Review Article

Therapeutic strategies for ischemia reperfusion injury in emergency medicine

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Ischemia reperfusion (IR) injury occurs when blood supply, perfusion, and concomitant reoxygenation is restored to an organ or area following an initial poor blood supply after a critical time period. Ischemia reperfusion injury contributes to mortality and morbidity in many pathological conditions in emergency medicine clinical practice, including trauma, ischemic stroke, myocardial infarction, and post-cardiac arrest syndrome. The process of IR is multifactorial, and its pathogenesis involves several mechanisms. Reactive oxygen species are considered key molecules in reperfusion injury due to their potent oxidizing and reducing effects that directly damage cellular membranes by lipid peroxidation. In general, IR injury to an individual organ causes various pro-inflammatory mediators to be released, which could then induce inflammation in remote organs, thereby possibly advancing the dysfunction of multiple organs. In this review, we summarize IR injury in emergency medicine. Potential therapies include pharmacological treatment, ischemic preconditioning, and the use of medical gases or vitamin therapy, which could significantly help experts develop strategies to inhibit IR injury.

Key words: Emergency medicine, inflammation, ischemia reperfusion, remote ischemic preconditioning, shock, therapeutic hypothermia

INTRODUCTION

When an organ or area of tissue is deprived of its blood supply, return of blood flow to the ischemic area is essential to prevent irreversible tissue necrosis and secure organ function. However, following this return of perfusion and concomitant reoxygenation, a paradoxical tissue response marked by initial inhibition of blood supply to an organ can happen. Such a pathological condition is known as ischemia and reperfusion (IR) injury and has been a focal point for clinical and basic research. Ischemia reperfusion injury augments pathologies in many conditions in the field of emergency medicine, including hemorrhagic shock and resuscitation, acute coronary syndrome, usage of surgical tourniquet, limb injury, and cerebral ischemia.

In this review, we aim to explain the pathophysiology of IR injury, which could provide emergency physicians with a strong basis for the investigation of novel therapeutic strategies for overwhelming IR injury-induced organ damage. We also summarize existing and possible approaches to the treatment of IR injury that have evolved from emergency/critical care medicine research. Although regional IR injury to a single organ is emphasized, we also discuss other conditions such as systemic reduction of perfusion and resuscitation that share similar pathophysiological mechanisms in emergency medicine.

MECHANISMS OF IR INJURY

Although the comprehensive mechanisms of IR injury remain to be fully expounded, they can generally be divided into two different states: the ischemic state and the reperfusion state (Fig 1).1

Ischemic state

The primary function of mitochondria is generation of adenosine triphosphate (ATP) through oxidative phosphorylation. Inhibition of oxidative phosphorylation, as it occurs during ischemia, leads to impairment of normal function.
In the mitochondria, the ischemic state induces anaerobic metabolism and electron transport chain dysfunction, leading to less ATP production. Decreased ATP production results in the dysfunction of Na\(^+\)-K\(^+\)-ATPase, resulting in increased intracellular calcium, hydrogen, and sodium, leading to the swelling of cells and impairment of cytoplasmic enzyme activity. An overload of calcium damages cells through multiple factors, destroying cell membranes, sparking cell apoptosis, and hampering mitochondrial function.\(^2\) Another mechanism implicated in the pathophysiology of ischemic injury is restriction of oxygen-sensing prolyl hydroxylase enzymes due to their need for oxygen as a cofactor. Hypoxia-triggered restraint of prolyl hydroxylase enzymes promotes the post-translational activation of hypoxia and inflammatory signaling cascades, which subsequently regulates the stability of the transcription factors nuclear factor-xB (NF-xB) and hypoxia-inducible factor. Thus, modifications in the transcriptional control of gene expression also happen during the ischemic period.

**Reperfusion state**

In the reperfusion state, mitochondrial damage and electrolyte imbalance result in the generation of huge amounts of reactive oxygen species (ROS) from various sources within minutes, including upregulation of the enzymes xanthine oxidase, nicotinamide adenine dinucleotide phosphate oxidase (NOX), cyclooxygenase, lipoxygenase, and inducible nitric oxide synthase (iNOS), mitochondrial electron-transport chain reactions, and catecholamine oxidation.\(^3\)

Reactive oxygen species, including peroxynitrate, superoxide, hydrogen peroxide, and hydroxyl radical, are molecules or fragments that possess an unpaired electron. Reactive oxygen species retention induces the destruction of cell and organelle membranes and DNA single-strand breakage with resultant enzyme inactivation, as well as activation of nuclear enzyme poly (ADP-ribose) synthetase, leading to cell death by necrosis, apoptosis, autophagy, mitoptosis, and necroptosis.\(^4\)

Lipid peroxidation, a chain reaction leading to polyunsaturated fatty acid oxidation, subsequently disturbs the biological membrane structure and generates toxic metabolites like malondialdehyde.\(^5\)

Ischemia reperfusion injury causes a complex of inflammatory immune responses without the contribution of pathogenic triggers, a process known as sterile inflammation. Sterile inflammation is associated with signaling events through pattern-recognition receptors like Toll-like receptors (TLRs), adaptive and innate immune system cell recruitment...
and activation, and complement system activation.\textsuperscript{6} Toll-like receptor 4 is an important pattern-recognition receptor; its mediated inflammatory response is an important function in organ injury in the IR process.

During initiation of post-reperfusion, danger-associated molecular patterns including peroxiredoxin, high mobility group box-1, nucleotides, purines, and nucleic acid fragments, are released and initiate inflammation. Danger-associated molecular patterns bind innate immune receptors such as TLRs and purinergic receptors on microglia and leukocytes, leading to their activation followed by activation of the inflammatory transcription factors NF-kB, activator protein 1, and mitogen-activated protein kinase.\textsuperscript{7,8} These molecules give rise to cytokines, chemokines, adhesion molecules (intercellular adhesion molecule-1 or E-selectin), matrix metalloproteinase-9, iNOS, and NOX, leading to exacerbation of ischemic injury.\textsuperscript{9} Autophagy, a cellular process associated with damaged or unnecessary proteins and organelle degradation, also contributes to the IR injury process.\textsuperscript{4} The acidic pH, although generally protective in ischemia, is normalized following reperfusion, and this rapid change to a normal intracellular pH level is paradoxically thought to enhance cytotoxicity.

Systemic inflammation and remote organ injury

Ischemia reperfusion injury primarily occurs locally, but post-revascularization, mediators from ischemic tissue can infiltrate the systemic circulation and influence other remote non-ischemic organ systems. For instance, exposure of plasma to ROS can produce chemotactic factors, which could cause sequestration of inflammatory activations in organs other than the initial ischemic injury site, eventually leading to multiple organ failure.\textsuperscript{10} Systemic inflammation evolves from a complex relationship between the primary insult and activation of coagulation and inflammation.

\textbf{ISCHEMIA REPERFUSION INJURY AND EMERGENCY MEDICINE}

It is critical to reduce the hypoperfusion time to protect organ function. Indirect tissue injuries can be aggravated by shock/resuscitation. Regarding sepsis, early treatment with antibiotics and timely resuscitation with adequate vasopressors and fluids are recommended to lessen hypoperfusion of peripheral tissue.

Tissue/systemic hypoperfusion associated with hemorrhagic shock is the most common cause of preventable trauma-related death. Resuscitative endovascular balloon occlusion of the aorta (REBOA) has recently been used as a different option for resuscitative thoracotomy (thoracotomy and aortic cross-clamping) for trauma patients. Use of REBOA is limited by substantial IR injury followed by acute kidney disease or pulmonary edema.\textsuperscript{11} Early reperfusion intervention for obstruction in the feeding vessels can reduce cell/organ damage. Early revascularization decreases infarct size with immediate intervention and notably results in better long-term clinical outcomes in both cardiac ischemia and cerebral ischemic stroke.\textsuperscript{12} However, ischemic tissue reperfusion in itself causes irreversible damage because of IR injury. Therefore, reduction of both reperfusion-mediated tissue injuries and ischemia is an important opportunity for the development of novel treatments.

The tourniquet is the most effective and universal first-aid device used to control hemorrhage of an injured limb in the prehospital environment. Like in organs, acute ischemia in a limb and return of blood flow to the extremity is a medical emergency associated with significant morbidity and mortality.\textsuperscript{13} Ischemia reperfusion injury occurs with a variety of surgical interventions where the blood supply is temporarily cut off and restored, such as in organ transplantation and coronary bypass surgery.

Post-cardiac arrest syndrome is also considered an aspect of systemic IR injury that leads to endothelial dysfunction with organ dysfunction, brain damage, and death.\textsuperscript{14} In cardiac arrest, systemic ischemia results in tissue and cellular damage by energy and oxygen store depletion. Paradoxically, reperfusion of blood to ischemic organs after successful resuscitation can worsen organ damage. As highly metabolic organs, the heart and brain are especially at risk for these damaging effects.

Ischemia reperfusion injury is associated with endothelial cell inflammation, higher vascular permeability, a vasodilat- ing/vasoconstricting factor imbalance, and complement system and coagulation activation. Endothelial dysfunction ends in microcirculation heterogeneity and a weakened response to endothelial-dependent vasoconstrictors and vasodilators, resulting in hypotension. In humans, microvascular dysfunction following IR injury can result in respiratory failure presenting as hypoxemia and pulmonary edema that is not caused by heart failure but instead by disturbed alveolar–capillary barrier function, leading to higher microvascular permeability and leakage of plasma fluid.\textsuperscript{15} Thus, multiple organ dysfunction necessitates intensive care support.

\textbf{THERAPEUTIC IR INJURY STRATEGIES}

Maintenance of blood flow

Obviously, the most effective and important strategy to prevent IR injury is to reduce the
hypoperfusion time. Periodic REBOA is a possible viable adjunct to maximize survival in lethal solid organ injury while minimizing the IR experienced with full REBOA.16 Intermittent REBOA allows titration of blood pressure while maintaining distal organ perfusion and decreases the ischemic burden in a severe hemorrhagic shock state. Periodic REBOA could also reduce the risk of post-resuscitation inflammatory and metabolic consequences and organ dysfunction.17

Therapeutic hypothermia

Therapeutic hypothermia has been known to reduce ischemic brain injury.18 However, ≤30°C hypothermia was compromised with complications including circulatory arrest. Mild or moderate hypothermia therapy was established that showed strong protective effects to ischemic injury without severe complications.19 Although optimal timing, temperature, or indication of hypothermia is still conflicting, inducing therapeutic hypothermia has been associated with improved neurological outcomes in post-cardiac arrest patients.20-22 Active control of temperature (target temperature management) is needed for post-cardiac arrest syndrome and fever must be avoided.23

Prolonged application of tourniquets for an injured limb can eventually result in ischemic necrosis of skeletal muscles and IR injury. Regional hypothermia of 10°C on an injured limb in a rabbit experimental model resulted in decreased ATPase activity, and decreased K⁺, lactate, and inflammatory cytokine levels.24 A recent study showed that external cooling with long-term zone 3 REBOA reduced ischemic muscle injury and led to lower compartment pressures after reperfusion in a pig model.25 The researchers achieved external cooling by placing bags filled with ice in both groins and wrapping the hind limbs and lower torso with a circumferential 4°C cooling blanket during 4 h of occlusion with zone 3 REBOA.25

Inducing a mild systemic 32–34°C hypothermia at the start of ischemia and maintaining that hypothermia during reperfusion conferred adequate cardioprotection in acute myocardial IR pig and rabbit experimental models.26,27 The neuroprotective effects of mild hypothermia were shown in a rat ischemic brain injury model.28 However, most clinical studies show little benefit from hypothermia in acute coronary syndrome patients. An analysis of ST-segment elevation myocardial infarction patients showed that therapeutic hypothermia induced outside the hospital (target temperature ≤35°C at reperfusion) did not improve myocardial salvage.29 Another trial was undertaken on 120 ST-segment elevation myocardial infarction patients (<6 h) scheduled for percutaneous coronary intervention. Hypothermia was induced by rapid 600–2,000 mL cold saline infusion and endovascular cooling or standard of care. Hypothermia did not reduce infarct size as measured on cardiac magnetic resonance imaging.30 Of note, subgroup and meta-analyses suggest that hypothermia’s advantages were still observable in patients with large infarctions and faster cooling before reperfusion.27

Pharmaceutical intervention

Edaravone

Delivering the potent free radical scavenger edaravone prior to ischemic liver reperfusion reduces oxidative stress in the reperfused liver and ensuing lung injury. Edaravone could be advantageous for averting lung injury triggered by liver IR.31 Using a rat model, Taniguchi et al. reported that edaravone decreased IR injury by diminishing oxidative stress and reducing ensuing damaging inflammation by decreasing expression of adhesion molecules and inflammatory cytokines.32

Vitamins

There are two broad divisions of antioxidants, classified by whether or not they are water-soluble (hydrophilic), like ascorbic acid (vitamin C), or lipid-soluble (hydrophobic) like β-carotene and α-tocopherol (vitamin E), which are membrane-bound. Hydrophilic antioxidants react with blood plasma and cell cytosol oxidants, whereas hydrophobic antioxidants protect cell membranes against lipid peroxidation.33 Scientists are investigating the role vitamin C plays in IR injury in a growing number of clinical and preclinical studies. The overwhelming oxidative stress that occurs during the IR injury process can rapidly deplete the body’s vitamin C stores because of tremendous cellular consumption. Levels of vitamin C in the plasma are dramatically reduced not just following cardiac arrest, but also in patients with many other critical illnesses.34 Vitamin C impairs expression of endothelial cell iNOS and neuronal nitric oxide synthetase, thereby reducing the plasma nitric oxide (NO) level, which causes guanylate cyclase activation, which counteracts vasoconstrictors’ effects. This could preserve the baroreceptor reflex and vascular resistance and, consequently, possibly maintain mean arterial pressure.35

Melatonin

Melatonin, known as a natural sedative, is a potent antioxidant that is able to easily cross the blood–brain barrier and cell membranes. In vivo, melatonin prevents slowed vascular decompensation and the cellular energetic breakdown
related to inflammation and IR injury mediated by inhibition of poly (ADP-ribose) synthetase activation.\textsuperscript{36} Melatonin also can stimulate antioxidative enzymes such as glutathione peroxidase, superoxide dismutase, and catalase.

**Anesthesia**

Commonly used anesthetic agents are known to have protective effects for IR injury. Anesthetics can penetrate the brain parenchyma and avert oxidative neuronal injury. Several mechanisms have been advocated, including direct and indirect effects. Propofol and ketamine have properties to scavenge ROS and peroxynitrite and inhibit lipid peroxidation.\textsuperscript{37} Procaine and lidocaine dose-dependently eliminate H\textsubscript{2}O\textsubscript{2} and safeguard endothelium-dependent vasorelaxation during IR injury and against ROS attack, possibly through scavenging.\textsuperscript{38} General anesthetics slow the cellular utilization of glucose and oxygen and restrain oxidative neutrophil metabolism. Anesthetics could avoid heightening extracellular glutamate concentration and impair excitatory glutamatergic receptor activation that boosts oxidative stress associated with IR injury.\textsuperscript{39}

**Bile pigments**

Bile pigments such as biliverdin/bilirubin are produced through heme degradation and have emerged as agents that potently suppress IR injury in rodent models. In a rat intestinal IR injury model, i.p. biliverdin injection led to a considerable reduction in inflammatory cytokine mRNA expression, reduced infiltration of neutrophils into the jejunal muscularis, and averted IR-induced inhibition of intestinal circular muscle contractility.\textsuperscript{39} The effects of biliverdin have been shown in swine liver IR injury, an acknowledged and relevant preclinical animal model. Application of biliverdin caused bilirubin to quickly appear in the serum and notably quelled IR-induced liver dysfunction as determined by multiple measurements including neutrophil infiltration, ammonia and urea clearance, and tissue histopathology, including hepatocyte death.\textsuperscript{40}

**Ischemic preconditioning**

Ischemic preconditioning (IPC), a short period of ischemia followed by brief reperfusion before a prolonged interval of ischemia, has been reported as a sufficient operative plan to decrease organ IR injury in clinical and experimental studies.\textsuperscript{41} Although the protective mechanism of IPC has not been fully elucidated, it might delay the ATP depletion rate during ischemia and ensuing ischemic episodes. Periodic reperfusion could be advantageous to the myocardium by flushing catabolites that accumulated during ischemia.\textsuperscript{42} Additionally, IPC escalates autophagy and decreases cellular damage and mitochondrial dysfunction in IR injury. Ischemic preconditioning increased expression of stress-responsive antioxidant enzymes such as heme oxygenase-1, which is greatly induced during the oxidative stress response, including IR conditions.\textsuperscript{43} Although these experimental studies have shown some benefit, the effects of IPC have been controversial in the clinical setting. The discrepancy could be explained by the IPC protocol or severity of IR injury.\textsuperscript{44}

Remote ischemic conditioning (RIC) is also a known promising strategy to prevent IR injury in several experimental and clinical models.\textsuperscript{45} In RIC, reversible short-term ischemia with reperfusion in one organ, tissue, or vascular bed confers remote tissue/organ resistance to IR injury. For example, brief ischemic episodes with intermittent reperfusion are introduced in a limb, leading to systemic protection against subsequent insults to the kidney, heart, liver, and other tissues.\textsuperscript{46} Although the mechanisms of RIC have not been fully elucidated, a protective signal is sent from the RIC site to target organs, which might involve systemic, neuronal, and humoral mechanisms. Various transmitting routes instigate many signaling cascades, including the survivor activating factor enhancement and reperfusion injury salvage kinase pathways.\textsuperscript{47} Protection is partially mediated by stromal-derived factor-1y, plasma-derived dialysate and NO, and microribonucleic acid-144 (Table 1).\textsuperscript{48} A systematic meta-analysis and review indicated that RIC improved the myocardial salvage index and myocardial infarct size after coronary intervention without mortality benefit.\textsuperscript{48}

**Therapeutic medical gas**

Recent clinical and experimental evidence showed that a number of gaseous molecules have significant physiological regulatory factors with anti-inflammatory, anti-apoptotic, and antioxidant protective effects on organs and cells.\textsuperscript{49-52} The use of medical gases for oxidative stress therapy is an evolving possibility. Medical gases can be given directly to patients by inhalation using a nasal cannula, ventilator circuit, and face mask.

Ischemia reperfusion injury has been treated using several therapeutic gases, including hydrogen (H\textsubscript{2}), hydrogen sulfide (H\textsubscript{2}S), NO, and carbon monoxide (CO).\textsuperscript{50,51} Carbon monoxide, one of the byproducts of the heme oxygenase system, can provide cytoprotection by modulating intracellular signaling pathways through its vasodilative and anti-apoptotic, anti-inflammatory, antithrombotic, and antiproliferative properties.\textsuperscript{53-55} The protective results of CO for IR injury have been extensively studied in experimental/clinical
models. Carbon monoxide leads to vascular dilation through activation of soluble guanylyl cyclase and inhibits pro-inflammatory signaling cascades. As high concentrations of CO are known to be harmful, the optimal and secure use of gaseous CO needs to be undertaken carefully. Carbon monoxide-releasing molecules, which can exert various pharmacological actions through release of controlled quantities of CO in biological systems, are currently being studied to tailor therapeutic strategies to prevent IR injury.\(^5\)

Endothelial NO synthase continuously generates the soluble gas NO in endothelial cells. Nitric oxide regulates endothelial function and basal vascular tone and supports blood oxygenation. Numerous studies have suggested endogenous NO production or its therapeutic use to attenuate IR injury. Nitric oxide prevents creation of hydroxyl radicals by impeding the main iron catalyst in the Fenton reaction.\(^5\) Furthermore, NO and iron react to form an iron–nitrosyl complex, hindering the catalytic functions of iron in the Fenton reaction.\(^5\) Nitric oxide prompts soluble guanylate cyclase and boosts vascular smooth muscle cell cyclic guanosine monophosphate, resulting in vasodilation and relaxation of vascular tone. Thus, NO actions on blood vessels can enhance tissue blood supply and diminish the inflammatory response by restraining P-selectin expression and leukocyte recruitment, leading to safeguarding the tissues from IR injury.\(^5\) Nitric oxide could be linked to both toxic and protective effects following oxidative insults, depending on the environment, NO levels and source, and timing of NO administration, suggesting a brief window for NO treatment of IR injury.\(^5\) Despite scarce high-quality clinical research, a wealth of current evidence suggests that use of NO-donor agents could be an effective therapy for IR injury in humans.\(^5\)

Hydrogen is a highly diffusible and flammable gas produced by bacteria in the human intestine. Although it seems like an important biological molecule with anti-apoptotic, anti-inflammatory, and antioxidant effects, the precise mechanisms of H\(_2\) remain puzzling. In a rat brain focal IR injury model, mitochondrial ROS production was shown to induce the mitochondrial permeability transition pore, resulting in mitochondrial swelling, rupture, and cytochrome c release, and finally apoptosis.\(^6\) Inhaled hydrogen therapy for lung transplant recipients can avoid lung IR injury and markedly improve lung graft function after lengthy cold preservation, transplant, and reperfusion.\(^6\)

Hydrogen sulfide is made endogenously from L-cysteine, a food-derived methionine product, by cystathionine-γ-lyase and cystathionine β-synthase. Therapeutic effects of H\(_2\)S have been reported in animal IR injury models. In rodents, H\(_2\)S can trigger a reversible hypothermic and suspended-animation-like state, and H\(_2\)S treatment reversibly lowers cardiovascular function without affecting blood pressure. Hydrogen sulfide’s impact on cytochrome c oxidase and mitochondrial functions can explain some of its antioxidant effects; its effects on gene expression could be associated with actions on the NF-κB and extracellular signal-regulated kinase pathways.\(^6\)

Interestingly, combined hydrogen/CO therapy showed improved therapeutic efficacy through both anti-inflammatory and antioxidant mechanisms and could be a clinically feasible strategy to prevent myocardial cold IR injury.\(^6\)

CONCLUSION

RECENT PATHOPHYSIOLOGICAL CONCEPTS and therapeutic strategies for overwhelming IR injury-induced organ damage or systemic inflammation in emergency medicine/critical care were summarized with a comprehensive review of published works. This review provides emergency physicians with a strong basis for the investigation of novel therapeutic strategies including pharmacological
treatment, ischemic preconditioning, and the use of medical gases or vitamin therapy, which could significantly help experts develop strategies to inhibit IR injury.

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