Chapter

Advancement in Reperfusion Injury Awareness and Mitigation

Vashisth Bhavsar, Ashish Patel, Shantilal Padhiyar, Tejas B. Patel and Vipul Prajapati

Abstract

Understanding reperfusion damage, raising knowledge of its underlying processes, and creating measures to lessen its negative consequences have all seen significant progress over time. The developing knowledge of the pathophysiological processes, such as oxidative stress, inflammation, calcium excess, and mitochondrial dysfunction, that lead to reperfusion damage. Clinicians may now identify biomarkers and use modern imaging techniques to identify reperfusion damage in its early phases, allowing for prompt treatment and better patient outcomes. Real-time evaluation of tissue viability during reperfusion is now possible thanks to the development of non-invasive monitoring techniques, which supports clinical judgment. The use of pharmaceutical substances that target certain pathways, such as antioxidants, anti-inflammatory substances, and calcium homeostasis regulators. Additionally, cutting-edge approaches like therapeutic hypothermia and remote ischemia conditioning have demonstrated promise in lowering reperfusion damage and enhancing patient prognosis. Our knowledge of the underlying processes has considerably increased thanks to improvements in reperfusion injury recognition and mitigation, which have also created new opportunities for therapeutic intervention. These developments are anticipated to result in more efficient methods for reducing reperfusion damage and eventually enhance patient outcomes in a variety of therapeutic situations via continuing study and cooperation.

Keywords: awareness, mitigation, reperfusion, injury, oxidative, inflammatory

1. Introduction

When blood flow is restored to tissues or organs after a time of insufficient blood supply, damage to the afflicted region results. This process is known as ischemia-reperfusion injury (IRI). This phenomena may have important effects on a number of medical disorders, such as trauma, organ transplantation, stroke, and heart attack. In order to reduce tissue damage and enhance patient outcomes, it is essential to understand the processes driving IRI.

Ischemia means reduced blood flow to a tissue or organ, causing a lack of essential nutrients and oxygen needed for normal operation. Several factors like blocked blood vessels, narrowed arteries, or decreased heart output can lead to this reduced blood

flow. Ischemia can have severe effects as tissues need a constant supply of oxygen and nutrients for their proper functioning [1].

Reperfusion is the process of restoring blood flow to ischemic tissue when a deficiency in blood supply has occurred. Reperfusion, however important to stop irreversible tissue damage, paradoxically can also cause more harm. A series of biochemical and cellular changes that take place after the blood flow is restored and the successive damage which will occur is, known as ischemia-reperfusion damage [2].

Adenosine triphosphate (ATP) is produced through the process of glycolysis when there is an oxygen shortage, which occurs during ischemia. This method is less effective. It leads to the elevation of metabolic waste products including lactate and reactive oxygen species (ROS). The quick rush of oxygen that occurs during reperfusion when blood flow is restored sets off a chain of events that exacerbates cellular damage [3].

The production of ROS, which includes superoxide anions, hydrogen peroxide, and hydroxyl radicals, is one of the main processes underpinning IRI. ROS are very reactive chemicals that harms lipids, proteins, and DNA as well as other biological components. Overwhelming antioxidant defense systems caused by excessive ROS generation result in oxidative stress and the start of inflammatory pathways [4].

After the rise of ROS it accompanies the increased inflammatory response is which is very critical. Tumor necrosis factor-alpha (TNF-alpha) and other pro-inflammatory cytokines are released after reperfusion, activating immune cells and drawing leukocytes to the site of damage. This inflammatory reaction is amplified by the immune cell invasion, leading to tissue dysfunction and damage [5].

Beyond this there is excessive release of excitatory amino acids like glutamate brought on by reperfusion damage. When too much glutamate binds to its receptors on neurons, such as NMDA receptors, AMPA receptors, and kainate receptors excitotoxicity happens. This results in an influx of calcium ions and eventual neuronal cell death. This mechanism is very important when it comes to stroke and brain damage [5].

Depending on the tissue or organ involved, ischemia-reperfusion damage may have different effects. IRI, for instance, can cause myocardial infarction, arrhythmias, and even myocardial stunning in the heart. IRI can lead to acute kidney injury and renal dysfunction in the kidneys. Similar to this, IRI can reduce liver graft function and raise the possibility of organ rejection.

The development of prospective treatment strategies has been made possible by our growing understanding of IRI's underlying processes. In experimental investigations, methods for lowering oxidative stress, controlling the inflammatory response, and avoiding excitotoxicity have showed promise. Aside from that, protective benefits have been shown for strategies such ischemic preconditioning, which applies small bouts of ischemia prior to the protracted ischemic insult [6].

IRI takes place when blood flow is restored to ischemic tissues or organs, a complicated pathological. It involves a series of actions that lead to tissue damage, such as oxidative stress, inflammation, and excitotoxicity. To improve patient outcomes for different medical conditions, we might find the answer in understanding the hidden processes and developing specific treatments that can reduce the negative effects of IRI.

2. Advanced pathological causes of ischemia reperfusion injury

When blood flow is restored to previously ischemic (lack of blood supply) tissue, harm known as ischemia-reperfusion occurs. It may have an impact on the heart,

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brain, liver, and kidneys, among other bodily organs. Ischemia-reperfusion damage has complicated underlying mechanisms that include several pathogenic processes. Advanced pathogenic causes of ischemia-reperfusion damage include the following:

1. Oxidative stress: The abrupt return of oxygen during reperfusion of ischemic tissue results in the production of reactive oxygen species (ROS). Cell injury and death can result from ROS-induced oxidative damage to cellular components such lipids, proteins, and DNA [7].

2. Inflammation: Ischemia-reperfusion causes an inflammatory reaction that is characterized by the discharge of pro-inflammatory chemicals, the attraction of immune cells, and the activation of several signaling pathways. Excessive inflammation can increase the damage brought on by ischemia-reperfusion and lead to tissue injury [8].

3. Ischemia disturbs the normal calcium equilibrium in cells, resulting in calcium excess. When blood flow is resumed, there is a sudden inflow of calcium, which causes an excess of intracellular calcium. The degradation of cellular membranes and proteins by enzymes such phospholipases and proteases, which are activated by high calcium levels, can lead to cell death [9].

4. Mitochondrial impairment: Mitochondrial function may be impaired by ischemia-reperfusion damage. The absence of oxygen causes diminished ATP synthesis and a buildup of metabolic waste products during ischemia. The abrupt return of oxygen once blood flow has been restored might cause mitochondrial enlargement, reduced ATP synthesis, and increased ROS production, aggravating cellular damage [10].

5. Endoplasmic reticulum stress: Ischemia-reperfusion may impair ER function, resulting in the buildup of unfolded or improperly folded proteins within the ER

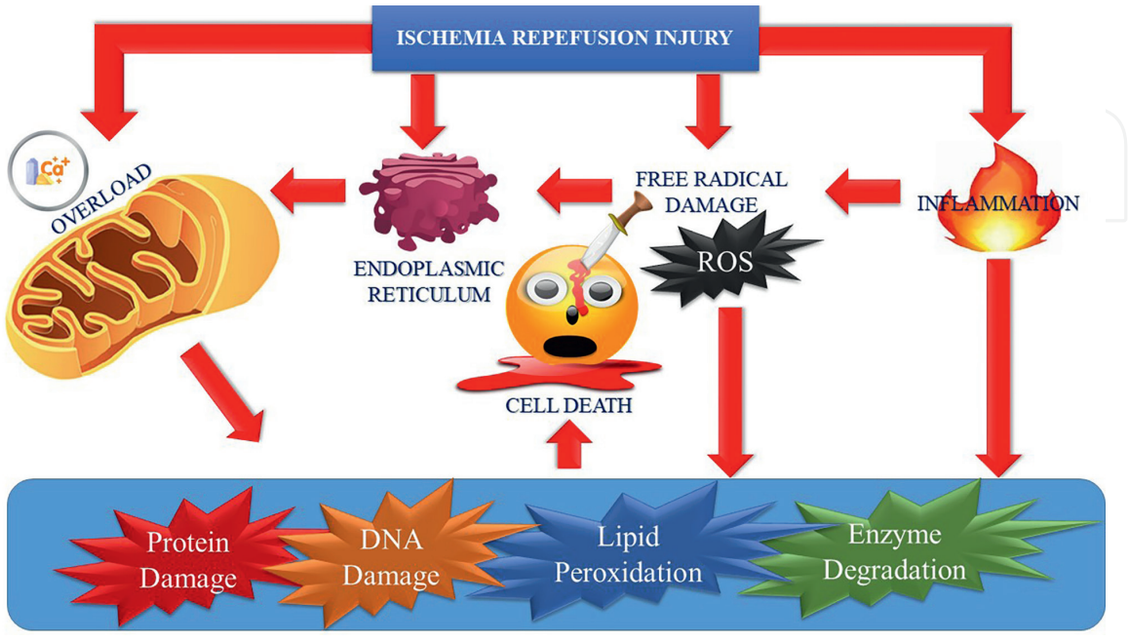

Figure 1.
Reperfusion.

lumen. This results in ER stress and the unfolded protein response (UPR), which can cause tissue damage and cell death [11].

6. Autophagy dysregulation: Autophagy is a cellular mechanism that breaks down and recycles damaged proteins and organelles. The normal control of autophagy can be upset by ischemia-reperfusion, which can result in either excessive autophagy (autophagic cell death) or deficient autophagy (accumulation of damaged cellular components), both of which can cause tissue damage [12].

These are a few of the more complex pathological causes of harm from ischemia and reperfusion. It's crucial to keep in mind that these processes are linked and may interact, enhancing the total harm done to the afflicted tissue. In order to reduce the effects of ischemia-reperfusion damage, treatment techniques can be developed with the aid of an understanding of these processes (**Figure 1**).

3. Therapeutic advancement and mitigation in treatment of ischemia reperfusion injury

Medical research is currently investigating improvements in therapy techniques and mitigation strategies for IRI. The following are some areas of concentration and prospective treatments that have made progress:

3.1 Mitochondrial-targeted therapies

Mitochondria play a critical role in IRI. Recent studies have focused on developing therapies that specifically target and protect mitochondria during reperfusion. To alleviate mitochondrial malfunction and lessen tissue damage, these strategies include antioxidants, peptides, and medications that specifically target the mitochondria [13]. The so-called "powerhouses of cells," mitochondria, are essential for sustaining cellular energy metabolism and controlling cell death pathways. The lack of oxygen and nutrients during ischemia causes mitochondrial malfunction and the buildup of reactive oxygen species (ROS), both of which eventually result in cell death [14]. Reperfusion causes an increase in ROS due to the abrupt restoration of oxygen, aggravating the damage. Mitochondrial-targeted medicines seek to reduce IRI by targeting oxidative stress and mitochondrial malfunction directly. In this field, a number of strategies have been investigated:

1. Mitochondrial antioxidants: To remove ROS and lessen oxidative stress, these substances directly target the mitochondria. Examples include SS-31, MitoQ, and MitoTEMPO. These antioxidants are able to reduce cell death pathways and enhance tissue repair by lowering mitochondrial oxidative damage.

2. Mitochondrial pore modulators: A crucial process that results in cell death is the opening of the mitochondrial permeability transition pore (mPTP) during IRI. Medications like sanglifehrin A and cyclosporine A target the mPTP and stop it from opening, maintaining mitochondrial function and lowering cell death [15].

3. Mitochondrial biogenesis inducers: Improving mitochondrial biogenesis, the process of creating new mitochondria, has demonstrated potential as a defense

against IRI. A number of substances, including resveratrol, PGC-1 activators, and exercise mimics, stimulate mitochondrial biogenesis and enhance cellular energetics, improving tissue lifespan [16].

4. Stabilizers of the mitochondrial membrane: The mitochondrial membrane's integrity is essential for preserving mitochondrial activity. The mitochondrial membrane is stabilized by substances like TRO40303 and elamipretide, preventing IRI from rupturing it and sustaining mitochondrial activity.In preclinical and early clinical investigations, these mitochondrial-targeted treatments have showed promise, highlighting their potential to lower IRI and improve patient outcomes [17]. To improve treatment plans, identify the most efficient therapeutic agents and doses, and evaluate long-term safety, further study is still required. Therapies that target the mitochondria provide a precise and cutting-edge way to reduce ischemia-reperfusion harm. These treatments have the potential to considerably enhance patient outcomes in a variety of medical illnesses where IRI plays a key role by particularly treating mitochondrial malfunction and oxidative stress. To fully grasp these interventions' therapeutic potential and turn them into successful patient treatments, more clinical trials and research are required [18].

3.2 Ischemic conditioning

Before the major ischemic event, tissues are subjected to small bouts of ischemia and reperfusion. This process is known as ischemic conditioning. Techniques for pre- and post-conditioning have showed promise in lowering IRI. The damaged organ is subjected to cycles of brief durations of ischemia and reperfusion using these techniques, which activates adaptive mechanisms and provides protection from further IRI.

1. Preconditioning is the process of introducing a protective state into a tissue or organ before an ischemia event takes place. This tactic entails exposing the tissue to numerous pharmacological stimuli or substances for brief intervals of sublethal ischemia [19]. Preconditioning aims to activate endogenous protective pathways and defensive systems that offer protection from ensuing protracted ischemia. Preconditioning is caused by a number of intricate processes, including signaling pathways involving adenosine, nitric oxide, protein kinases, and reactive oxygen species. These pathways set off a series of actions that eventually promote tissue healing after reperfusion, boost cellular survival, and reduce inflammation. Preconditioning has been investigated in different organs, including the heart, brain, liver, and kidneys, and has shown promising results in reducing IRI and improving functional outcomes [20].

2. On the other hand, postconditioning entails putting preventative measures in place right away once blood flow has been restored. This method seeks to interfere in the crucial early reperfusion phase, when damage processes are either begun or enhanced. A series of short cycles of ischemia and reperfusion or the injection of certain pharmacological substances are frequently used in postconditioning [21]. Interrupting harmful processes including oxidative stress, calcium excess, inflammation, and cell death pathways that are brought on by reperfusion is the aim. Postconditioning methods enable the reduction of tissue damage, maintenance of organ function, and improvement of damaged tissue healing [17].

3. Techniques for preconditioning and postconditioning both have the potential to lessen ischemia reperfusion damage and enhance patient outcomes. These methods have been thoroughly investigated in preclinical models and have proved effective in testing. The intricacy of the underlying systems, the need for more clinical studies, and other variables have made it difficult to translate these ideas into clinical practice. Nevertheless, current research continues to develop and examine these methods in an effort to create efficient therapies that can prevent ischemia reperfusion harm to organs and tissues and enhance patient outcomes in a variety of clinical contexts [22].

4. Certain receptors, including those for A3 adenosine, δ opioids, α_1 norepinephrine, β_2 bradykinin, UCN, and APN-BPN, up-regulate the mitochondrial permeability transition pore (mPTP) during the preconditioning phase. This causes an excess production of porins, which damages DNA and reduces the production of crucial proteins. In the preconditioning phase, prosurvival kinases like Akt and Erk1/2 are activated, which reduces the damage sustained after IRI damage [23] (**Figure 2**).

Techniques for pre- and post-conditioning are crucial tactics in the study of ischemia reperfusion damage. These methods have a great deal of promise for minimizing tissue injury, promoting tissue repair, and boosting patient outcomes in a variety of therapeutic settings. These methods will be improved by additional research and developments in our knowledge of the underlying systems, which will also open the door for their application in clinical settings [4, 11].

3.3 Pharmacological interventions

The ability of several pharmacological treatments to lower IRI has been researched. Adenosine receptor agonists, bradykinin receptor agonists, nitric oxide

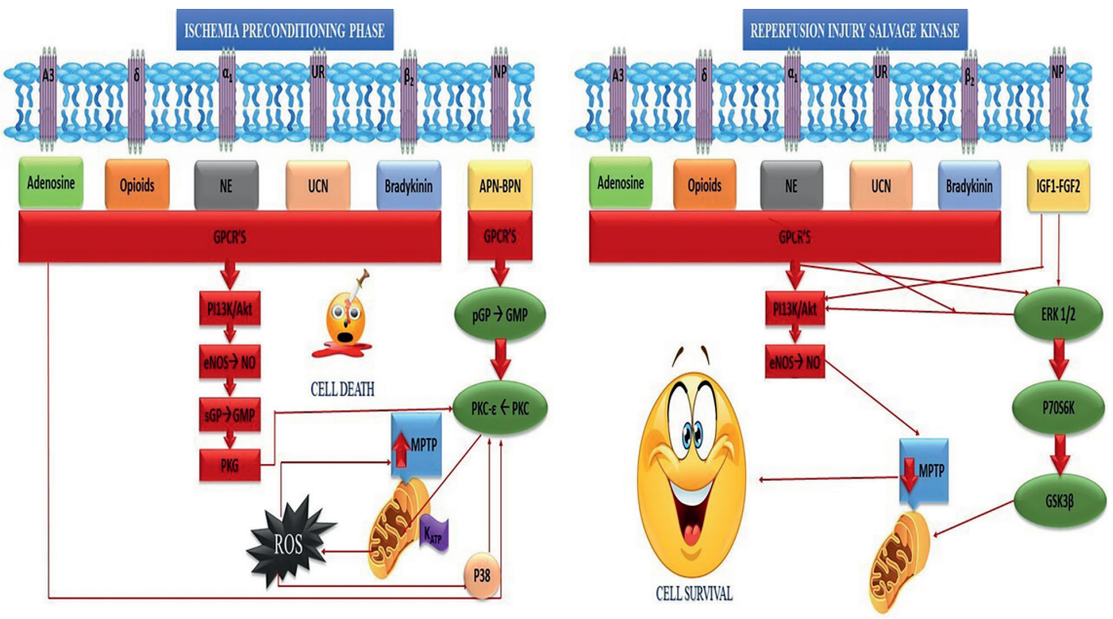

Figure 2.
Advantages preconditioning and postconditioning.

donors, and anti-inflammatory medications are a few examples. These medications work by minimizing oxidative stress, decreasing inflammation, and enhancing blood flow, among other IRI-related processes.

1. Opponents of the adenosine receptor An endogenous nucleoside known as adenosine interacts with the body's A1, A2A, A2B, and A3 receptors. In several organs, including the heart, liver, and kidneys, adenosine receptor agonists have shown protective benefits against IRI [24]. These agonists work by decreasing inflammation, encouraging vasodilation, and preventing the production of mediators that cause inflammation. These substances can lessen tissue damage brought on by IRI by triggering adenosine receptors [25].

2. Bradykinin, a peptide that regulates pain and inflammation, has antagonists for its receptor [26]. Vasodilation, enhanced vascular permeability, and the release of anti-inflammatory chemicals have all been linked to bradykinin receptor activation. In the context of cardiovascular disorders, bradykinin receptor agonists have been studied for their ability to mitigate IRI-induced damage. These agonists can aid in the defense against IRI by encouraging vasodilation and decreasing inflammation [16].

3. Donors of Nitric Oxide: Nitric oxide (NO) is a signaling molecule that plays a role in a number of physiological processes, such as vasodilation, anti-inflammation, and the inhibition of platelet aggregation [27]. NO has been demonstrated to have protective benefits in the setting of IRI by increasing blood flow, lowering oxidative stress, and preventing leukocyte activation. Compounds that release nitric oxide (NO) gradually are known as nitric oxide donors. It has been investigated if certain donors, such as organic nitrates and nitrovasodilators, can reduce IRI by increasing NO bioavailability and exerting vasoprotective and anti-inflammatory effects [28].

4. Anti-inflammatory medications: IRI is characterized by inflammation, and treating this inflammatory response has been the main goal of treatment approaches [29]. Anti-inflammatory medications have been researched for their ability to lessen IRI, including corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and immunomodulatory therapies. These medications can reduce immune cell activation, limit the synthesis of inflammatory mediators, and lessen the tissue damage brought on by IRI. Anti-inflammatory medications have the potential to improve IRI in multiple organs by modifying the inflammatory response [30].

Anti-inflammatory medications, nitric oxide donors, adenosine receptor agonists, and bradykinin receptor agonists have shown promise in preventing ischemia-reperfusion damage. These pharmacological medicines can aid in preventing tissues and organs from suffering injury as a result of ischemia and subsequent reperfusion by specifically targeting IRI-related pathways such inflammation, vasoconstriction, and oxidative stress. To investigate their efficacy, ideal dosage, and potential adverse effects in various therapeutic circumstances, more investigation and clinical trials are required.

3.4 Stem cell therapy

Therapies based on stem cells have demonstrated promise in reducing IRI. In particular, the capacity of mesenchymal stem cells (MSCs) to control inflammation, encourage tissue repair, and improve angiogenesis has received substantial research. In preclinical research and early clinical trials for IRI in multiple organs, MSCs have shown encouraging outcomes.

1. Modulation of Inflammation: MSCs' immunomodulatory abilities allow them to control the immune system and lessen inflammation. They can influence the activity and performance of immune cells such T cells, B cells, natural killer (NK) cells, and macrophages [31, 32].

2. MSCs can develop into a variety of cell types, including osteoblasts, chondrocytes, adipocytes, and myocytes, therefore promoting tissue repair. They also release a variety of bioactive chemicals, including growth factors, cytokines, chemokines, and extracellular vesicles, that aid in tissue healing [33, 34].

3. Angiogenesis is boosted: MSCs have pro-angiogenic qualities and can encourage the growth of new blood vessels. They release angiogenic substances such fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF), which promote endothelial cell migration, proliferation, and the development of capillary-like structures [35, 36].

4. MSCs have extraordinary capacities to control inflammation, encourage tissue healing, and boost angiogenesis. Due to these qualities, they are promising therapeutic agents in regenerative medicine and have a huge potential for the treatment of a wide range of ailments, wounds, and tissue damage.

3.5 Remote ischemic conditioning (RIC)

In RIC, a remote organ or tissue is subjected to brief episodes of ischemia and reperfusion, which causes the target organ to activate defense systems. IRI has been successfully decreased by RIC in a variety of organs, including the heart, kidney, and liver. It is a non-invasive method that can be economical and have several uses in clinical practice [37]. In RIC, a blood pressure cuff is repeatedly inflated and deflated on a limb, causing momentary episodes of ischemia and reperfusion. The temporary ischemia episodes trigger a protective response in distant organs, improving tolerance for ischemic assaults in the future. The possibility of RIC to lessen tissue damage during cardiac surgery, heart attacks, strokes, organ transplantation, and other ischemia-related disorders has been studied. Pharmacological RIC: In order to duplicate the preventive benefits of RIC without requiring physical treatments, researchers are investigating the use of pharmacological medicines [38]. For instance, the capacity of medications like adenosine, erythropoietin, and distant ischemic preconditioning (RIPerC) mimetic compounds to pharmacologically produce RIC-like effects has been studied.

1. Remote ischemia Preconditioning (RIPC) is a technique for preventing further ischemia damage by administering RIC before the ischemic stimulus. To improve RIPC protocols, novel strategies have been devised, such as figuring out the appropriate conditioning time, cycles, and length.Researchers are examining the

synergistic benefits of integrating remote ischemic conditioning (RIC) with different treatment modalities. Examples include combining RIC with stem cell therapy, therapeutic hypothermia, and medication therapies in an effort to increase the overall protective benefits [39].

2. The value of RIC Cardiovascular Health: RIC has demonstrated potential in lowering the extent of myocardial infarctions, enhancing heart function, and minimizing negative outcomes in patients having cardiac surgeries. Patients with heart failure, coronary artery disease, and other cardiovascular disorders could possibly benefit from it. Neuroprotection: In stroke patients, RIC has shown potential neuroprotective benefits that may lessen ischemic brain damage and enhance neurological outcomes [40]. The best RIC protocols for various stroke subtypes are still being investigated, as is the use of RIC in neurodegenerative illnesses. Renal Protection: RIC has been investigated for its capacity to safeguard the kidneys from ischemia harm after heart surgery and kidney transplantation. The ability to lessen acute kidney damage and enhance renal function has been demonstrated. Other Potential Applications: RIC is being investigated in a number of other domains, including limb ischemia, sepsis, spinal cord damage, and liver transplantation, among others [36, 41, 42].

4. Limitations and challenges in the treatment of ischemia reperfusion injury

Although ischemia–reperfusion damage therapies have come a long way, there are still certain restrictions and difficulties. A few of these are:

1. Duration sensitivity: Treatments for ischemia-reperfusion damage must be effective quickly. The damage after reperfusion will be more severe the longer the ischemia phase lasts. Rapid response is essential, however in some circumstances, it might not be possible because of delays in identifying the issue or getting medical help [21].

2. There is a limited therapeutic window for effectively treating ischemia-reperfusion damage [43]. In order to avoid excessive damage without running the danger of negative side effects, therapies must be given at the proper time. This might be difficult, especially in urgent situations or uncertain clinical settings.

3. The absence of particular remedies despite the fact that there are broad steps to reduce ischemia-reperfusion harm is still a problem. It is still difficult to create treatments or medications that prevent reperfusion damage without sacrificing the positive outcomes of reperfusion [44].

4. Patients may be more vulnerable to ischemia-reperfusion damage if they have pre-existing medical problems like diabetes or cardiovascular disease [45]. The intricacy of the healing process is increased by managing these underlying issues at the same time as treating the injury.

5. Additional considerations include patient variability, which makes it difficult to develop therapies that work for everyone and forces the use of individualized

strategies for better results. IRI severity can vary greatly across persons and various organs [46]. IRI is a multi-factorial, intricate process that uses a number of different paths and processes. Trying to address each of these issues at once is challenging. Therapies that focus on particular components of the injury might not be enough to produce the best results [47].

5. Conclusions and future prospective

The management and treatment of many medical diseases have significantly improved as a result of the development in reperfusion injury knowledge and mitigation. Reperfusion damage can have negative consequences and impair patient outcomes because it happens when blood flow is restored to tissues after an interval of ischemia. Healthcare professionals have made outstanding strides in reducing reperfusion damage and enhancing patient outcomes, nevertheless, because to considerable research, cutting-edge technologies, and improved treatment approaches.

The greater comprehension of its underlying processes is one of the most important developments in the knowledge of reperfusion damage. Deeper understanding of the intricate molecular and cellular mechanisms that take place during reperfusion damage has been attained by scientists and researchers [48]. This information has made it possible to create tailored interventions and treatments.

Numerous methods have been investigated in terms of mitigating measures. Antioxidants, anti-inflammatory drugs, and adenosine receptor agonists are a few examples of pharmacological therapies that have demonstrated promising outcomes in lowering reperfusion injury and limiting tissue damage [49]. Reperfusion harm has also been lessened as a result of improvements in medical technology, such as better imaging methods, fresh surgical techniques, and inventive medication delivery systems.

Additionally, better detection and prompt response have resulted from healthcare professionals' greater understanding of reperfusion damage. When individuals at risk for reperfusion injury are identified early, preventative interventions can be done, which lessens the degree and amount of tissue damage [50]. The sharing of information and expertise has been enhanced by multidisciplinary cooperation between doctors, surgeons, pharmacologists, and researchers, resulting in more efficient treatment plans.

However, difficulties continue to persist despite these tremendous gains. Reperfusion damage is still a complicated phenomenon, and further investigation is required to completely understand it [51]. Additionally, meticulous assessment and validation are needed for the conversion of laboratory results into clinical practice. To evaluate the safety and effectiveness of novel medicines and interventions, clinical trials and long-term research are essential.

The improvement of patient outcomes has showed significant promise with awareness and mitigation. Healthcare personnel are now better able to prevent, identify, and treat reperfusion damage because to a mix of scientific advancements, technology advancements, and cooperative efforts [52]. Our capacity to lessen the destructive effects of reperfusion damage and raise the standard of patient care will be further enhanced by ongoing research and the incorporation of new information into clinical practice.

In order to better patient outcomes in the face of this disorder, researchers and physicians continue to focus on creating targeted medicines and understanding the underlying processes [21].

It is unclear why numerous cytoprotective treatments, although showing promise in animal models of acute myocardial IRI, have failed to improve clinical outcomes in IRI patients. As a result, novel mitochondrial targets both inside and outside the particular tissue under IRI need to be the focus of creative techniques in order to enhance the translation of cytoprotective medicines into the clinical context for the benefit of patients. Targeting cytoprotective therapy to the ischemic tissues using nanoparticles and mitochondria with chemical alteration (such as MitoQ and MitoSNO) may increase the effectiveness of tissue protection. Additionally, the identification of the MPTP as well as other mitochondrial channels such as mitochondrial calcium unipors and Na^{+}/Ca^{2+} exchanger may lead to the development of brand-new cytoprotective treatments. Finally, research is required to determine how aging and co-morbid conditions affect the effectiveness of cytoprotective treatments.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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Appendices and nomenclature

ATP	Adenosine Triphosphate
ROS	Reactive oxygen species
TNF-α	Tumor Necrosis Factor-alpha
ER	Endoplasmic Reticulum
MitoTEMPO	(2- (2,2,6,6-Tetramethylpiperidin-1-oxyl-4-ylamino)-2-oxoethyl) triphenylphosphonium chloride
mPTP	Mitochondrial Permeability Transition pore
PGC-1α	Peroxisome proliferator-activated receptor-γ coactivator 1α
NO	Nitric oxide
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
HGF	Hepatocyte Growth Factor
FGF	Fibroblast Growth Factor
VEGF	Vascular Endothelial Growth Factor
RIC	Remote Ischemic Conditioning
RIPerC	Remote Ischemic Preconditioning
MCU	Mitochondrial Calcium Unipors
NCX	Na^{+}/Ca^{2+} exchanger

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Author details

Vashisth Bhavsar[1*], Ashish Patel[2], Shantilal Padhiyar[3], Tejas B. Patel[4] and Vipul Prajapati[3]

1 Department of Pharmacology, Dharamsinh Desai University, Gujarat, India;

2 Department of Chemistry, Charusat University, Changa, Nadiad, Gujarat, India

3 Department of Pharmaceutical Chemistry, Dharamsinh Desai University, Gujarat, India

4 Department of Pharmaceutics, Dharamsinh Desai University, Gujarat, India

*Address all correspondence to: vashisthbhavsar@gmail.com

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