Pathophysiology of Myocardial Ischemia Reperfusion Injury: A Review

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Abstract

Cardiovascular events are one of the leading causes of death in the world. Thrombolysis, percutaneous transluminal coronary angioplasty, and coronary bypass surgery are the general treatment strategies of cardiovascular events. All of these treatment strategies can cause a myocardial ischemia reperfusion (MI/R) injury, which is known to occur on the restoration of coronary blood flow after a period of myocardial infarction (MI). Although there is an only way to save the myocardium from necrotic and apoptotic damages, “reperfusion achieved by the restoration of blood flow often aggravates cardiac dysfunction. It is believed that MI/R injury is related to the increased reactive oxygen species (ROS), calcium overloading, and the loss of membrane phospholipids especially during the reperfusion. The harmful effects of ROS on cardiac tissue during the MI/R can be prevented by endogenous antioxidant systems. Also, the complement system plays a crucial role in the inflammatory events of ischemic injury; thereupon it is important in the pathogenesis of the MI/R injury. Polymorphonuclear leukocytes in the reperfusion period are also associated with MI/R injury. Therefore these circumstances can increase the irreversible tissue damage. Although sometimes the reperfusion is provided, blood flow cannot be supplied to the myocardial tissue. This is called a no-reflow phenomenon. A lot of exogenous antioxidant agents can be used to prevent this process of injury. Due to these properties of antioxidants, a number of studies have been carried out and have been reported anywhere in the world. These studies demonstrated that these agents can be used in the MI/R-induced tissue damage and protect the heart against ROS-related myocardial injury.

Key Words: Myocardial ischemia-reperfusion, free radicals, no-reflow, necrosis, antioxidants

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1. Overview Of The Myocardial Ischemia Reperfusion Injury

In spite of the advances in the treatment of ischemic heart diseases in the last three decades, acute myocardial infarction (AMI) remains the leading cause of death in the developed countries [1]. Myocardial ischemia reperfusion (MI/R) injury occurs during the invasive treatments such as, thrombolysis [2], angioplasty [3], coronary by-pass [4] and heart transplantation [5] (Fig. 1).

The re-flow of blood to ischemic myocardial tissue triggers necrosis and apoptosis (programmed cell death) in the myocytes [4]. Previously, we also reported that MI/R could cause an elevation of myocardial necrosis and apoptosis. In addition, melatonin [6] and caffeic acid phenethyl ester (CAPE) [7] treatments prevented MI/R-induced apoptotic and necrotic cell death which were confirmed histopathologically and biochemically. For a long time, necrosis has been considered to be the sole cause of the cell death in AMI. Now, it is clearly known that apoptosis also plays an important role in the process of myocyte deaths subsequent to AMI. The apoptotic process is initiated after the onset of ischemia, and enhanced during reperfusion. Therefore it is thought that inhibition of apoptosis can attenuate the MI/R injury [8].
Figure 1. Algorithms of the myocardial ischemia-reperfusion injury. The reasons of ischemia and the results of reperfusion injury are shown.
There are some hypotheses and findings used to explain the pathogenesis of MI/R such as oxidative stress, Ca\(^{2+}\) overloading, loss of membrane phospholipids, neutrophil mediated endothelial dysfunction, progressive decrease in microvascular flow and depletion of the high energy phosphate store [9]. Oxidative stress is mostly related to the increased formation of reactive oxygen and nitrogen species (ROS and RNS), which transmogrify the phospholipids and proteins leading to lipid peroxidation. These changes are considered to the change membrane permeability and configuration in addition to producing functional modification of various cellular proteins [10] (Fig. 1).

Oxidative stress can cause to some cellular defects such as decreasing of the sarcolemmal Ca\(^{2+}\) ATP-ase pump and Na\(^+\)-K\(^+\) ATP-ase activities. These alterations lead to a decrease in the Ca\(^{2+}\) effluxes and an increase in the Ca\(^{2+}\) influxes, respectively. Oxidative stress has also been reported to suppress the sarcoplasmic reticulum Ca\(^{2+}\) ATP-ase pump and thus inhibits Ca\(^{2+}\) sequestration from the cytoplasm in cardiomyocytes. ROS change the activity of Ca\(^{2+}\) regulatory mechanism and this results in intracellular Ca\(^{2+}\) overload and cell death [11].

Another possible mechanism of the MI/R injury is complicated and associated with the activation of polymorphonuclear neutrophils (PMNs). Previous studies have shown that this cascade of injury is related to the inflammatory response and involved with circulating PMNs and the coronary endothelium [12]. Herein, the aim of this review is to evaluate the possible mechanisms in the pathophysiology of the MI/R injury.

2. Pathophysiology

2.1. Introduction

The term “ischemia” refers to lack of the blood flow, which leads to insufficient oxygen and nutrient supply to the tissue. Therefore, this situation strongly triggers the tissue damage. In the severity of the damage, not only ischemia’s seriousness, but also its duration is also important. If its duration is less than 40 min, cellular and functional alterations are reversible and can be treated. If it is between 40-50 min, there is a certain progressive functional loss and irreversible damage, if it is more than 50 min, some events occur, which resembles reoxygenation or reperfusion injury; however, they do not have the same mechanisms [13].
Ischemic tissue indicates some pathological abnormalities [14]:

a) hypoxia; ischemic myocardial injury results in the decreased oxygen tension with the loss of oxidative phosphorylation,

b) ischemia leads to anaerobic metabolism and accumulation of the toxic compounds,

c) Acidosis resulted from catabolic reaction.

In the experimental studies, the metabolic changes in ischemia which is provided by clamping the main coronary artery are summarized as follows;

a) stopping the aerobic metabolism,

b) decreasing in the creatine phosphate (CP),

c) initiating the anaerobic glycolysis,

d) accumulation of the some glicolicit products, such as lactate, alpha-glycerolephosphate (GP).

All of these changes mentioned above lead to the loss of myocardial contractility, changes in the membrane potential and ECG alterations including animal models such as ST elevations, T negativity, ventricular fibrillation and atrio-ventricular complete block (Fig 3a-d). When the cells expose to the irreversible damage, ATP levels decrease, anaerobic glycolysis stops, H⁺, AMP, insignia, lactate and GP increase, osmolarity reaches a high level, membrane damage begins, cellular and mitochondrial swelling occur and lastly amorphous densities are observed in the mitochondria [15].

2.2. THE MECHANISMS OF REPERFUSION INJURY

The early reperfusion is an undoubted precondition for the survival of ischemic myocardium. However, reperfusion has been known as the “Double edged sword”. Since reperfusion itself may lead to an accelerated and additional myocardial injury therefore, this circumstance is often called reperfusion injury. MI/R injury is widely accepted as a stimulus for myocyte damage and possible cardiac failure. It is well known that the pathogenesis of reperfusion-induced myocardial injury is multifactorial [16].
For the first time, Tennant and Wiggers [17] clearly revealed that the reperfusion of ischemic myocardium potentially led to malignant ventricular arrhythmias. Then Jolly et al. [18] indicated that ROS, formed just after an ischemic period, play an important role in the MI/R injury. ROS are extremely reactive reagents that induce functional and structural damages of the proteins, lipids, and nucleic acids in the cardiac myocytes. The harmful effects of ROS on cardiac tissue during the MI/R can be prevented by endogenous antioxidant systems including enzymatic and non-enzymatic pathways [19]. The following studies indicate that Polymorphonuclear leukocytes (PMNLs) in perfect reperfusion are associated with this injury. This event occurring in the first seconds of reoxygenization and increasing the irreversible tissue damage is called “Oxygen Paradox” [20]. In the study of Hill and Ward [21], it was stated that the complement system played a crucial role in the inflammatory events of ischemic injury. Thus, it is possible to say that oxygen, blood cells and complement system activation in blood are extremely important in MI/R injury phenomenon.

In sum, MI/R leads to a well characterized sequence of hazardous events on myocardial tissue such as [9,22] (Fig. 1) ;

a) arrhythmias,

b) myocardial stunning,

c) increased infarct size ratio,

d) oxygen paradoxes,

e) no-reflow phenomenon,

f) impairment of the contractile function

To increase the rescued tissue in the optimum conditions and appropriate time, reperfusion must be provided. Infarct size depends on the ischemia duration, collateral blood flow, consumption of oxygen amount, and the reperfusion form.

2.2.1. Free Oxygen Radicals

Free radicals are atoms or groups of the atoms with an unpaired number of electrons and can be formed when oxygen interacts with certain molecules. Some of the powerful hazardous
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radicals are superoxide (O$_2^-$), hydroxyl radical (OH$^-$) and hydrogen peroxide (H$_2$O$_2$). ROS are derived from a variety of sources such as the activated neutrophils, xanthine oxidase system, arachidonic acid pathways and the electron transport chain of mitochondria [23]. These highly reactive radicals can trigger to develop a chain reaction. It is well known that ROS cause MI/R-induced cardiac dysfunction, lipid peroxidation, inhibition of mitochondrial electron transport chain and Na$^+$-K$^+$ ATPase activity of membrane Na channels. Antioxidant treatments can improve recovery of the heart contractile function, ion transport activities, ATP content and reduce infarct size induced by MI/R [24].

There are many antioxidant mechanisms called as “antioxidant defense systems”. Antioxidants can source from endogenous or exogenous conformations. Endogenous antioxidants are divided into two classes; (1) enzymatic (e.g., superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione reductase (GRd) and (2) non-enzymatic endogenous antioxidants (e.g., melatonin, glutathione, methionine, cysteine, hemoglobin and myoglobin). Exogenous antioxidants include vitamins (e.g., ascorbic acid, alpha-tocopherol, beta-carotene), inorganic antioxidants (e.g., selenium), synthetic antioxidants (e.g., butylated hydroxyanisole) and plant-derived polyphenols. Organisms mostly use glutathione, GSH-Px, glutathione transferase, SOD, CAT and a variety of other antioxidants to protect themselves against the generation of ROS [25]. Pentose monophosphate pathway leads to reduced glutathione production with obtaining NADPH and helps GSH-Px, which plays a role in detoxification of the lipid peroxidation. In addition vitamin C, vitamin E and selenium, GSH-Px's cofactors, have important roles in the antioxidant defense system of the cell.

In accordance with the above mentioned knowledge, previously our research team focused on some the antioxidant agents such as melatonin, CAPE and aminoguanidine (AG) against I/R injuries. Previously, we investigated the impacts of these agents in the different events induced by I/R such as skin flap injury [26], liver injury related to MI/R [27], myocardial infarct size and oxidative changes [6] and MI/R induced apoptotic cell death [7]. Ischemia-depended injury includes free radical formation and neutrophil activation [26]. These mechanisms lead to direct tissue damage and cause remote organ injuries with the end products. Particularly oxygen-based reactants may play a central role in the remote organ injury [28]. We applied a MI/R protocol on rats and examined its effect on the end (remote)
organs such as liver [27], testis [28] and kidney [29] tissue. To produce myocardial injury, the left main coronary artery was occluded for 30 min, followed by 120 min reperfusion, in anesthetized rats. In our results, MI/R led to a significant increase in serum MDA and NO levels, whereas, melatonin and CAPE administration significantly reduced these productions. Also, the MI/R protocol induced severe testicular damage and antioxidant agents, CAPE and especially melatonin showed protective effects on the testicular damage [28]. One of our melatonin related studies was designed to investigate its effects on the MI/R-induced cardiac infarct size and oxidative changes. In this study, melatonin was given 10 min before ischemia via the jugular vein. Infarct size was found significantly greater in the MI/R group than in the melatonin-treated group. Also, MDA levels were significantly higher however; GSH levels were lower in the MI/R group than in the control group. Melatonin significantly reduced the MDA generation and increased the GSH levels. According to these results, we indicated that melatonin improved the antioxidant capacity of the heart and attenuated the degree of lipid peroxidation after the MI/R [6]. In another study, we examined the effects of AG, known as iNOS inhibitor, on percentage of infarct size in the anesthetized rats. With the same MI/R protocol AG was given 10 min before occlusion. When compared to the MI/R group, AG administration statistically reduced the myocardial infarct size. In this study we revealed that AG reduced NO-related side effect in the MI/R injury [30].

2.2.2. Role of Neutrophil Activation in the Reperfusion Injury

Neutrophils are the most abundant type of white blood cells in mammals. They are generally referred to as either neutrophils or PMNs. Neutrophils are normally found in the blood stream and during acute phase of the inflammation. They are one of the first-responders of inflammatory cells to migrate towards the site of the inflammation and they migrate through the blood vessels, then through interstitial tissue, following chemical signals such as interleukin-8 (IL-8), C5a, and leukotriene B4 in a process called chemotaxis [31]. Occlusion of coronary artery causes cardiomyocyte dysfunction. It is well known that the common cause of AMI is coronary atherosclerosis. Also, it is stated that protease inhibitors, platelet factors and complements can be a coronary risk factor. And then, inflammation and intimal damage lead to improved coronary atherosclerosis [32]. The reperfusion of infarcted myocardium has been accepted as the choice of treatment for AMI and markedly accelerates the development of an inflammatory reaction in the infarcted tissue. Inflammation is extremely important in the
healing of tissue after injury [33]. However, the restoration of the blood flow to ischemic tissue causes an extension of ischemia-related tissue damage.

The genesis of post ischemic inflammation is complex and involves genetic up-regulation of endothelial cell adhesion proteins and inflammatory cytokines, activation of vascular endothelium and infiltration of neutrophils. It is well established that the neutrophils are the most important compounds of this response [34]. Inflammatory pathologic condition includes two main events; vascular and cellular responses [35].

**Vascular Events:** There are two remarkable changes at vascular flow and permeability:

1) **Vascular flow and diameter:** Vasodilatation occurs in the arterioles and at an earlier time this dilatation leads to an increase in the warm and blushing. The proteins pass into the extravascular fluid from the circulation. Blood flow in vessels slows (stasis) and leukocytes migrate to the vessel walls.

2) **Increasing vascular permeability:** Vasodilatation causes an elevation of the hydrostatic pressure and thereby the fluid filtration is increased from the capillaries. This fluid structure exerts exudative property. And then interstitial osmotic pressure increases and lastly edema formation occurs.

**Cellular Events:** The most important function of leukocytes is migration to the area of injury. According to the circumstances as follows:

1) migration and rolling,

2) adhesion,

3) phagocytosis and intravascular destruction,

4) extracellular releasing of the leukocyte products.

Leukocytes must be absolutely contacted with the endothelial to migrate inside of the tissue. C5a and superoxide anion (O') increase this adhesion process [36]. Activated neutrophils release ROS and proteases. Free radical scavenger includes SOD and peroxide destructors (CAT and GSH-Px enzymes) attenuate the harmful effects of this injury which is formed by cytotoxic ROS. However these agents are in the cell, therefore it is thought that, they can be inadequate in the damage which sources from extracellular events. Consequently it can be an
appropriate treatment to use free radical scavenger agents from outside [18]. According to Giclas et al. [37] the subcellular membranes of myocytes activate the complement system. Many studies have indicated that AMI activates complement system and causes neutrophil activation. Activated neutrophils release some mediators such as ROS, platelet activating factor (PAF), thromboxane and leukotriens thereby lead to tissue damage [38, 39].

In sum, oxidative stress and inflammatory process are important in the pathogenesis of coronary artery disease. Infiltrating macrophages and neutrophils lead to transformation of stable coronary artery plaques to unstable lesions [40]. MPO, a proinflammatory enzyme and a hemoprotein that is stored in azurophilic granules of PMNs and macrophages and MPO activity is known to be related to the tissue neutrophil accumulation [41].

No-Reflow Phenomenon

Sometimes, although the reperfusion had been provided, coronary arteries cannot achieve adequate perfusion to the myocardial tissue. Since there is a flow deficiency to the epicardial vessels and microvascular tissues, this phenomenon is called no-reflow. The main determiner of the no-reflow is neutrophil activation on the microvascular bed. Activated neutrophils adhere to the capillary endothelial and block the blood flow mechanically. Alongside this mechanic blockage, they can cause a microvascular constriction (cellular edema) through the releasing of mediators. This phenomenon restricts the beneficial effects of reperfusion, and causes repetitive myocardial ischemic attacks and arrhythmias. Also no-reflow phenomenon can increase the ratio of necrosis and may decrease the contractile functions. Additionally the decreased blood flow hampers the drugs to reach for their targeted region [42] (Fig. 2).

In fact there are a lot of chemotactic agents such as arachidonic acid products and leukotrien B4 can cause no-reflow phenomenon. These agents either indicate chemotactic impacts or activate the inflammatory cells. Also it had been revealed that C5a induced the neutrophil aggregation and degranulation. Leukotrien B, formed in arachidonic acid metabolism, is a potent neutrophil attracted agent. It stimulates $O_2^-$ production in neutrophils, and increases the adhesion of neutrophils to the vessel wall and alters the capillary permeability and vessel sensitiveness like C5a. Additionally, apart from this, other members of chemotactic agents are fibrinogen, fibrino-peptid B, plasminogen activator, kallikrein and PAF which activate the
neutrophils to migrate to the tissue. IL-1, released from neutrophils, also is a chemotactic agent for neutrophils and is a primer mediator of acute phase reactions [43]. Besides, neutrophils lead to damage, cell groups of activated neutrophils in vessel cause no-reflow phenomenon with hampering the reperfusion after a short ischemic period.

Figure 2. No-Reflow Phenomenon. The main determiners of no-reflow are presented on microvascular bed.

It is examined by a lot of investigators; there is a relation between infarct size and neutrophil infiltration. After the onset of ischemia, infiltration of neutrophils and increasing of infarct size become too clear in first 24 h [34].

There are many different techniques to diagnose no-reflow status:

a) **Myocardial contrast echocardiography (MCE):** This technique is used in the clinic to document MI/R-induced no-reflow and its negative clinical implications.
b) **Magnetic resonance imaging (MRI):** It can evaluate myocardial perfusion during the first pass of the contrast agent [44].

c) **Myocardial blush:** Thrombolysis in myocardial infarction (TIMI) perfusion grade has been proposed as a measure of the filling and clearance of contrast in the myocardium.

d) **Measurements of intracoronary pressure:** With this technique it is possible to measure pressure gradient across the target artery.

e) **Intravascular ultrasound (Virtual histology):** Progress in imaging resolution is ongoing and intravascular ultrasound can now help in the differential diagnosis of angiographic no-reflow because it permits exact analysis of the epicardial vessel integrity.

f) **Electrocardiography:** Decreasing of the rapid ST segment is highly specific for myocardial reperfusion (or the absence of no-reflow on MCE) although less sensitive. Elevation of the ST segment after coronary reperfusion therapy is associated with clinical outcomes. ST segment monitoring is a helpful method to evaluate the myocardial reperfusion.

g) **Biochemical markers:** Serial measures of serum myoglobin, creatine kinase-MB or troponin I/T at baseline and at 60 min or 90 min after the reperfusion therapy have been a useful technique for the assessment of infarct related artery patency.

h) **Myocardial scintigraphy:** Myocardial scintigraphy is considered as the first evidence for the no-reflow phenomenon in humans, is quite burdensome; therefore it is not used in the emergency clinic settings.

i) **Nuclear magnetic imaging and positron emission tomography:** This technique is applied in the research centers, because of the technical difficulty and invasive character [45].

j) **Coronary angiography:** TIMI blood flow can evaluate the level of coronary flow during angiography. TIMI 0 or 1 flow is thought a failure of reperfusion and TIMI 2 or 3 flow tell us reperfusion is successful. However some thrombolysis trials demonstrate there is an equally poor prognosis for patients with TIMI 1 and 2 flow.
compared with TIMI 3 flow. Therefore TIMI 2 flow is associated with a no-reflow zone and only TIMI 3 flow can be accepted to indicate success of reperfusion [46].

k) **Intracoronary Doppler:** The no-reflow phenomenon has three main components characteristically: reduced antegrade systolic flow, systolic flow reversal and forward diastolic flow with a rapid deceleration slope. With intracoronary doppler measurements, these patterns can be indicated [47].

In the treatment of the no-reflow phenomenon, in sum, vasodilators, antithrombotic drugs, post-conditioning procedures, distal embolic protection devices, proximal protection devices, percutaneous intracoronary thrombectomy, direct stent application, human bone marrow-derived angioblasts, beta blockers, angiotensin receptor blockers and angiotensin converting enzyme inhibitors are used [45,46].

### 2.2.3. Activation of Complement System in the Reperfusion Injury

Activation of Complement System is a direct mediator of tissue damage and an important inducer of the acute inflammation response. However, it often prevents tissue damage in the autoimmune and inflammatory diseases. Therefore, it is estimated that the complement activation has an inhibitory property. This inhibition which blocked the C3 and C5 activators is found among the endogenous regulatory proteins. Especially, complement receptor 1 (CR1 or named CD35) is the best inhibitory feature. CR1 is found in a restricted number of cell types. sCR1 blocks classic and alternative complement pathways. It decreases the infarct size in the reperfusion injury at the ratio of % 94 [47]. Also it hampers the complement activation in the tissue. sCR1 is an important agent in the complement depended tissue damage. Therefore, sCR1 related with symptoms is a good evidence for the direct role of the complement system in the tissue damage. Complement activation following AMI was firstly described by Hill and Ward, with subsequent evidence suggesting that myocardial cell necrosis results in the release of subcellular membrane constituents that are abundant in the mitochondria and capable of triggering the complement cascade (C1, C2, C3, C4) [48].

During the reperfusion period, the complement system causes tissue damage and cell death through directly and indirectly. Evidence shows the role of complement activation in the ischemic injury is that, if it can be suppressed with “Cobra Venom Factor”, the expected injury size will be decreased [49].
Vascular damage, occurred by complements in the MI/R, is examined in two stages. In the early stage, as a result of complement activation, active forms of C3a, C4a and C5a (anaphlatoxins) are produced. Anaphlatoxins release histamine from mast cells and basophills, and cause an increasing of the permeability. Besides, C5a attracts the PMNLs to the tissue and increases inflammatory response against the muscle cells. After the complement activation C5b-9 complex (Membrane Attack Complex/MAC) is formed. By the mediation of this complex, complement system can cause tissue damage on its own. The MAC is observed at least six hours after the symptoms. It makes a pore on membrane and leads to cell swelling and lyses [50].

Figure 3. Example of the measured ECG, heart rate and blood pressure signals through BIOPAC MP-100 A-CE data acquisition system. ST elevations (a), T wave negativity (b), ventricular fibrillation (c), atrio-ventricular complete block (d).

Figure 3a. ST elevations

Figure 3b. T wave negativity
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Figure 3c. Ventricular fibrillation

Figure 3d. Atrio-ventricular complete block

Discussion

Myocardial ischemia is characterized by an absolute or relative decrease in the blood supply, a shortage of oxygen, glucose and other nutrients. Ultimately this can cause severe damage because of the potential for an accumulation of the metabolic wastes. All of these circumstances induce myocardial injury such as necrosis, arrhythmias and apoptosis [51] (Fig. 1). The restoration of blood flow is called reperfusion. The early reperfusion is important to maintain the viability of ischemic tissue. However reperfusion of the ischemic myocardium leads to more severe damage paradoxically, compared with the ischemic injury. After the
reperfusion of the ischemic myocardium, ROS can be formed, which are seen as one of the most important causes of the reperfusion injury. ROS have an unpaired electron, and attacks to all biomolecules in the cell due to its high reactivity [16]. This event is a cascade of ongoing that may last until the scavenging of free radicals and removing of peroxides from the environment. The endogenous antioxidants such as SOD, CAT, GSH-Px, glutathione and vitamin E create a line of defense against the oxidative stress. The deterioration of the balance between formation rate of oxidant molecules and antioxidant defenses leads to the oxidative stress. Some antioxidant agents such as melatonin, CAPE, and AG can be used to prevent from this process. After the reperfusion of infarcted myocardium which has been accepted as the choice of treatment for AMI, an inflammatory reaction develops in the tissue. Inflammation is important in the healing of tissue after I/R-induced injury [33]. However the restoration of the blood flow to ischemic tissue causes an extension of ischemia-related tissue damage. Neutrophils are the most important compounds of this event. Activated neutrophils also release ROS and proteases. Free radical scavengers and peroxide destructors endeavor to attenuate the harmful effects of the injury which is formed by cytotoxic ROS [41]. The complement system activation has also roles in the MI/R injury.

Taken together, to treat a disease, it is important to know its mechanism(s) with all details. In this review, we summarized the pathophysiology of the MI/R injury. MI/R injury fundamentally comprises the oxidative stress and inflammation-related events. It is demonstrated that antioxidant and anti-inflammatory agents can decrease the possible damage related to the MI/R injury in the experimental conditions. It would seem worthwhile to test the antioxidants such as melatonin in the clinical trials for prevention cardiac damage associated with MI/R-induced injury.

**Conflict of Interest Statement**

All authors declare that they have no conflicts of interest.
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