Myocardial ischemic reperfusion injury – A review

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ABSTRACT
Myocardial ischemic reperfusion injury leads to the development of myocardial infarction and cardiovascular disease. Death due to these diseases is increasing at a high rate. Tissue damage due to ischemia and reperfusion results in the development of the above-mentioned diseases in heart. During prolonged ischemia, various physiological changes such as a decrease in ATP levels and intracellular pH occur due to dysfunction of ATPase, and accumulation of lactate in myocardial tissue. The consequences of these reactions include increased accumulation of mitochondrial calcium, followed by cell swelling and death. Due to NF-kappa-B signal pathway activation and severe Cx43 degradation, a serious myocardial infarction occurs after ischemia/reperfusion injury. Knowledge related to the mechanism of ischemia-reperfusion injury and its related treatments is important. This review explains the prevalence, risk factors, mechanism, modern medicine and traditional medicine for myocardial ischemia-reperfusion injury. Numerous medicinal plants have been scientifically evaluated for cardioprotective activity. Herbs that have been reported to exhibit therapeutic potency against ischemic reperfusion injury are discussed in detail. There are a lot of diseases that are caused due to ischemic perfusion injury and end up in a significant rise in the rate of mortality. The details about ongoing research related to new drug development against myocardial ischemic perfusion injury are discussed here.

INTRODUCTION
Globally, cardiovascular disease (CVD) is the leading cause of morbidity and mortality. CVD accounts for 35% of global deaths (Mohseni et al., 2017). This disease leads to complications and disability. According to the World Health Organization (WHO), the prevalence of death due to CVD in the world has been calculated as 12 million people/year and it will rise up to 25 million years (Kazemi et al., 2009). Among various CVD, coronary artery disease and acute myocardial infarction (AMI) is the leading cause of death.

In recent decades, the prevention and treatment of these diseases have reduced the death rate in North America and Western Europe. But the death rate was found to be increased in Eastern Europe and Asia. In the United States of America, 1–1.5 million people suffer from AMI, of which approximately 33% death has been recorded annually (Hadjian, 2004). Primary percutaneous coronary intervention and fibrinolytic therapy return blood flow to ischemic myocardium and border infarct size. However, the restoration of blood flow results in pathological and biochemical changes on injured myocardium com-
monly referred to as reperfusion injury. In this chapter, the pathophysiology and potential therapeutic strategies for reperfusion injury have been discussed. Ischemic reperfusion injury is a big hurdle to treat myocardial infarction.

**Risk factors of IRI**

The majority of ischemic-reperfusion injury is due to thromboembolic or atherosclerosis. Some major risk factors that cannot be modified, which includes advancing age, hereditary factors and for male. Additional effects include consumption of tobacco, alcohol consumption, smoking, hyperlipidemia, hypertension, lack of physical exercise, obesity and various metabolic disorders like diabetes (Boengler et al., 2009).

**Mechanism of Ischaemic reperfusion injury**

In 1960, Jennings and his colleagues reported Ischemia followed by reperfusion results in injury. Ischemic reperfusion injury (IRI) is in many forms. Some of them are reperfusion-induced arrhythmias, myocardial stunning, microvascular obstruction, and lethal myocardial reperfusion injury. Though the exact mechanisms are not fully known, various molecular, cellular, and tissue alterations such as cell death, inflammation, neurohumoral activation, and oxidative stress are determined in IRI. This identified that IRI cells might be instructed to die by cellular signaling mechanism by apoptosis, autophagy, necrosis, necroptosis (Kroemer et al., 2009).

**Apoptosis**

**Extrinsic and Intrinsic pathways are involved in apoptosis**

Fas, TNFα, and TRAIL receptors are activated in the extrinsic pathway. These receptors are activated by a number of death domain that contains proteins like FADD and TRADD to the receptor complex, which results in activation of protease caspase-8, this, in turn, cleaves and activates caspase-3. Caspase-3 proteolysis many cellular proteins (Whelan et al., 2010).

IRI causes apoptosis by the “intrinsic” pathway, induce the translocation and integration of pro-death members of the Bcl2 protein family (e.g., Bax, Bak) into the outer mitochondrial membrane. These proteins increase the permeability of another membrane, and release proapoptotic proteins cytochrome c, Smac/DIABLO, Omi/HtrA2, and endonuclease-G (endo G) from the intermembrane space, most notably. Cytochrome c bind with cytosolic protein apaf1 causes apoptosome. These indicate the caspase-9 and caspase-3. This caspase-activated by Smac/DIABLO and Omi/HtrA2. The DNA fragmentation was mediated by endoG (Broughton et al., 2009).

**Autophagy**

In Autophagy, the main mechanism of the cell was the disposal of damaged organelles and protein aggregates; this, in turn, persists the normal function of a cell. Even though the uncontrolled autophagy may lead to cell death and can contribute to IRI. Autophagy begins with the isolation of damaged cell membrane/ organelle. The isolated membrane covers the constituents to form the vesicular autophagosome; this leads to fuses with a lysosome and degrade the materials. Mammalian target of rapamycin (mTOR) is the main regulator inhibits autophagy. However, under ischemia, mTOR is inactivated. The formation of a phagophore was initiated by Atg13 and Atg17 kinase. It was further made easier by the complex consisting of a class III PI3K called vps34, vps15, and beclin-1. The elongation of the membrane and completion of the autophagosome was initiated by the complex Atg12, Atg5, and Atg8 (also called LC3). The joining of the autophagosome to the lysosome was mediated by the small GTPase Rab7 and the lysosomal membrane protein LAMP2 (Gottlieb and Mentzer, 2010).

**Necrosis and Necroptosis**

Necrosis was described morphologically by swelling of cellular organelles, mitochondrial dysfunction, and lack of nuclear fragmentation, plasma membrane rupture, and leakage of intracellular contents. The concept of necrosis is termed as necropsis; specifically, cell stress or death receptor activation organises and initiates a group of serine/threonine kinases called receptor-interacting proteins (RIPs), which serves as mediators of necrosis (Smith and Yellon, 2011). Activation of RIPs 1 and 3, in turn, leads to increased ROS production either through activation of NADPH oxidases, or increased mitochondrial oxidant production (Vandenabeele et al., 2010). Necrostatin-1 decreases TNFα-initiates necrotic cell death by inhibiting RIP1 kinase activity supports the concept of receptor-induced necrosis throughs a controlled cellular process (Smith and Yellon, 2011).

A potential mitochondrial aimed for RIP-mediated necrosis is the MPT pore. The MPT pore was large and it has a nonspecific channel in the inner mitochondrial membrane. This MPT pore was opened for excessive production of ROS and Ca²⁺ overload of the mitochondrial matrix (Kroemer et al., 2007). These processes occur during IRI.

**Inflammation**

The inflammatory response is also important for tissue and wound repair. Inflammation observed
in the absence of pathogens is commonly referred to as sterile inflammation. In response to sterile inflammation observed during I/R, a large number of signals leads to the production of neutrophils and macrophages and produce additional cytokines and chemokines, which in turn activates lymphocytes and other pro-inflammatory stimuli. ROS, hydrolytic enzymes, and pore-forming molecules were produced by activated neutrophils. These molecules cause extensive damage to parenchymal cells.

During the process of reperfusion, the innate immune cells release oxygen and neutrophils to the ischemic tissue. The discharge of oxygen into the damaged tissue, Increases the production of ROS with the help of enzymes such as Xanthine oxidase and NADPH oxidase. The formation of proinflammatory stimuli was promoted by generated ROS, changes the expression of adhesion molecules on the top of leukocytes and endothelial cells, and this decreases the levels of potent antiadhesive agent nitric oxide which further destroys endothelial NOS activity and oxidation of soluble guanylylcyclase (sGC), this was further increases the inflammatory responses. Neutrophil infiltration and formation of pro-inflammatory mediators that promote leukocyte adhesion and finally induce reperfusion injury (Kviety and Granger, 2012).

Calcium Accumulation in IRI

Myocardial ischemia results in the accumulation of intracellular sodium, hydrogen, and calcium ions, followed by tissue acidosis. Reperfusion causes rapid renormalization of pH, alterations in ion flux, in turn, results in increased cytotoxicity (Bond et al., 1991). An attempt to renormalize pH affects Sodium protein exchanger and sodium bicarbonate transporter, consequently lead to intracellular sodium accumulation. The high concentration of sodium in the cytosol activates sodium-calcium exchanger and inhibits SERCA Ca2+-ATPase further increases calcium release from the sarcoplasmic reticulum to the cytoplasm (Tani and Neely, 1989). Increased calcium causes myofibrillar hypercontractility, ATP depletion, ultrastructural damage to mitochondria, damage in mitochondrial permeability transition pore and myocardial stunning (Kusuoka et al., 1987).

Oxidative Stress

Reperfusion injury activates Xanthine oxidase, results in the generation of free radicals. These oxygen species react with the cell’s lipids, proteins, nucleic acid and quickly overwhelm the cell’s antioxidants (Thompson-Gorman and J, 1990).

Free radicals also cause the opening of mPTP results in further release of free radicals from mitochondria (Zorov et al., 2000). Nitric oxide is a free radical generated from endothelium. It causes vasodilation, platelet aggregation, leukocyte adhesion, and free radical scavenging. The high concentration of nitric oxide may potentiate ROS-mediated toxicity by promoting the formation of peroxynitrite (Beckman et al., 1990).

Modern medicine for Ischemic Reperfusion injury

Nitroglycerin or Glyceryl Trinitrate Nitroglycerin has beneficial effects in IRI, including dilation of the coronary arteries. Especially, caffeine and aspirin...
could reduce the infarct size. Morphine could delay the onset of protection in patients with ST-elevation. Anti-platelet agents such as dipyridamole, cilostazol and ticagrelor may protect the myocardium from IRI due to their favorable effects on adenosine cell reuptake and intracellular cAMP levels (Birnbaum et al., 2015). Non-ST elevation myocardial infarction (NSTEMI) patients are often managed with the blood thinner heparin (O’connor et al., 2010).

In the Invivo system of reperfusion injury, Adenosine shows the decrease in infarct size, improvement of regional myocardial blood flow and improves the regional function of the ischemic area. Including that adenosine retain the post-ischemic coronary flow reserve, coronary blood flow and post-ischemic regional contractility. The treatment of adenosine in a patient with acute MI, which was combined with smaller infarcts, less no-reflow phenomenon and initiate Left ventricular function (Quintana et al., 2004).

Traditional medicines for myocardial ischemic reperfusion injury

Numerous medicinal plants have been scientifically evaluated for cardioprotective activity. Herbs that have been reported to exhibit therapeutic potency against Ischemic reperfusion injury are mentioned in this chapter.

One of the subtype enzyme phosphodiesterase (PDE) was blocked by the phosphodiesterase inhibitor drug. The activation of intracellular messenger’s like cAMP and cGMP was prevented by PDE subtypes.

Most of the active phytoconstituents isolated from herbal plants exhibit different therapeutic properties. Notably, compounds isolated from various plants like tetramethylpyrazine were reported to inhibit phosphodiesterase, an enzyme prevent the inactivation of cAMP and cGMP, which in turn activates protein kinase C and protects the heart from Ischemic reperfusion injury (IRI). These active compounds are also used as a supplement for cardiovascular disease (Quintana et al., 2004).

Curcuma oil failed to confer protect the damage caused by ischemia and reperfusion in rat heart. Along with that, the noted reversal of ADP initiates platelet aggregation (p < 0.05) was evident in the rat (Prakash et al., 2011).

(MI)Angina pectoris, stroke, diabetes, sepsis, and other conditions. However, Tan IIA is not easy to be grabbed through the intestinal pathway. Sodium tanshinone IIA sulfonate (STS) was initiated to increase the bioavailability of the herb.

Tanshinone II-A is an important source of the major lipophilic components that was extracted from the root of *Salvia miltiorrhiza* Bunge, and Nowadays, this was used in China and other neighbouring countries to treat myocardial infarction patients.

Tanshinone II-A has a cardioprotective effect, which was abolished by LY294002, a specific inhibitor of phosphatidylinositol 3-kinase. The result reveals that tanshinone IIA postconditioning protects the myocardium from ischemia-reperfusion injury through the PI3K/Akt pathway (Yuan et al., 2014).

The protective effects of *Lyciumbarbarum* polysaccharide increased the activity of Superoxide dismutase and Glutathione peroxidase with decreased malondialdehyde content. It also inhibits intracellular free calcium concentration elevation and decrease of mitochondrial membrane potential in ischemia-reperfusion treated hippocampal neurons (Rui et al., 2012).

The complex preparation of puerarin and Danshen was called as Shenge, which shows the importance in effect of cardioprotection against the acute ischemic myocardial injury in the rat. This also been used as an effective medicine for prophylaxis and for the treatment of ischemic heart disease (Wu et al., 2007).

The aqueous extract from *SalviaeMiltiorrhizae* and *RhizomaChuanxiong* shows the effective compatibility on reducing the size of myocardial infract and reduce the activity enzyme CK-MB, and thus reducing myocardial I/R injury (Zhang et al., 2010a).

Sal B, which was isolated from the Chinese herb *Radix SalviaeMiltiorrhizae* shows the beneficial effect on cardioprotection against myocardial ischemic injury in rats. This effect might be due to scavenging oxidative stress- triggered overproduction and accumulation of reactive oxygen species, alleviating myocardial ischemia injury and cardiac cell death (Qiao and Xu, 2016).

Magnolol is an active compound obtained from *Magnolia Officinalis*, which suppresses the ischemia reperfusion-induced ventricular arrhythmias. The cardioprotective activity of magnolol was mediated by its antioxidant activity in myocardial ischemia/reperfusion (Lee et al., 2001).

Due to NF-kappa-B signal pathway activation and severe Cx43 degradation, a serious myocardial infarction occurs after ischemia/reperfusion injury. *ShuangshenTongguan* Recipe inhibits the activation of NF-kappa B, the over-excretion of TNF-alpha and ICAM-1 in serum, and the degradation of Cx43 to decrease the myocardial infarction size (Liu et al., 2005). *Scutellaria baicalensis* extract exhibits a significant reduction in myocardial infarct size. This
Fructus Schisandrae (FS), was evaluated for its 2,2′-bicarboxylate (DDB), compounds isolated from dimethoxy-5,6,5′,6′-dimethylene-dioxy-biphenyl-Schisandrin B (Sch B) and dimethyl-4,4′-et al., associated with ischemic-reperfusion injury (et al., 2003).

These Lotuses are generally called as Makhana in India. Mostly it is consumed directly and also used as the main ingredient in Indian cuisines and sweet dishes. However, not many people are aware of its health benefits and nutritional value.

These seeds can be consumed raw or cooked depending on the taste. Apart from being a nutritious snack, it can also be used as medicine as it was being used in medieval times. The essential micronutrients found in lotus seeds are of vast importance to the human body.

The Nelumbunucifera seeds treated rats’ show resistance to ischemic reperfusion injury. It has evidence noted in postischemic ventricular function and reduced myocardial infarct size. These seeds treated rats’ shows markedly increased the amount of thioredoxin-1 (Trx-1) and thioredoxin-related protein-32 (TRP32) against control hearts. This suggested that these seeds makhana has the ability to induce TRP32 and Trx-1 proteins and scavenge ROS (Das et al., 2006).

Guanxinkang is an important compound of six Chinese herbs, namely Radix Astragali, Trichosanthes, Radix SalviaeMiltiorrhizae, Allium macrostemon, Pinelliatuberifera, and Radix Puerariae. Its decoction has definite intervention effects on myocardial I/R injury. This effect might be due to the opening of the potassium channel, decreasing Ca\(^{2+}\) influx and inhibiting Ca\(^{2+}\) overload (Zhang et al., 2010b).

The herbal combination of Withaniasomnifera, Curcuma longa and Ocimum sanctum reveals the severity of changes in Pathology and notably preserved the myocardial creatinine phosphokinase confirming it myocardial salvaging effects (Gupta and Mohanty, 2013).

Administration of Emblicaofficinalis extracts to the rat, which leads to myocardial adaptation by augmenting endogenous antioxidants. Significant decrease in myocyte injury, myocardial TBARS shows the increased activity of Superoxide dismutase, catalase, reduced glutathione and Glutathione peroxidase occurred on treating Ischemic myocardial rats with extract of Emblicaofficinalis. Thus the extract protects the rat heart from oxidative stress associated with ischemic-reperfusion injury (Rajak et al., 2004).

Schisandrin B (Sch B) and dimethyl-4,4′-dimethoxy-5,6,5′,6′-dimethylene-dioxy-biphenyl-2,2′bicarboxylate (DDB), compounds isolated from FructusSchisandrae (FS), was evaluated for its cardioprotective activity by both Invitro and exvivo methods. Though the cardioprotective effect has not been exhibited in the Invitro method, better protection has been observed in the exvivo study. This has been proved by the significant decrease in lactate dehydrogenase leakage and improvement in contractile force recovery (Yim and Ko, 1999).

Bacopamonnieri, a medicinal Ayurvedic herb, has improved the myocardial function injured by ischemia/reperfusion. This has been evidenced by the protection of coronary blood flow, contractile force and lowers in infract size (Srimachai et al., 2017).

Hippophaerhamnoides pulp oil protects the heart damaged by I/R by the mechanism mediating activation of the Akt/eNOS signaling pathway (Suchal et al., 2016).

Withaniasomnifera is a well-known medicinal plant that exhibits antioxidant activity and protects the heart from apoptosis induced by Ischaemia reperfusion (Mohanty et al., 2008).

Panax ginseng is a well-known traditional Chinese medicine. Its whole plant extract prevents and protects the heart from the blockage of androgen receptors (Pei et al., 2013).

The alcoholic extract of Terminalia arjuna augments endogenous antioxidant activity in the rat heart and also prevents the myocardium from isoproterenol initiates myocardial ischemic reperfusion injury (Karthikeyan et al., 2003).

CONCLUSION

Myocardial ischemic reperfusion injury leads to the development of various diseases and increases the death rate. The development of a drug against these disorders is highly in need of the basic mechanism. Research on ischemia-reperfusion injury is increasing for the past few decades. This review enlightens mechanisms and various treatments for ischemia and reperfusion injury.

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