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Potential Future Therapies of Myocardial Ischemia Reperfusion Injury

Review Article

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Abstract

Cardiovascular diseases are one of the leading causes of death in the world. Angioplasty, heart transplantation, thrombolysis, and coronary bypass are general treatment approaches of cardiovascular diseases. All of these approaches can cause myocardial ischemia reperfusion (MIR) injury that is known to occur on return of blood flow after myocardial infarction (MI). MIR injury fundamentally consists of inflammation-related events and oxidative stress. Many anti-inflammatory and antioxidants are suggested for the treatment of injury. However, despite a better understanding of pathophysiology of MIR injury, the majority of the clinical trials to prevent it have been disappointing. Therefore, this review article provides a brief overview of the potential future natural and synthetic therapies recently published in the research science for the treatment of MIR injury.

Introduction

Although recently there are many advances in the treatment of ischemic heart diseases, Acute Myocardial Infarction is the leading cause of mortality in developed countries [1]. Blood flow restoration to earlier ischemic myocardium leads to Myocardial Ischemia Reperfusion (MIR) Injury [2]. MIR injury appears during invasive treatments for example, angioplasty [3], heart transplantation [4], thrombolysis [5], and coronary by-pass [6]. Our objective is to review new therapeutic strategies presently under research for preventing MIR injury, as there is still no promising therapy for it. An intriguing research area for MIR injury therapy shows potential in Therapeutic hypothermia and Hydrogen sulfide treatment. However clinical application for them is still nebulous. We have concentrated basically on the research science that has been published within the past 24 months and shows potential for treatment of MIR injury.

Pathophysiology

The pathophysiology of MIR injury is multifactorial [7]. The reactive oxygen species (ROS) is produced just after an ischemia and plays an important role in MIR injury [8]. These oxygen species are highly reactive having an unpaired electron and attacks to all cell biomolecules [7]. These highly reactive species can cause MIR-induced lipid peroxidation, cardiac dysfunction, inhibition of Na^+-K^+ ATP-ase activity of Na membrane channels and mitochondrial electron transport chain [9]. Antioxidant treatments including enzymatic pathways and non-enzymatic pathways can reduce infarct size induced by MIR; improve revival of the heart contractile function, activities of ion transport and ATP content [10,11]. After reperfusion of infarcted myocardium, which is the conventional choice of treatment for acute myocardial infarction, an inflammatory reaction develops in tissue. The inflammation is essential for tissue healing after MIR-induced injury [12]. Conversely, the blood flow restoration to ischemic tissue leads to an extension of ischemia-associated tissue damage [9]. Neutrophils are main compounds of this response [13]. The activated neutrophils also release mediators such as, platelet activating factor, ROS, leukotrienes andthromboxane thereby leading to tissue damage [14,15]. The other factor that plays a role in MIR injury is complement system [16]. The myocardial cell necrosis leads to release of constituents of subcellular membrane, which are found abundant in mitochondria and are ableto trigger complement cascade [17]. In addition to these factors, sometimes although the reperfusion is supplied, blood flow cannot be provided to myocardial tissue. This is known as 'no-reflow phenomenon' [9].

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Potential Future Treatments For Mir Injury

Embelin administration [18]

It has been observed that systemic ischemia-reperfusion injury occurring after the cardiac arrest (CA) is a main factor that causes problems [19]. Neutrophil extravasation and endothelial activation following ischemia-reperfusion injury stimulates activation of inflammatory cascade, ultimately triggering systemic inflammatory response syndrome and leading to myocardial dysfunction with multiple organ failure [20]. The previous studies support that anti-inflammatory activity is beneficial for MIR injury after resuscitation [21]. Embelin is naturally occurring plant that has been used as anti-inflammatory to relieve fever and rheumatism [22]. It also reportedly possesses antidiabetic [23], hepatoprotective [24], antioxidant [25], antibacterial [26] and anti-inflammatory activities in other organs [27-29]. However, as embelin was not been tested for its anti-inflammatory activity on MIR injury after CA, recently a study was been formed to test its activity in a rabbit model [30]. It was observed that embelin reverts Interleukin-1 beta (IL-1β), Interleukin 6 (IL-6) and Tumor necrosis factor alpha (TNF-α) to basal levels and reduces levels of cardiac troponin I (cTnI) in serum, apoptotic index (AI), nuclear factor-kappa B (NF-κB) p65 and the necrosis ratio. Furthermore, it was seen to improve myocardial and hemodynamics function and myocardial morphology. Therefore, embelin shows potential to protect the heart against the MIR injury following CA by its anti inflammatory abilities.

Mechanical Tissue Resuscitation [30]

Negative pressure wound treatment increases cell preservation by decreasing tissue edema, inflammation and enhancing blood flow within areas that border a region of permanent cell death [31-33]. This resuscitation of tissue may lessen the final magnitude of cell death within tissue positioned at risk for additional injury during reperfusion. Mechanical tissue resuscitation (MTR) while using a bioabsorbable matrix could be either placed using a marginally invasive method following percutaneous revascularization process or used at the period of open revascularization surgery. MTR is an effective treatment for burns [33], traumatic brain injury [34] and acute myocardial infarction [35]. Early cell death as well as delayed programmed cell death, which is seen after MIR, decreases with MTR treatment during reperfusion. This cardioprotective treatment is, furthermore, related with increased blood flow and significant reduction in interstitial water. MTR with a resorbable device is anefficientand straightforward mechanical strategy for reducing cardiac muscle cell loss after myocardial infarction as an added treatment to surgical revascularization.

Protocatechuic Acid [36]

Protocatechuic acid (PCA), a phenolic compound, is plentiful in edible vegetables and fruits. PCA is well absorbed by humans and animals and is one of the chief metabolites of complex polyphenols such as procyanidins and anthocyanins, which arereportedto be closely related to reductions of mortalities in neurodegeneration, coronary heart disease and cancer [37,38]. PCA has beneficial effects on treatments of neurodegenerative disease [39], inflammation disease [40,41] and cancer [42,43]. However, in a recent study, PCA significantly reduced serum TNF- α level, infarct size and platelet aggregation in *in vivo* rat model of MIR injury [36]. Experimental data collected in a primary neonatal rat cardiomyocyte model of hypoxia/reoxygenationinjury indicated that in response to PCA, there was an upregulated expression of phosphorylated Akt in the cardiomyocytes subjected to hypoxia/reoxygenationinjury and significant inhibition of the expression of cleaved caspase-3and the apoptotic rate. Therefore, PCA can give a noteworthy protection against MIR injury that may be at least moderately due to its inhibitions against MIR injury including the platelet aggregation, cardiomyocytes apoptosis and inflammatory response.

Naloxone Post conditioning [44]

Ischemic post conditioningis confirmed to protect brain and heart, however has been found problematic to conduct clinically [45-47]. As an exogenous intervention, the pharmacological postconditioning presents similar endogenous protective mechanism as Ischemic postconditioning. Pharmacological postconditioning has confirmed many advantages such as controllability, convenient operation, predictability and safety, proposing that it can be used to prevent MIR injury [48-50]. Naloxone, an antagonist of opioid receptors, can specifically antagonize the opioids and endogenous opioids, enkephalins and endorphins. It is responsible for many basic researches on antagonism of opioid receptors because of its great affinity to opioid receptor [51]. Additionally, naloxone can break and reverse the toxicity of the endogenous opioid receptors. It also plays a substantial protective function in brain and renal ischemia-reperfusion injury [52,53]. Naloxone is also able to protect the reperfused cardiac muscle by inhibition of lipid peroxidation and release of the inflammatory mediators and improvement of energetic metabolism [54, 55]. In a recent study, cell apoptosis andp-c-Jun NH2-terminal kinase (p-JNK) was observed to be significantly lower in the ischemia-reperfusion myocardial tissues after the naloxone treatment as compared to ischemia-reperfusion group in Sprague Dawley rats [44]. Furthermore, naloxone postconditioning is able to significantly improve pathological injury of the ischemia cardiac muscle. Naloxone has less side effects and low price and therefore, may produce huge social and economic benefit if used extensively for prevention of MIR injury.

Betulinic Acid [56]

Betulinic acid, a triterpene, has many botanical sources and is one of the constituents chemically derived from botulin. This substance is found in abundant quantity in outer bark of white birch trees [57,58]. It has been found to possess activities like anti-inflammatory [59,60] and antitumor [61-63]. Recent studies have established the evidence of betulinic acid protecting against renal [58] and cerebral ischemia reperfusion injuries [64]. In a recent study performed in an open-chest anesthetized rat model, it was observed that pretreatment with betulinic acid improves cardiac function and attenuates lactate dehydrogenase (LDH) and creatine kinase (CK) activities compared with ischemia-reperfusion rat group [56]. Therefore, betulinic acid may moderate the release of CK and LDH, prevent cardiomyocytes apoptosis and in turn alleviating the extent of the MIR injury.

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Table 1: Summary of different new research methods of treatment for MIR injury.

Sr. No.	Materials	Properties and Uses	Studied in	Advantages	References
1.	Embelin	Antidiabetic, hepatoprotective, antioxidant, antibacterial, anti-inflammatory	Rabbit	Improves myocardial and hemodynamics function and myocardial morphology	18
2.	Mechanical tissue resuscitation while using a bioabsorbable matrix	Treatment for burns, traumatic brain injury, acute myocardial infarction, MIR injury	Swine	Reduces cardiomyocyte death after myocardial infarction as an adjunctive treatment to surgical revascularization	30
3.	Protocatechuic Acid	Treatment for neurodegenerative disease, inflammation disease and cancer	*in vivo* rat model of MIR injury and primary neonatal rat cardiomyocyte model of hypoxia/ reoxygenationinjury	significant protection against MIR injury with underlying mechanism associated with anti-platelet aggregation, anti-inflammatory response and preventing cardiomyocytes from apoptosis by activation Akt	36
4.	Naloxone Postconditioning	Antagonism of opioid receptors, great affinity to opioid receptor, substantial protective function in brain and renal ischemia-reperfusion injury, treatment for MIR injury	Sprague Dawley rats	Low price and less side effects	44
5.	Betulinic Acid	Anti-inflammatory, antitumor	Open-chest anesthetized rat model	Reduces release of CK and LDH and prevent cardiomyocytes apoptosis	56
6.	Aliskiren	Increases levels of cardiac bradykinin	Female Sprague Dawley rats	Reduces valsartan-induced increase in angiotensin II levels	65
7.	Baicalein	Protects kidney, brain and heart against ischemia reperfusion injury	Mouse	Suppresses apoptosis and activity of Caspase 3 in cultured myoctes in response to simulated MIR	66
8.	VitaePro (lutein, zeaxanthin and astaxanthin)	Lutein- prevents peroxidation of lipids Zeaxanthin- decrease oxidative stress and end-stage liver disease Astaxanthin- anticancer	*ex vivo* MIR injury rat model	Decreases apoptosis and oxidative stress	67
9.	α- lipoic acid	Low redox potential and Treats conditions like lipid abnormality, diabetic polyneuropathy and stroke	*in vitro* and *in vivo* study Adult male Sprague-Dawley rats	Activation of PI3K/Akt/Nrf2 Pathway and preserves cardiac Function	68
10.	Mesenchymal Stromal Cells	Differentiates into an array of cell types	Pre-clinical study using rat and porcine model	Improved cardiac functioning, suppress oxidative stress, reduction in the size of an infarct, hindrance of fibrosis, increased angiogenesis and tissue repair	69
11.	Fusion of GLP-1 with domain antibody to serum albumin	Regulates glucose homeostasis by inhibiting glucagon secretion stimulating insulin secretion, promoting satiety and delaying gastric emptying	Male Sprague–Dawley rats	Long-acting GLP-1 agonists	70
12.	Suberoylanilidehydroxamic acid	Treatment of cancer	*in vitro* model using rabbit	Salvages the systolic function and decreases the infarct size	82
13.	Chemerin15	phagocytosis of the cells that are apoptotic; stops pro-inflammatory mediator production by macrophages	*in vitro*; murine myocardial infarction model	reduces neutrophil adhesion and chemotaxis; inhibits the integrin's activation and its clustering	83
14.	Thymoquinone	Antioxidant; anticonvulsant; analgesic, potential anti-cancer drug	*ex vivo*	Inhibition of pro-inflammatory cytokines	84
15.	Cyclosporine	Immunosuppressive	*in vivo:* rabbit model and clinical trial in patients	Reduction in infarct size	85

Aliskiren [65]

Aliskiren, which is a renin inhibitor escalates the levels of bradykinin and kallikrein in the cardiac tissue. In this research study, female Sprague-Dawley rats were treated for 4 weeks prior to MIR injury with drugs such asaliskiren and valsartan (angiotensin II receptor antagonist)either alone or in combination, co-administered with AT_2 receptor antagonist PD123319 (30 mg/kg per day) or B_2 receptor antagonist icatibant (0.5 mg/kg per day). It was found that aliskiren decreases valsartan-induced increases in angiotensin II levels and increases levels of cardiac bradykinin. Angiotensin AT_1 receptor blockers and Angiotensin-converting enzyme (ACE) inhibitors lessen MIR injury mediated via bradykinin B_2 receptor- and angiotensin AT_2 receptor mechanisms.

Baicalein [66]

12/15-Lipoxygenase (LOX), a catalyst involved in the transformation of arachidonic acid to hydroxy-eicosatetraenoic

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acids (HETEs). Its levels are increased within the brain, myocardium and endothelial cells in response to ischemia or hypoxia. Baicalein (5,6,7-trihydroxyflavone) is a flavone, isolated from roots of *Scutellariabaicalensis* (Lamiaceae) and also reported to be present in *Oroxylumindicum* (Bignoniaceae). Being a specific LOX inhibitor, Baicaleinprotects the kidney, heart and the brain against ischemia reperfusion injury .On studying the mouse model, it was observed that the 12/15-LOX was unregulated in a significant number in the peri-infarct area which surrounded the primary infarction. Inhibition of 12/15-LOX by Baicaleinblocks effects such as cardiac injury, TUNEL positive cardiomyocytes, inflammatory responses and oxidative stress. Baicalein also suppresses apoptosis as well asthe activity of Caspase 3 in cultured myocteswhen an MIR injury is simulated. Associated mechanisms are the activation of AKT pathway and ERK1/2 and inhibition of activation of JNK1/2, p38 MAPK and NF-kB/p65.Baicalein is a novel therapeutic drug for MIR injury.

VitaePro [67]

VitaePro is a mixture of antioxidants such as lutein, zeaxanthin and astaxanthin in oil of safflower (*Carthamustinctorius* L., Compositae). The main function of antioxidants is that they act as cardioprotective compounds.Lutein, a xanthophil pigment, has been demonstrated to prevent peroxidation of lipids in cortex in a diabetic rat cerebral cortex, induced by streptozocin. Zeaxanthin, a major carotenoid pigment present in the retina of eye has been demonstrated to decrease oxidative stress and end-stage liver disease. Astaxanthin is a carotenoid pigment that protects the epithelial cells of human lens against UV-B insults and possesses anticancer activity. On comparison study between VitaePro and Vitamin E in their cardioprotective activity in an *ex vivo* rat model of MIR injury, it was found that VitaePro is a better cardioprotectant on the basis of increased left ventricular functional revival, enhanced aortic flow, decrease in the infarct size and decrease in the levels of thiobarbituric acid reactive substances. VitaePro can be taken orally and decreases the MIR injury by decreasing apoptosis and oxidative stress. However to make its use in clinical application, the *in vivo* activity of VitaePro is still to be established.

α- lipoic acid (αLA) [68]

αLA, a thiol antioxidant is present in food such as spinach, tomatoes, and broccoli or is synthesized by the human liver. It is a cofactor for various metabolic enzymes, which include α-keto-glutarate dehydrogenase and puryvate dehydrogenase. It is currently clinically used for treating conditions like lipid abnormality, diabetic polyneuropathy and stroke. αLA and dihydrolipoic acid (its reduced form) are ideal antioxidants as they have a low redox potential which scavenge reactive oxidative species and help to regenerate Vitamin E and C which are endogenous antioxidants. Hence, it can be put to use in treating oxidative MIR injury. In an *in vivo* study carried out on Adult male Sprague-Dawley rats, the administration of αLA significantly reduced the levels of necrotic cell death markers which include creatinine kinase and lactate dehydrogenase in the serum, partially preserved the function of the left ventricle, decreased the apoptosis and necrosis of cardiomyocytes, a reduction in the myocardial infarct size, inhibition of TNF-α level and accumulation of neutrophils which leads to reduction in the inflammation. The possible mechanism of action is the activation of PI3K/Akt pathway (which mediates a protecting effect), prevention of stimulation of iNOS gene expression, increased Nrf2 Nuclear Translocation (this up regulates expression of a group of oxidative enzymes which include NADPH-regenerating enzymes, HO-1, superoxide dismutase and glutathione S-transferase, these help to fight against the oxidative stress), inhibition of JNK1/2 and activation of ERK1/2. In *in vitro* studies, it is reported to slacken the MIR injury.

Mesenchymal Stromal Cells (MCS) [69]

MCS are embryonic connective tissues cells, which are derived from the mesoderm of adult muscle, umbilical cord, corneal stroma, adipose tissue, etc. These multipotent cells have the ability to differentiate into an array of cell types. A large number of experiments are designed to investigate its use in acute kidney injury. Many preclinical models have also been set up to test its efficacy in diseases of lungs, liver and intestine. It has been shown that there is an enhancement in the recruitment of MSC via CXCR7- and CXCR4-dependent pathway and SDF-1 to the injured organ in response to hypoxia. MCS are able to readily transmigrate into an inflamed tissue and get incorporated into the endothelial layer. They possess the ability to release mediators, which are locally generated in an inflammatory response such as IL-6, IL-10, NO, TGF-b, IDO and prostaglandin E2 (PGE2). They have the ability to release growth factors such as hepatocyte growth factor (HGF), monocyte chemoattractant protein-1 (MCP-1), fibroblast growth factor (FGF), insulin-like growth factor (IGF), stromal cell- derived factor- 1(SDF-1), vascular endothelial growth factor (VEGF) and also can stimulate angiogenesis and proliferation which are categorized under cellular repair programs and hence, benefitting the treatment of MIR injury. The induction of T-cell expansion by MCS can prevent against allograft rejection and hence indirectly protect against MIR injury. The pre-clinical study using rat and porcine model has shown effects such as improved cardiac functioning, suppress oxidative stress, reduction in the size of an infarct, hindrance of fibrosis, increased angiogenesis and tissue repair. On intravenous treatment of the analogue MSC- conditioned media in rats the outcome was a surge in the capillary density, which supports the cardiac function. Administering the same analogue to pigs, the therapeutic effects included a reduction in infarct size, improved cardiac repair and early protection of myocardium against ischemia. There is an increase in the number of clinical trials for its forthcoming clinical applications.

Fusion of Glucagon-like peptide-1 (GLP-1) with domain antibody to serum albumin [70]

In reaction to nutrient ingestion, an incretin hormone known as GLP-1 is secreted by intestinal L-cells. It is responsible for regulation of glucose homeostasis by stimulating insulin secretion inhibiting glucagon secretion, promoting satiety and delaying gastric emptying.GLP-1 receptors are expressed in both coronary and heart vasculature. The receptor activation of GLP-1 by agonists leads to arange of cardiovascular outcomes including cardioprotectionagainst MIR injury both *in vivo* [71-76] and *ex vivo* [77-79]. The activated GLP-1 holds extremely short half-life of 2 min after administrating exogenously because it is quickly cleaved as well as inactivated due to protease dipeptidyl peptidase-IV [80,81]. Such a short half-life is

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a limitation to its use as a therapeutic agent as determined by the fact that studies with exogenously administered GLP-1 are reserved to continuous infusion dosing procedure. Many of GLP-1 receptor agonists have been recognized showing a long plasma half-life. Exendin-4 is a 39 amino acid peptide. It is derived from the saliva of gila monster.It possesses insulinomimetic and insulinotropic properties through activation of GLP-1 receptors. But although having extended plasma half-life (60 mins) than native GLP-1, exendin-4 needs twice daily injection to attain anti-diabetic effects. Alternative strategy is to createGAlbudAb (GLP-1 is genetically fused with DOM7h-14, which is a domain antibody, dAb) with replacement of alanine at position 8 by glycine to give peptide dipeptidyl peptidase-IV resistant leading to extended half-life. In a recent research study performed on male Sprague-Dawley rats, there was comparison between long acting GAlbudAb and exendin-4 (GLP-1 agonist having short half-life) for infarct sizefollowing MIR injury. It was observed that exendin-4 and GAlbudAb decrease the infarct size by 23% and 28% respectively compared to vehicle after MIR injury. Furthermore, it was observed that both exendin-4 and GAlbudAb improve post-ischemic cardiac contractile role. However, cardioprotection provided by GAlbudAb is better than that provided by exendin-4 as it is more sustained in duration. Moreover, extremely low plasma concentration of exendin-4 fails to protect heart from MIR injury, signifying that sustained activation of GLP-1 receptor plays a main role in offering cardioprotection in the setting of MIR injury. Long-acting GLP-1 agonists like GAlbudAb may demand additional evaluation as unique therapy to reduce MIR injury.

Suberoylanilidehydroxamic acid (SAHA) [82]

SAHA, a histone deacetylase inhibitor that interferes with the function of deacetylase, is approved for the treatment of cancer. The classical uses of histone deacetylase inhibitor are in neurology and in psychiatry, where they are used as anti-epileptics and mood stabilizers and also used in treating cancer. They are currently under investigation for the treatment of parasitic diseases, HIV, inflammatory diseases and heart ailments. In the *in vitro* model using rabbit, it was observed that the SAHA partially salvaged the systolic function, decreased the infarct size and SAHA pretreatment in rat ventricular cardiomyocytes reduced the cell death. It induces the autophagic flux, which leads to recycling of cellular components. Therefore, it proves to be a novel therepy for MIR injury and demands for further clinical studies.

Chemerin15 [83]

To prevent complications that are associated with extreme inflammatory responses, it is important to control neutrophil activation and neutrophil adhesion. ChemR23 that is expressed in neutrophil granules is rapidly upregulated upon activation of neutrophil.Chemerin15 (C15) is a 15-aa peptide that is derived from chemerin (a chemoattractant protein). It promotes phagocytosis of the cells that are apoptotic, through receptor ChemR23. It also stops pro-inflammatory mediator production by macrophages. It is observed that *in vitro* studies, C15 reduces neutrophil adhesion andchemotaxis and inhibits the integrin's activation and its clustering. It is also seen to modulate neutrophil physiology, thereby inducing detachment of adherent cell from inflamed endothelium, while also reducing recruitment of neutrophil and cardiac damage in a murine myocardial infarction model. ChemR23 mediates all these effects. Consequently, pathway of C15/ChemR23 is identified to be a new regulator and therefore curative target in pathologies driven by neutrophil.

Thymoquinone [84]

Thymoquinone is a volatile oil constituent, which is derived from seeds of *Nigella sativa*. It is an antioxidant and has anticonvulsant and analgesic effects, also showing potential anti-cancer effect. Thymoquinone reduces ROS generation, apoptosis and infarct size in an *ex vivo* study performed on rat heart. It also enhanced ventricular function and coronary flow of ischemic hearts. It attenuates the ischemia reperfusion-induced up-regulation of Stress-activated protein kinase/c-Jun NH(2)-terminal kinase (SAPK/JNK),P38-MAPK expression and Tumor necrosis factor alpha (TNF-α) and increases ratio of Bcl-2/Bax. As there is inhibition of ROS generated-NF-kappaB induction, itleads to inhibition of pro-inflammatory cytokines. Therefore, this natural compound can be employed as one of the therapies in treating MIR injury.

Cyclosporine [85]

The detrimental effects of reperfusion occur in a form of mitochondrial dysfunction, which has been considered as permeability transition. The membrane potential collapses because of the opening of nonspecific high-conductance channel in the inner mitochondrial membrane. This leads to cardiomyocyte death. Cyclosporine, along with being immunosuppressive, also inhibits mitochondrial permeability transition. It reduces the infarct size in patients having acute myocardial infarction. It is hypothesized that cyclosporine causes inhibition of mitochondrial permeability transition by preventing interaction of cyclophilin D with pore component, that is induced by calcium.Although this mechanism is uncertain for reducing the infarct size since cyclosporine is not seen to specific for cyclophilin D, it has some other intracellular effects too. In a rabbit model, it was observed that NIM811 (a cyclosporine nonimmunosuppressive derivative) binds to matrix cyclophilin D, and causes significant reduction of infarct size when being administered at the time of reperfusion. Although long-time use of cyclosporine has many detrimental effects like hepatic and renal toxicity, cyclosporine is a good candidate to use at the time of reperfusion as it is related with reduction in infarct size. However, further detailed study in larger clinical trial has been suggested for the confirmation.

Conclusion

ROS produced after an ischemia plays a main role in MIR injury by causing lipid peroxidation, cardiac dysfunction, inhibition of Na^+-K^+ ATP-ase activity of Na membrane channels and mitochondrial electron transport chain. Along with ROS, an extensive inflammatory reaction having neutrophil as the main component, complement system and no-reflow phenomenon can lead to MIR injury. Acute Myocardial Infarction is the leading cause of mortality in developed countries and yet there is no promising therapy for the treatment of MIR injury. The new therapies discussed in this review article are studied in animal models or *in vitro* studies and have shown to be efficient by offering several advantages such as improving myocardial

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and hemodynamics function and myocardial morphology, giving anti-inflammatory response, decreasing apoptosis and oxidative stress and low price with less side effects. Thus, these potential treatments can decrease the magnitude of impact caused by MIR injury. Therefore, much work still remains to be done and these new methods are suggested to be studied in clinical trials as well to make it routine way of treatment for MIR injury.

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