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REVIEW ARTICLE

Cardioprotective Strategies After Ischemia–Reperfusion Injury

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Abstract

Acute myocardial infarction (AMI) is associated with high morbidity and mortality worldwide. Although early reperfusion is the most effective strategy to salvage ischemic myocardium, reperfusion injury can develop with the restoration of blood flow. Therefore, it is important to identify protection mechanisms and strategies for the heart after myocardial infarction. Recent studies have shown that multiple intracellular molecules and signaling pathways are involved in cardioprotection. Meanwhile, device-based cardioprotective modalities such as cardiac left ventricular unloading, hypothermia, coronary sinus intervention, supersaturated oxygen (SSO_2), and remote ischemic conditioning (RIC) have become important areas of research. Herein, we review the molecular mechanisms of cardioprotection and cardioprotective modalities after ischemia–reperfusion injury (IRI) to identify potential approaches to reduce mortality and improve prognosis in patients with AMI.

Key Points

At present, myocardial infarction still has a high incidence of a disease and mortality. The area of myocardial infarction is often closely related to ischemia–reperfusion injury.

This review summarizes the mechanisms by which ischemia–reperfusion occurs and strategies to protect the heart by reducing defect reperfusion injury.

This provides a new approach to reduce the size of myocardial infarction and reduce mortality.

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1 Introduction

Prolonged myocardial necrosis, which arises as a result of coronary artery occlusion and death of myocardial tissue, is associated with cardiogenic shock and risk of death. Acute myocardial infarction (AMI) causes more than 15% of all deaths worldwide each year, with a higher incidence in men than women [1]. Currently, the mainstay of treatment for AMI is early and effective reperfusion of the infarcted artery, such as thrombolytic therapy and percutaneous coronary intervention (PCI). However, timely reperfusion is often accompanied by non-negligible reperfusion injury.

Evidence shows that myocardial infarct size, as measured by cardiac magnetic resonance (CMR) imaging or technetium-99m sestamibi single-photon emission computed tomography (SPET) within 1 month after AMI, was strongly associated with all-cause mortality and hospitalization for heart failure at 1 year [2]. Therefore, scholars are focusing their attention on cardioprotection. Interestingly, a variety of molecules and signaling pathways in organisms may be involved in cardioprotection, such as NLRP3, miRNAs, and extracellular vesicles (EVs). These molecules and signaling pathways are worth exploring. In addition, extensive research has been conducted into adjuvant treatment modalities for the heart after myocardial infarction. Cardioprotective modalities such as left ventricular unloading, myocardial cooling, supersaturated oxygen (SSO_2), and stimulation of the vagus nerve are all being explored. In this review, we address the mechanisms of ischemia–reperfusion injury (IRI) development and cardioprotective strategies.

2 Molecular Mechanisms of Cardioprotection

Many molecules and signaling pathways are involved in the process of cardioprotection. Figure 1 lists three signaling pathways involved in cardioprotection, including the reperfusion injury salvage kinase (RISK) pathway, the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, and the NO/cGMP/PKG pathway. All of these pathways converge to the mitochondria, acting through the opening of the mitochondrial ATP-sensitive potassium channel (mKATP) and the mitochondrial permeability transition pore (mPTP). Reviewed below are important molecules involved in cardioprotection [3–5].

2.1 Cytosolic Molecules: SUMOyation

Small ubiquitin-like modifier (SUMO) is a 10-kDa polypeptide. SUMO1–3 are ubiquitously expressed, whereas SUMO4 is limited to lymph node, kidney, and spleen [6]. The role of SUMO1 in cardiac function was tested in myocardium-specific SUMO1-expressing transgenic mice, and the results showed that SUMO1 overexpression inhibited pressure overload-induced cardiac hypertrophy and dysfunction, suggesting a cardioprotective role for SUMO1 [7].

SUMOylation is a lysine-targeted post-translational modification (PTM) [8, 9]. It is becoming increasingly apparent that many SUMO chemical molecules are localized in the extranuclear compartment and that they are involved in the regulation of protein functions, including intracellular trafficking, apoptosis, protein stability, and enzyme activity [10–12].

2.1.1 NF-κB

Nuclear factor (NF)-κB is a master regulator of cell survival and inflammation and plays an important role in various cardiac pathogenesis including ischemic preconditioning [13]. When cells are stimulated by agonists such as tumor necrosis factor (TNF), NF-κB dissociates from inhibitor of κB (IκB) and translocates into the nucleus and transactivates proinflammatory genes [14]. SUMOylation has been reported to be involved in different levels of NF-κB regulation. IκBα can be modified by SUMO1 to protect it from ubiquitination and degradation, thereby limiting NF-κB activation [15, 16]. IκB kinase, an important regulatory kinase complex that regulates NF-κB signaling, consists of two kinases (IKKα and IKKβ) and a regulatory subunit, nuclear factor-κB essential modulator (NEMO). It has been reported that depletion of NEMO in cardiomyocytes promotes apoptosis and subsequent cardiac dysfunction via inhibiting the expression of

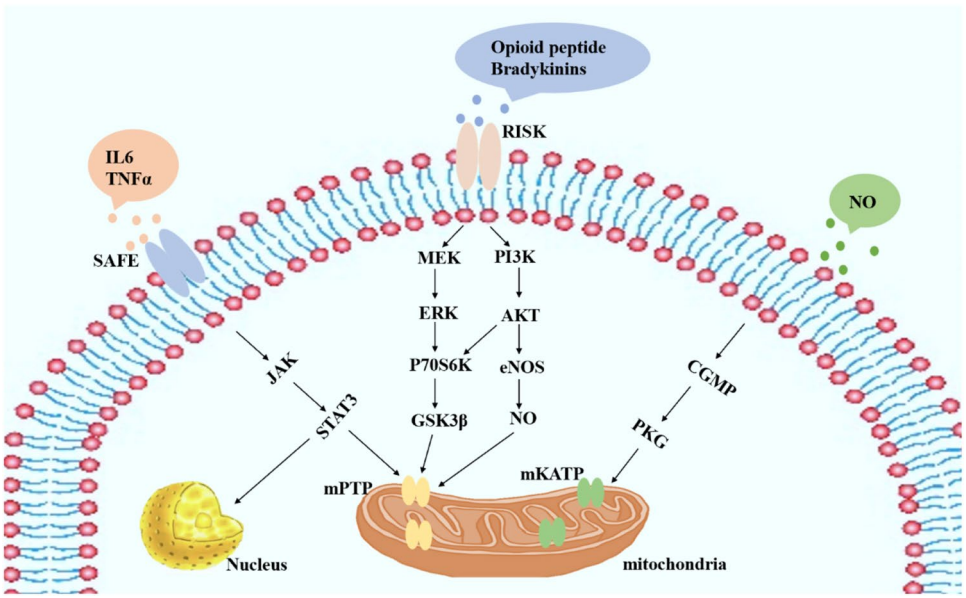

Fig. 1 The main protection mechanisms in the IR injury. There are three major pathways : **a** the reperfusion injury salvage kinase (RISK) pathway, including phosphatidylinositol 3-kinase/Akt (PI3K/Akt), extracellular signal-regulated kinase (ERK1/2), and the downstream target glycogen synthase kinase-3 beta (GSK3β); **b** the NO/cGMP/PKG pathway, where NO stands for nitric oxide, cGMP for cyclic guanosine monophosphate, and PKG for protein kinase G; and **c** the survivor activating factor enhancement (SAFE) pathway, including the tumor necrosis factor alpha (TNFα) and the transcription factor transducer and activator of transcription-3 (STAT3). All of these pathways converge to the mitochondria, acting through the opening of the mitochondrial ATP-sensitive potassium channel (mKATP) and the mitochondrial permeability transition pore (mPTP).

antioxidant genes such as superoxide dismutase 2 and ferritin heavy chain [17, 18]. In summary, activation of NEMO/IKKγ–NF-κB signaling can be cardioprotective by inhibiting apoptosis.

2.1.2 Protein Kinase C (PKC)

PKC contains multiple putative SUMOylation sites. Inactive PKCα is SUMOylated at the Lys465 site which can be de-SUMOylated by sentrin-specific peptidase1 (SENP1). It was shown that PKCα activation by calcium was achieved only after de-SUMOylation by SENP1 [19]. This suggests that SUMOylation can play an inhibitory role in PKCα kinase function. It is well known that PKCα negatively regulates cardiomyocyte contraction and that three specific extracellular PKCα substrates play a role in this regard [20]. First, PKCα phosphorylates inhibitor 1 (I-1) at Ser67, which upregulates protein phosphatase 1 activity, leading to more phosphatidylcholine (PLN) dephosphorylation and reduced sarcoplasmic reticulum (SR) Ca^{2+} ATPase (SERCA2) pump activity [21]. Second, PKCα activation increases G protein-coupled receptor kinase 2 (GRK2) phosphorylation and activity and impairs β-agonist-stimulated ventricular function via abolishing cyclase activity [22]. Lastly, PKCα can phosphorylate cardiac troponin I (cTnI), cTnT, titin, and myosin binding protein C, the effect of which is to decrease the Ca^{2+} sensitivity and contractility of cardiomyocytes [23–26]. In conclusion, inhibition of PKCα kinase activity by SUMOylation can be cardioprotective.

2.1.3 Adenosine Monophosphate-Activated Protein Kinase (AMPK) and Ubiquitin–Proteasome System (UPS)

AMPK is a stress-activated kinase, which can orchestrate the cellular response to a variety of stresses in the heart by regulating metabolism, protein synthesis, degradation, autophagy, and apoptosis. AMPK is a complex of three subunits: a catalytic subunit (α) containing a serine-threonine kinase domain (KD) with a Thr172 phosphorylation site, which is the target of liver kinase B1 (LKB1), and calcium–calmodulin-activated protein kinase kinase-β (CAMKKβ) and two regulatory subunits (β and γ). Most studies have shown that endogenous AMPK activation is protective against cardiac insults, including ischemia/reperfusion and pressure overload [27–30]. Rubio et al. reported that AMPK SUMOylation (SUMO2) stimulates AMPK activation and inhibits its ubiquitin-dependent degradation [31]. In addition, Yeh's group recently found that LKB1 K178 SUMO1 modification promotes LKB1 binding to AMPKα SIM and accelerates AMPK activation [32]. These data suggest that the LKB1–AMPK SUMOylation can be cardioprotective. Robbins and his colleagues showed that depletion of Ubc9, the SUMO E2 conjugating enzyme, in cardiomyocytes caused accumulation of protein aggregates inside these cells and impaired cardiac function [33]. In addition, they found that Ubc9-mediated SUMOylation increased autophagy, thereby reducing protein aggregate formation, fibrosis, and hypertrophy, while improving cardiac function and survival [34]. In conclusion, most of the cardiac extranuclear SUMOylation events are cardioprotective against cardiac damage.

2.2 Mitochondrial Molecules

Mitochondria are essential organelles for the proper functioning of cardiac muscle cells and are known as the "energy processing plant." In addition, mitochondria are involved in many important processes such as cell differentiation, information transfer, and apoptosis. Impaired mitochondrial function is an important cause of IRI [35–38]. Therefore, mitochondria can be an important research target for cardioprotective mechanisms. C. Penna et al. demonstrated that direct targeting of mitochondria with diazoxide activates the RISK pathway via a redox signaling, favors discretemitochondrial protein S-nitrosylation, and decreases signals of death [39]. Furthermore, by comparing exercised (5 days/week for 5 weeks) and sedentary Wistar rats, Doria Boulghobra et al. found that exercise training increases nitric oxide (NO) bioavailability in mitochondria, results in SNO of key proteins involved in the mitochondrial response to stress, and modulates Ca^{2+}-dependent mPTP opening and reactive oxygen species (ROS) production in conditions that mimic ischemia–reperfusion [40]. All of these can demonstrate that mitochondria are involved in the process of IRI and that they can be targeted for cardioprotection after IRI.

2.3 NLRP3

The nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are able to identify various damage-associated molecular patterns (DAMPs) and inflammatory factors, such as those released during ischemia–reperfusion. In particular, NLRP3 has been widely investigated in the setting of cardiac ischemia–reperfusion. The very low levels of NLRP3 expression in the healthy heart remain unchanged up to 3 h after reperfusion, while a significant increase has been detected by 6 h [41, 42]. The NLRP3 inflammasome is involved in many important processes, such as the efflux of cellular potassium, the release of cathepsin from damaged lysosomes, metabolic and mitochondrial dysfunction, Ca2þ-induced calpain activation resulting in the release of caspase-1 from actin, and impaired autophagy/mitophagy [43, 44]. The most important thing is that deletion of NLRP3 protein inhibits the ischemic preconditioning in an NLRP3

inflammasome-independent manner through an IL-6/STAT3-dependent mechanism [45]. Several experimental results indicate that the activation of NLRP3 inflammasome after reperfusion may concur with the progression of cardiac IRI, promoting cardiomyocyte loss by inducing pyroptosis, and favoring adverse remodeling by inducing the release of interleukin (IL)-1b and IL-18. However, reduced infarct size and improved cardiac function have been observed after inhibition or deficiency of one of the components of the NLRP3 inflammasome or using several NLRP3 inhibitors and gene silencing [46–49]. Interestingly, the fact that ischemic preconditioning (IPreC) was ineffective in NLRP3-deficient mice suggests that NLRP3 may play a double role in the ischemia–reperfusion heart, being able to trigger protective signaling and participating in IPreC, but also able to concur with the progression of cardiac injury and promoting cardiomyocyte loss after ischemia–reperfusion [50]. Furthermore, more about the inflammasome-independent role of NLRP3 and inflammasome protective signaling in AMI is described in detail in another review article [51, 52]. In conclusion, most of the studies proved that NLRP3 has a cardioprotective effect on the heart, and some of them suggested that its effect is two-sided. With in-depth research, scholars are becoming more aware of the complexity of the mechanism, which requires further experiments to confirm.

2.4 MicroRNA

Numerous studies have shown that microRNAs may regulate cytoprotective mechanisms and exert cardioprotection against ischemia–reperfusion [53]. Multiple microRNAs are described as key regulators of cardiocytoprotection and improvement of cardiac function after AMI. Among these microRNAs, miR-1 antagomir delivery exerted a significant protective effect on heart function, decreasing cardiomyocyte apoptosis and alleviating myocardial fibrosis and remodeling in the mouse model of MI. A study has shown that miR-1 antagomir decreased 19s proteasome, 20S proteasome, and ubiquitin ligase E3 levels, which play a pivotal role in the selective recognition and degradation of oxidized proteins. Meanwhile, both miR-21 and miR-146a showed a protective role against hypoxia-induced myocardial apoptosis and inflammation in the context of IRI [54–57]. In addition, miR-125b has been studied well, and knockdown of miR-125b-5p after transfection of its inhibitor results in enhanced post-AMI mortality and left ventricular dysfunction in a mouse model of AMI [58]. In summary, microRNAs have been proven to be involved in the mechanism of IR injury and cardioprotection, and mimics or antagomirs of certain microRNAs may serve as potential multitarget drugs for several cardiovascular pathologies.

2.5 mitochondrial-Derived Vesicles (MDVs) and EVs

Mitochondria are highly dynamic organelles; their function is crucial for maintaining cellular homeostasis. Mitochondrial dysfunction and dysregulation of mitochondrial remodeling processes play critical roles in the pathogenesis of cardiovascular disease [59]. Recently, mitochondrial-derived vesicles (MDVs) have been identified as a novel mechanism in mitochondrial quality control [60]. In cardiomyocytes, the formation of MDVs is a physiological process that is accelerated by oxidative stress [61]. MDVs emerge as an essential quality control mechanism in response to mitochondrial stress, in addition to mitophagy and fission/fusion processes that regulate mitochondrial turnover. MDVs may play a role in the cellular response to hypoxia. MDV formation in rat cardiomyocytes increased initially under hypoxic conditions, but decreased with prolonged hypoxia [62]. Doxorubicin, a chemotherapeutic agent known for its cardiotoxic potential [63], increased the generation of TOMM20+/PDH− and TOMM20−/PDH+ MDVs in rat cardiomyocytes. Doxorubicin-treated C57BL/6 mice exhibited a more than two-fold increase in cardiac MDV budding compared with control mice. MDV formation in the heart was observed under basal conditions and can be regarded as a physiologic process induced in response to cellular stressors, such as oxidative stress, which further modulates MDV cargo loading. Unfortunately, the role of MDVs in human cardiomyocytes or heart tissue, as well as the vascular system, is still unknown [64].

EVs are membrane-bound particles secreted from cells that carry biomolecules, such as proteins, nucleic acids, and lipids [65, 66]. Several studies have found mitochondrial content in EVs, establishing a link between EVs and MDVs. Interestingly, EVs may aid in mitochondrial uptake. Mitochondria-containing EVs improved bioenergetics in hypoxia-injured cardiomyocytes and left ventricular function in a mouse model of myocardial infarction [67]. This was not observed after injection of isolated naked mitochondria, strengthening the idea that vesicular delivery increases mitochondrial uptake. The therapeutic approach of transferring functional mitochondria to damaged cells or tissue, also known as mitochondrial transplantation, is gaining increasing attention [64]. Large animal and clinical trials should be conducted in the future to assess the safety and efficacy of EV-mediated mitochondrial transfer.

3 Cardiac Protection Strategies

3.1 Left Ventricular Unloading of the Heart

Burhoff defines acute left ventricular (LV) unloading as any manipulative, therapeutic, and interventional approach

aimed at reducing total LV mechanical power. Cardiac LV unloading in AMI is aimed at preserving the myocardium, avoiding adverse ventricular remodeling and resulting heart failure [68, 69]. Limiting the size of myocardial infarction by LV unloading was initially used in patients with cardiogenic shock [70–72], or in high-risk patients with PCI and impaired LV function [73, 74].

Impella is a percutaneous interventional microaxial flow pump based on the Archimedean spiral principle, where impeller rotation assists the heart in generating blood flow, increasing cardiac output, peripheral tissue perfusion and coronary blood flow, and prolonging patient survival. Several animal studies have shown that initiating LV unloading via the Impella device reduces myocardial oxygen consumption during the ischemic and reperfusion phases and decreases infarct size [75–77]. Initial research by Meyns et al. in 2003 demonstrated that LV unloading using Impella-reduced myocardial oxygen consumption resulted in correlated infarct size (IS) reduction in a sheep model of AMI [78]. Some studies have demonstrated that the use of the Impella in patients undergoing high-risk coronary interventions can reduce LV end-diastolic pressure, elevate blood pressure, and maintain effective coronary perfusion pressure [79]. In the DTU-STEMI pilot trial (Table 1), patients with AMI were randomized into two groups: one group underwent intervention immediately after Impella implantation, and the other group underwent intervention 30 min after reduction of cardiac LV load with Impella. Interestingly, the study concluded that delayed reperfusion therapy after 30 min of LV load reduction significantly reduced myocardial infarct size in a subset of patients [80]. This demonstrates the safety and feasibility of Impella implantation in humans, and explores a new option for reperfusion therapy in patients with AMI, which needs to be validated in large-scale trials. However, using Impella devices for LV unloading starting prior to revascularization and delaying revascularization requires a femoral 14F access, which is invasive. Meanwhile, the mechanisms by which LV unloading affects the size of myocardial infarction are still unclear. It has been suggested that activation of the RISK pathway may be involved by maintaining the integrity of myocardial energy and mitochondrial function [81], which warrants further research.

3.2 Cryocardial Cooling

TTM (targeted temperature management) has been used to reduce systemic low-flow and no-flow reperfusion injury after cardiac arrest [82–86]. In the ischemic heart, TTM has shown infarct size reduction in several preclinical models with a variety of animal species, ischemia durations, cooling methods, cooling durations, magnitudes of cooling, and timings of cooling initiation [87, 88]. A study in rabbits identified a linear relationship between the myocardial infarct area and temperature when heart rate was controlled and body temperature was maintained at 35–42 °C. Moreover, a reduction in myocardial infarct area could only be achieved when cooling began during the ischemic phase, with no benefit of hypothermia following the initiation of reperfusion [89]. Clinical trials thus far have demonstrated that hypothermic myocardial cooling is beneficial only in patients cooled to < 35 °C and in those with anterior myocardial wall involvement [90]. The COOL-AMI EU trial showed a 40% reduction in myocardial infarct size 4–6 days after myocardial infarction in patients with STEMI using the ZOLL Proteus cooling system to achieve a mean temperature of 33 °C before and after PCI, compared with the PCI-only group [91]. Intracoronary cooling has been proposed as a promising method for improving IRI, which has been demonstrated in a porcine model of myocardial ischemia–reperfusion [92, 93]. The EURO-ICE trial of intracoronary cooling in patients with reperfusion after myocardial ischemia is ongoing [94]. Although the induction of hypothermia is associated with improvements in IRI, it may promote platelet activation, delay reperfusion, and cause hemodynamic instability when large amounts of cold fluid are infused.

3.3 Coronary Sinus Intervention

Increased coronary sinus pressure can induce a retrograde perfusion gradient in the ischemic myocardium and improve myocardial perfusion. Therefore, myocardial ischemia can be improved by regulating coronary sinus pressure. Existing methods of coronary sinus intervention include the retroperfusion technique, retroinfusion, and coronary sinus obstruction techniques [95]. The retroperfusion technique involves active pumping of blood into the coronary sinus, which has been shown to improve myocardial metabolism and reduce myocardial ischemia in animal models [96]. The reperfusion technique involves pumping substances into the coronary sinus, such as blood or other substances. Obstruction of the coronary sinus induces collateral blood flow into the area lacking perfusion. The diversion of blood flow improves subendocardial ischemia, which has been demonstrated in a canine model with anterior descending branch occlusion complicated by coronary sinus occlusion [97]. The most commonly used method of coronary sinus intervention is pressure-controlled intermittent coronary sinus occlusion (PiCSO). A coronary sinus pressure transducer is placed at the coronary sinus orifice, and a gradual increase in coronary sinus pressure can be observed during each cardiac cycle. The balloon is inflated until a pressure plateau (approximately 70 mmHg) is reached and then the balloon is deflated, allowing redistribution of coronary blood flow to the ischemic zone [98]. PiCSO has been shown to reduce cardiomyocyte edema in dogs during AMI and to

Table 1 Clinical trials of cardioprotective strategies

	Cardioac protection strategies	Year	Patients	Conclusions
AMI HOT 1	SSO_2	2007	269	Intracoronary hyperoxemic reperfusion was safe and well tolerated after PCI for AMI, but did not improve regional wall motion, ST-segment resolution, or final infarct size. A possible treatment effect was observed in anterior AMI patients reperfused < 6 h after of symptom onset
AMI HOT 2	SSO_2	2009	301	Among patients with anterior STEMI undergoing PCI within 6 h of symptom onset, infusion of SSO_2 into the LAD infarct territory results in a significant reduction in infarct size with non-inferior rates of MACE at 30 days
COOL-AMI EU	Cryocardial cooling	2017	50	There was no excess of adverse events and no clinically important cooling-related delay to reperfusion. A statistically non-significant numerical 7.1% absolute and 30% relative reduction in infarct size warrants a pivotal trial powered for efficacy
Low-lLevel tragus stimulation for the treatment of ischemia and reperfusion injury	Stimulation of the vagus nerve	2017	95	LL–-TS reduces myocardial ischemia-reperfusion injury in patients with STEMI. This proof-of-concept study raises the possibility that this noninvasive strategy may be used to treat patients with STEMI undergoing primary percutaneous coronary intervention
IC-HOT	SSO_2	2019	100	Following primary PCI in acute anterior STEMI, infusion of SSO_2 via the LMCA was feasible and was associated with a favorable early safety profile
DTU-STEMI	LV unloading	2019	50	We report that LV unloading using the Impella CP® device with a 30-minute delay before reperfusion is feasible within a relatively short time period in anterior STEMI
PiCSO in ACS study	Coronary sinus intervention	2020	45	PiCSO, as an adjunct to pPCI, was associated with a lower infarct size at 5 days after anterior STEMI in a propensity score-matched population
CAMI-1	CRP mono-collection	2021	93	This pilot study in humans reveals a correlation between CRP concentration and MI size. CRP concentrations in STEMI can effectively be reduced by CRP apheresis without relevant side effects. CRP apheresis has the potential to interfere with deleterious aspects of STEMI. By lowering CRP levels, it resulted in the loss of correlation of CRP concentrations with MI sizes as well as LV function

ACS acute coronary syndromes, *AMI* acute myocardial infarction, *CRP* C-reactive protein, *LAD* left anterior descending coronary artery, *LL–-TS* low-level tragus stimulation, *LMCA* left main coronary artery, *LV* left ventricular, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PiCSO* pressure-controlled intermittent coronary sinus occlusion, *pPCI* primary PCI, *SSO_2* supersaturated oxygen therapy, *STEMI* ST-segment elevation myocardial infarction

accelerate the removal of harmful molecules [99]. Khattab et al. showed that PiCSO improved coronary perfusion pressure and improved myocardial oxygen consumption in a porcine closed-chest infarction model [100]. A clinical trial of PiCSO also demonstrated a reduction in myocardial infarct size in patients with STEMI in the anterior approach, which demonstrates the safety of PiCSO as an adjunctive therapy. The first randomized controlled trial of PiCSO is underway in patients with AMI (PiCSO-AMI-I; NCT03625869), which will determine the effect of PiCSO on myocardial infarction by CMR on day 5. Another randomized controlled trial (PiCSO-AMI-II) is ongoing in Europe and North America. The trial enrolled 300 patients with anterior STEMI presenting within 12 h of symptom onset. The primary efficacy endpoint was infarct size measured by CMR at 5 days. The primary safety endpoint was the performance target for device- and procedure-related adverse events at 30 days. Major adverse cardiac events and heart failure endpoints will be captured in the acute phase and up to 3 years.

3.4 Supersaturated Oxygen

The rationale for investigating the benefit of increasing plasma oxygen tension during myocardial ischemia has been provided by experiments that revealed both increase in coronary blood flow and ischemia alleviation during hyperoxia [101, 102]. A 1950s animal study of coronary sinus obstruction showed that the mortality rate in animals with coronary occlusion decreased with increased coronary sinus pressure [103]. Chardrack et al. ligated the coronary arteries of 162 dogs and the survival rate of the dogs was 52.5% at 1 atmosphere and rose to 77.8% at 4 atmosphere [104]. Several animal studies have demonstrated that hyperbaric oxygen improves IRI, reduces myocardial infarct size, and improves survival [105, 106]. Subsequently, researchers found that water carries ten times more oxygen than blood, and the application of water–oxygen reperfusion in animal experiments improved LV function and reduced infarct size [107]. Multiple studies have since demonstrated the benefits of SSO_2. In 2002, a US–Italian multicenter study of 29 post-PCI patients with acute infarction treated with hyperbaric oxygen using the TherOx® device for 60–90 min demonstrated the safety of SSO_2 [108]. In 2007, the AMI HOT trial demonstrated the benefits of SSO_2 for adjunctive treatment of patients with anterior myocardial infarction within 6 h of symptom onset [109]. The 2019 IC-HOT trial demonstrated the feasibility and safety of transfusion of SSO via the left main coronary artery [110]. Starting in 2021, the TherOx® device has been routinely used as an adjunctive therapy for myocardial infarction at the Hannover Medical School [111]. In the same year, the ISO-SHOCK trial, which evaluated the administration of SSO_2 into the coronary arteries of patients with acute myocardial infarction and cardiogenic shock, was initiated with an anticipated completion date of 2025.

3.5 Stimulation of the Vagus Nerve

The vagus nerve is the main parasympathetic component of the body and is vital for maintaining physiological activity. The main effects of the vagus nerve on the heart include lowering heart rate, slowing atrioventricular conduction, and decreasing myocardial contractility [112]. IRI can activate the sympathetic nerve, further complementing and aggravating myocardial injury. Activation of the vagus nerve by electrical stimulation, pressure, or chemical reflexes, which further reduces heart rate and increases coronary blood flow through NO-dependent mechanisms, may improve myocardial ischemia [113]. In a rat model of AMI, stimulation of the vagus nerve had protective effects on the heart, likely due to the activity of glucagon-like peptide 1 [114]. Stimulation of the vagus nerve also reduced the production of mitochondrial ROS in pigs, significantly reducing the size (about 59%) of myocardial infarction and the probability of ventricular fibrillation [115]. In a randomized controlled trial, patients undergoing PCI for STEMI were divided into two groups; the low-level tragus stimulation (LLTS) combined with sham group, and a LLTS alone group, where stimulation was performed 2 h after reperfusion. The results showed a decrease in cardiac biomarkers and an improvement in left ventricular ejection fraction in the LLTS alone group [116]. Vagus nerve stimulation is often accompanied by side effects such as nausea, vomiting, dizziness, and hoarseness. To improve the specificity of vagus nerve stimulation for cardioprotection, many selective vagus nerve stimulation (sVNS) models have been developed, such as fiber selective stimulation, spatially selective stimulation, and kilohertz electrical stimulation [117]. According to the current study, several mechanisms have been related to cardioprotection through efferent vagal stimulation, including improved mitochondrial function, attenuation of ROS formation, antiapoptotic cardiomyocyte signaling, and reduction of systemic and local inflammatory responses [118]. It is useful to continue to research the mechanisms by which the vagus nerve protects the cardiovascular system.

3.6 Remote Ischemia Regulation

Davidson et al. proposed a mechanistic basis for cardioprotection based on the mode of protection, time of application, cellular targets and intracellular targets. It can be divided into ischemic regulation, pharmacological cardioprotection, and physical intervention. Among them, ischemic modulation can be further divided into preischemic injury modulation, postischemic injury modulation, and RIC. As of now, RIC seems to be the most promising method for cardiac repair. RIC is the application of reperfusion to the vascular bed, corresponding tissues, and organs after a short period of ischemia. These ischemic reperfusions allow tissues and organs far from the point of application to resist damage caused by reperfusion after prolonged ischemia. Loukogeorgakis et al. investigated the neuromodulatory process of distal ischemic preconditioning of endothelial cells (RIPC). The early phase of RIPC is 4 h, followed by a maintenance phase that lasts for at least 48 h after 24 h of RIPC stimulation [117]. Their study found that the use of the autonomic ganglion blocker trimethaphan (trimethaphan 16 mg/min intravenous infusion) reduced both the early and maintenance phases of RIPC, suggesting that protection in both phases is dependent on preservation of autonomic function [119–122]. The exact mechanism of cardioprotection by RIC is not yet fully understood. In particular, it has been suggested that RIC involves the activation of three different pathways: the humoral, the neuronal, and the systemic pathway. Studies suggest that RIC may activate defense mechanisms in the cardiovascular system through humoral pathways and neuronal pathways at distal stimulation sites. They depend on

the anatomical site (renal, mesenteric, or skeletal muscle) in which the ischemia–reperfusion stimulus has been applied. For instance, adenosine and erythropoietin are involved in RIC induced by renal IR, while bradykinin, cannabinoids, opioids, and CGRP, or adenosine, NO, opioids, noradrenaline, ROS, apolipoprotein-A-I, GLP- 1, stromal cell-derived factor-1a, prostanoids, IL-10, glycine, exosomes, and microRNAs can account for RIC after mesenteric or skeletal muscle ischemia–reperfusion, respectively. RIC reduces the platelet activation process of IRI and attenuates endothelial injury and inflammatory processes [123–126]. EVs have been proposed as a source of RIC signaling that initiates the protective effect of ischemia–reperfusion [127]. The specific mechanisms underlying these effects must be further explored.

3.7 C-Reactive Protein Monocollection

C-reactive protein (CRP) is a non-specific marker of inflammation and is one of the key players in the body's natural immune barrier. CRP is associated with inflammation, infection, malignancy, and cardiovascular disease. CRP is also a mediator of myocardial infarction, which may promote localized tissue damage [128]. Elevated CRP predicts second-year heart failure, as well as cardiovascular mortality in patients with STEMI [129]. Therefore, lowering CRP levels is a potential method by which to reduce reperfusion injury [130]. The CAMI-1 clinical trial of 83 patients with STEMI showed that single extraction reduced CRP levels and did not correlate with final infarct size (FIS) or LV function [131]. A randomized controlled trial (NCT04939805) using CRP monocollection as an adjunctive treatment for patients with STEMI is currently underway in Austria and Germany, with results expected in the coming years.

4 Conclusion

Stenosis and occlusion of coronary arteries can lead to myocardial ischemia and infarction. Early unblocking of coronary arteries and restoration of blood flow reconstruction can reduce the infarcted area of the myocardium and improve prognosis. However, animal tests have demonstrated that almost half of the infarct size can be attributed to IRI [132, 133]. As a result, many scholars have focused their attention on cardioprotective mechanisms and strategies. Current studies suggest that SUMOylation of multiple substances in the cytoplasm and mitochondria can have cardioprotective effects. Several members of the miRNA family play important roles in cardioprotection. NLRP3 regulates a variety of signaling pathways. MDVs and EVs may be involved in mitochondrial translocation. All of these could be targets for cardioprotection.

Myocardial infarct size partially determines the prognosis of patients with myocardial infarction, although regular administration of antiplatelet agents as well as statins after PCI does not greatly reduce the incidence of heart failure and recurrent myocardial infarction. Therefore, mitigating the potential for myocardial injury as a result of postischemic reperfusion and reducing the size of myocardial infarction, have become important research areas of

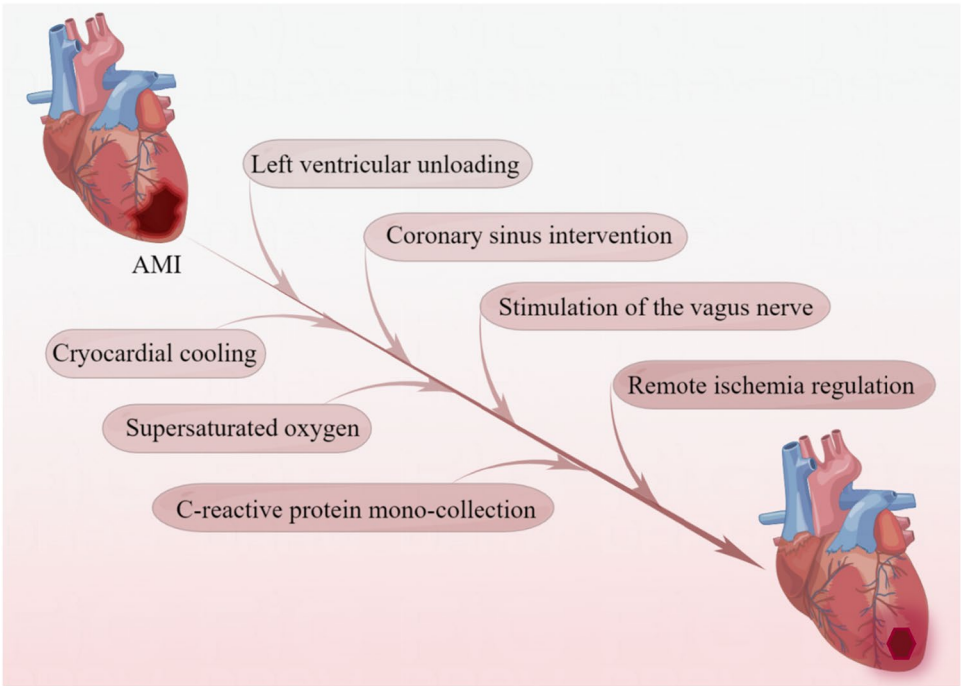

Fig. 2 Cardioprotective strategies after ischemia–-reperfusion injury.

focus. Recently, cardiac-assisted protection methods have shown potential for improving prognosis in patients with myocardial infarction. LV unloading, myocardial cooling, coronary sinus intervention, SSO_2, stimulation of the vagus nerve, RIC, and CRP monocollection are effective cardioprotection methods that have been identified in recent years (Fig. 2). Most of these methods may prolong the time in the catheterization chamber, except for CRP monophoresis. However, only SSO_2 has been shown to reduce myocardial infarct size in patients with antegrade STEMI. In addition to this, some studies have found that low doses of carbon monoxide can maintain the stability of the mitochondrial membrane potential and may have cardioprotective effects [134].

Unfortunately, although cardioprotective strategies are effective in reducing myocardial infarct size in some populations, they have low benefit in metabolic syndrome populations. Metabolic syndrome is known to be an important risk factor for myocardial ischemia, such as diabetes and obesity. Studies suggest that the diabetic heart is resistant to cardioprotective strategies, although clinical evidence is lacking [135]. Meanwhile, data suggest that susceptibility to the IR damage is increased and cardioprotection effectiveness is reduced in obesity [136]. In addition, being old has been identified to be an independent determinant of the extension of AMI and the outcome of cardioprotective strategies after an ischemia–reperfusion episode [137]. There have also been studies showing that the estrogen status of females modulates the susceptibility of the heart to IRI. Similarly, reduction in testosterone levels in older men worsens cardiovascular outcomes [138–140]. Future research on cardioprotection could focus on metabolic syndrome, older adults, and sex.

Most of the cardioprotective strategies discussed in this review have been validated in animal studies, and large-scale clinical trials are needed to confirm the results reported so far. Meanwhile, more research is needed to understand the mechanisms of cardioprotection and associated signaling pathways, which can provide new approaches for the prevention of IRI.

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