permeability transition pore; NAD^+, oxidized nicotinamide adenine dinucleotide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells (p65 = RelA subunit); p53, tumor protein p53; PARP1, poly(ADP-ribose) polymerase 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PIAS, protein inhibitor of activated STAT; pS727, phosphorylation at serine 727; pY701/pY705, phosphorylation at tyrosine 701 and 705; ROS, reactive oxygen species; SAFE, survivor activating factor enhancement pathway; SIRT1, sirtuin 1 (silent information regulator 2 homolog 1); SOCS1/SOCS3, suppressor of cytokine signaling 1 and 3; STAT1/STAT3, signal transducer and activator of transcription 1 and 3; tofacitinib, pan-JAK inhibitor (JAK1/JAK3-preferring); TNF-α, tumor necrosis factor alpha.

4. Clinical Implications

4.1. Protective Effects

Studies of sevoflurane conditioning have evaluated myocardial injury using endpoints ranging from mitochondrial and biochemical changes to infarction, ventricular performance, and electrical instability. Infarct size has been particularly useful because it provides a direct measure of irreversible myocardial injury. In a closed-chest porcine model subjected to 45 min of distal left anterior descending coronary occlusion followed by 120 min of reperfusion, infarction encompassed 55.0 ± 3.9% of the area at risk in control animals and 17.5 ± 4.4% in animals exposed to sevoflurane [44]. This corresponds to an approximately 68% relative reduction in infarct size. The magnitude of infarct reduction reported in experimental studies is variable and depends on factors such as species, duration of ischemia, anesthetic concentration, and the timing of sevoflurane administration [12,13].

Infarct-size measurements also provide a means of describing myocardial salvage. The myocardial salvage index represents the proportion of myocardium initially placed at risk by ischemia that remains viable following reperfusion and can be calculated from the difference between the area at risk and final infarct size [45]. Preservation of viable cardiomyocytes has potential consequences for subsequent myocardial function because surviving cells can resume oxidative ATP production, calcium cycling, and sarcomeric contraction after reperfusion.

For this reason, experimental studies have also examined ventricular performance after ischemia using measurements such as left ventricular developed pressure, dP/dt, end-diastolic pressure, cardiac output, fractional shortening, and LVEF. Improvements in several of these parameters have been reported following sevoflurane preconditioning or postconditioning [12,13]. Functional recovery, however, does not necessarily parallel changes in infarct size. Viable myocardium may remain transiently dysfunctional as a consequence of post-ischemic stunning, allowing substantial myocardial salvage to coexist with impaired early contractility.

The electrical effects of sevoflurane have also been examined in reperfusion models. Ischemia produces several changes capable of promoting ventricular arrhythmias, including ATP depletion, potassium accumulation, acidosis, calcium overload, altered intercellular conduction, and heterogeneous repolarization [3]. In an isolated working rat-heart model, Oguchi and colleagues compared different timings of sevoflurane exposure during global ischemia and reperfusion. Ventricular fibrillation developed during reperfusion in 100% of untreated hearts, compared with 63% when sevoflurane was given before ischemia and 25% when exposure continued throughout the experimental period. Administration confined to the reperfusion period was associated with a 100% incidence of ventricular fibrillation [46]. The corresponding duration of ventricular fibrillation was 375 ± 269 s in controls, 104 ± 98 s

with preischemic exposure, 303 ± 189 s with reperfusion-only exposure, and 93 ± 245 s with continuous administration [46].

The same experiment found no significant differences among groups in cardiac output or maximum LV dP/dt during reperfusion [46]. This finding illustrates that the electrical, structural, and mechanical manifestations of ischemia–reperfusion injury may respond differently to the same conditioning protocol. Across the broader experimental literature, sevoflurane exposure has been associated with changes in reperfusion ventricular tachyarrhythmias, infarct size, oxidative stress, cardiac enzyme release, and measures of ventricular recovery [12,13]. These endpoints provide complementary ways of describing the myocardial response to anesthetic conditioning rather than a single uniform measure of cardioprotection.

4.2. Clinical Evidence

Clinical investigation of volatile-anesthetic cardioprotection has focused largely on cardiac surgery. CABG and valve procedures provide a setting in which the myocardium undergoes a relatively defined period of ischemic exposure associated with aortic cross-clamping and cardioplegic arrest, followed by reperfusion. Trials comparing volatile anesthetics with intravenous techniques have consequently examined biochemical, hemodynamic, electrophysiological, and clinical outcomes.

Postoperative cardiac troponin has been one of the most commonly reported measurements. In patients undergoing aortic valve replacement with cardiopulmonary bypass, Cromheecke and colleagues observed lower postoperative troponin I release together with differences in early myocardial functional recovery in patients anesthetized with sevoflurane [47]. Evidence from CABG studies has also been pooled across multiple randomized trials. Straarup and colleagues analyzed 30 studies involving 2578 patients and reported lower peak postoperative cardiac troponin I following volatile anesthesia in the on-pump CABG subgroup [48]. Similarly, a meta-analysis by Symons and Myles incorporating 27 randomized trials and 2979 patients found lower postoperative troponin I concentrations among patients receiving volatile anesthetics [49].

Hemodynamic measurements have also differed between anesthetic strategies in some studies. In the Symons and Myles analysis, the pooled postoperative cardiac index was approximately 20% higher following volatile anesthesia, with an estimated difference of about 0.22 $L \cdot min^{-1} \cdot m^{-2}$ [49]. The same analysis identified a lower requirement for postoperative inotropic support in patients assigned to volatile anesthetics [49]. These endpoints provide a clinical counterpart to experimental measurements of post-ischemic ventricular performance, although ventricular function after cardiac surgery is additionally affected by surgical revascularization, cardioplegia, cardiopulmonary bypass, loading conditions, and vasoactive therapy.

Differences have also been reported in measures of postoperative recovery. The 27-trial analysis found an approximately 2.7 h shorter period of mechanical ventilation and an approximately 1-day shorter hospital stay in patients receiving volatile anesthetics [49]. A subsequent meta-analysis encompassing 89 randomized trials and 14,387 CABG patients reported reductions of approximately 4.14 h in ICU stay and 1.22 days in hospital stay [50]. Considerable heterogeneity was present for both outcomes, reflecting variation in anesthetic protocols, surgical practice, extubation strategies, and institutional discharge criteria.

Clinical arrhythmia data show a smaller difference than that observed in many experimental reperfusion models. Among 29 randomized trials involving 3084 patients included in the 2019 meta-analysis, the relative risk of postoperative arrhythmia with volatile anesthesia compared with TIVA was 0.89 (95% CI, 0.77–1.03; $p = 0.11$) [50]. Interpretation of this endpoint differs from the experimental literature because clinical studies often report

postoperative arrhythmias collectively, whereas laboratory experiments commonly measure ventricular tachycardia or ventricular fibrillation specifically during the immediate reperfusion period.

Myocardial infarction has been examined as a separate clinical endpoint. Across 28 randomized trials comprising 8574 patients, the relative risk of postoperative myocardial infarction with volatile anesthesia compared with TIVA was 0.94 (95% CI, 0.73–1.21; $p = 0.64$) [50]. Thus, studies reporting differences in postoperative troponin or hemodynamic measurements have not necessarily demonstrated corresponding differences in the incidence of clinically defined myocardial infarction.

The largest randomized evaluation of clinical outcomes was the MYRIAD trial, which enrolled 5400 patients undergoing elective CABG across 36 centers in 13 countries [51]. At 1 year, mortality was 2.8% among patients assigned to a volatile-anesthetic regimen and 3.0% among those receiving TIVA (RR 0.94; 95% CI, 0.69–1.29; $p = 0.71$). Thirty-day mortality was 1.4% and 1.3%, respectively [51].The trial also found no significant difference in myocardial infarction or its other major secondary outcomes. Taken together, the clinical literature therefore describes the effects of volatile anesthesia across a spectrum of endpoints, from cardiac enzyme release and postoperative hemodynamics to arrhythmias, myocardial infarction, recovery measures, and mortality.

5. Future Research

5.1. Limitations in Current Research

An important consideration for future research is the biological difference between experimental models and human patients. Laboratory studies commonly use young, otherwise healthy animals, whereas clinical populations frequently include older patients with diabetes, hyperlipidemia, hypertension, renal dysfunction, ventricular hypertrophy, atherosclerosis, and other comorbidities capable of modifying cellular responses to ischemia and conditioning [52]. Chronic medications add another source of variation. Sulfonylureas, for example, interact with ATP-sensitive potassium channels implicated in volatile-anesthetic conditioning, while several commonly used cardiovascular and metabolic medications influence overlapping signaling pathways [12,13,52]. Greater characterization of comorbidities and medication exposure may therefore help clarify differences in conditioning responses among patient populations.

Another important limitation is related to the fact that the majority of clinical studies on this topic are carried out on patients undergoing cardiac surgery, whereas patients experiencing myocardial ischemia are often treated non-surgically via medical or catheter-based interventions. This may limit the generalizability of existing data to the non-surgical population. Additionally, significant methodological challenges exist in clinical trial designs outside the operating room as most non-surgical facilities lack the equipment and expertise to safely administer sevoflurane.

5.2. Future Studies

Given the substantial differences between animal models and patient populations and the current lack of patient trials, prospective human trials are critical to close this gap and better understand the role of sevoflurane in the treatment of MIRI. Future clinical studies should complement conventional biomarkers such as troponin with structural and longer-term measurements and target specific molecular mechanisms. Studies of inhibitors of JAK/STAT (e.g., Baricitinib, Tofacitinib), SIRT (e.g., Selisistat), PI3K (e.g., Umralisib) may inform novel therapeutic modalities.

Cardiac magnetic resonance imaging can quantify infarct burden, microvascular obstruction, ventricular volumes, LVEF, and myocardial salvage, providing information that

cannot be obtained from circulating biomarkers alone [53]. Follow-up beyond the immediate perioperative period could additionally evaluate ventricular function, heart-failure hospitalization, recurrent myocardial infarction, major adverse cardiac events, and cardiovascular mortality. Combining acute biomarkers, imaging, and longer-term outcomes in appropriately powered multicenter studies would provide a broader description of how experimentally observed conditioning effects correspond to myocardial injury and recovery in patients.

6. Conclusions

Sevoflurane is a commonly used anesthetic agent whose potential for mitigating MIRI provides a strong potential therapy for those experiencing myocardial ischemia. Its use has been shown to have important benefits in those undergoing cardiac surgery. In vitro and in vivo studies in human tissues will be necessary to provide deeper mechanistic insights. Development of future treatments will require enhanced clinical protocols and provider training to allow early intervention. Prospective trials across demographic and clinical settings will be necessary to inform therapeutic efficacy.

Author Contributions: Conceptualization, S.D.; methodology, writing—original draft preparation, A.B., G.P., N.B. and S.D.; writing—review and editing, A.B. and S.D.; visualization, K.U. and S.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. The APC was funded by District Medical Group.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

MIRI	Myocardial Ischemia–Reperfusion Injury
MPTP	Mitochondrial permeability transition pore
ROS	Reactive oxygen species
mtDNA	Mitochondrial DNA
TLR	Toll-like receptor
DAMP	Damage-associated molecular pattern

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