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Review Article

PROTECTION AGAINST MYOCARDIAL ISCHEMIA REPERFUSION INJURY

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ABSTRACT

Ischemia reperfusion injury refers to a series of pathologic events, which occur after restoration of perfusion to ischemic tissue. Ischemia reperfusion injury associated inflammatory reactions which occur at the blood endothelium interface are extremely critical to the pathogenesis of tissue damage. Myocardial ischemia results in a characteristic pattern of metabolic and ultrastructural changes that leads to irreversible injury. Indeed, such transient periods of ischemia are encountered in the clinical situations of angina, coronary vasospasm, balloon angioplasty, and are not associated with concomitant myocardial cells death. Early and fast restoration of blood flow has been established to be the treatment of choice to prevent further tissue injury. Unfortunately, restoring blood flow to the ischemic myocardium, named reperfusion, can also induce injury. This phenomenon is therefore termed myocardial ischemia reperfusion injury. The use of antiplatelet and anti-thrombolytic agents or primary percutaneous coronary intervention (PPCI) is the most effective strategy for reducing the size of a myocardial infarct and improving the clinical outcome. A number of new therapeutic strategies currently under investigation for preventing myocardial reperfusion injury have the potential to improve clinical outcomes in patients with acute myocardial infraction treated with PPCI.

Keywords: Acute myocardial infraction; Anti-platelet; Anti-coagulants; Endogenous Cardioprotection; myocardial ischemia; primary percutaneous coronary intervention; Reperfusion injury

INTRODUCTION

Cardiovascular diseases are responsible for a third of all deaths; ischemic heart disease is the leading cause. According to the World Health Organization, by 2020, ischemic heart disease will be the single most common cause of death[1].Ischemia is defined as an insufficient supply of the nutrient and oxygen to the cardiac muscle. During ischemia, the level of glutathione, phosphocreatine and ATP are reduced while hypoxanthine level gets elevated. Altered ion distribution, i.e. increase in intracellular Ca2+/Na2+, cellular swelling, cytoskeleton disorganization and acidosis of cells occur[2]. During reperfusion injury, blood flow supply returns to the cardiac muscle that causes release and activation of intracellular Ca2+ channel, formation of cellular edema and damage to lipid membrane[3]. There is currently no effective therapy for preventing myocardial ischemic reperfusion injury, Hence, restoration of antegrade coronary flow and preservation of the viability of the ischemic and reperfused myocardium should be the main goal in the treatment on myocardial ischemia[4]. However, the exact mechanism of ischemia reperfusion injury is not fully known. Molecular, cellular, and tissue alterations such as cell deaths, inflammation, neurohumoral activation, and oxidative stress are considered to be of paramount importance for Ischemia reperfusion injury development[5]. In this review paper we explore the literature regarding the pathophysiology of myocardial ischemia reperfusion injury and pharmacological treatments to reduce ischemic reperfusion injury.

Pathophysiology of Ischemia-Reperfusion Injury:

Myocardial ischemia/reperfusion injury was first discovered by Jennings in 1960[6]. It develops when coronary blood supply to myocardium is reduced. Restoration of blood flow to ischemic heart is necessary for maintaining heart physiology.[7] The nonlethal episodes of ischemia and reperfusion prior to global myocardial ischemic insult have proved to reduce myocardial injury, which is termed as preconditioning. Reperfusion can elicit a cascade of adverse events that paradoxically causes injury of tissue.[8] During reperfusion after ischemic stress, hypoxanthine is oxidized by xanthine oxidase which produces reactive oxygen species (ROS).[9] Ischemia followed by reperfusion is a stronger cause of apoptosis than sustained ischemic insult. Ischemia due to an anaerobic metabolism causes catabolism of adenine nucleotide and leads to depletion of adenosine triphosphate (ATP).[10] At the time of reperfusion, xanthine oxidase metabolizes the hypoxanthine to xanthine and forms uric acid that leads to the formation of huge amount of reactive oxygen species, i.e. superoxide anion (O2), hydrogen peroxide (H2O2) and hydrogen radical (OH).[11] Myocardial IR injury usually causes inflammation on the cardiac muscle and leads to hypoxia.[12] This phenomena damages tissues by activating leukocytes, cytokines, reactive oxygen species and frequently develops during heart transplantation, infarction and sepsis.[13] When reperfusion is late and the infarction is extensive, the interior develops areas of severe microvascular injury with loss of the endothelial barrier, interstitial bleeding, and flow arrest (noreflow areas).[14] No-flow areas are associated with extensive infarctions and poor prognosis, suggesting that they contribute to cell death. However, there is no definitive evidence to support this theory, and considerable data indicate that no-flow areas are produced in already necrotic zones.[15] What does seem likely is that areas

without reperfusion hamper healing and favor scar expansion and subsequent adverse remodeling.[16]

Therapeutic strategies for reducing myocardial reperfusion injury:

Many therapeutic strategies that have successfully limited or prevented ischemic reperfusion injury in controlled, experimental models have yielded equivocal results in clinical practice or have not reached human clinical trials. Furthermore, few studies have examined the efficacy of combined strategies in attenuating ischemic reperfusion injury. Thus, at present, timely reperfusion of the ischemic area at risk remains the cornerstone of clinical practice. Thus, drugs remain to be developed for many potentially useful targets for treating reperfusion injury.[17]

Endogenous Cardio protection:

The first treatment successfully used in patients with STEMI was ischemic postconditioning.[18] In contrast with drug treatments, PostC reduces reperfusion injury by introducing brief episodes of ischemia, at the moment when reperfusion begins, which has a protective effect without the need for external agents (endogenous cardioprotection).[19] The protective effect of Postconditioning is mainly due to its ability to delay the normalization of intracellular pH for a few minutes, by slowing metabolite washout secondary to flow interruptions, and to the reduction in oxidative damage, which preserves the NO-cGMP-PKG signaling pathway and inhibits Na+/H+ exchange.[20] Recently, a form of endogenous protection has been described that involves remote induction (generally in the extremities) of intermittent myocardial ischemia immediately before or in the first few minutes of reperfusion: remote ischemic conditioning.[21] One advantage of remote ischemic conditioning over Postconditioning is that it does not require manipulation of the coronary artery during the first few minutes of reperfusion, but the mechanisms by which it exerts its protective effect remain unclear.[22]

Pharmacological Treatments:

During the past 10 years, many clinical trials have been performed to find coadjutants pharmacological interventions to ameliorate the myocardial damage associated with ischemic reperfusion injury.[23]

Cyclosporine:

Mitochondria are increasingly recognized as the linchpins in the evolution of cardiac injury during ischemia and reperfusion. Modulation of mitochondrial oxidative metabolism during ischemia or early reperfusion protects mitochondrial function and decreases myocardial cell death.[24] Cyclosporine is a potent inhibitor of mitochondrial PTP and under experimental conditions; it has been shown to limit ischemia reperfusion injury.[25] Recently, a study was done to determine whether administration of cyclosporine at the onset of reperfusion reduces the infarct size in patients with acute MI undergoing PPCI. This small trial demonstrated that administration of cyclosporine at the time of reperfusion is associated with a smaller infarct than that seen with placebo by some measures.[26]

Adenosine:

Adenosine has been studied as a cardio protective agent due to its ability to improve microvascular function, replenish high-energy phosphate stores in endothelial cells and myocytes inhibit oxygen free radical

formation, and inhibit neutrophil activity and accumulation.[27] Adenosine, a degradation product of adenosine monophosphate, has a potent vasodilatory action, among other effects. In addition to its effects on the vasculature and leukocytes, it directly acts on cardio myocytes, increasing no availability and, therefore, activating the cGMP/PKG pathway.[28] Intracoronary adenosine is a safe and inexpensive treatment, its early use in reperfused patients could be easily adopted. Subsequently, its use was proposed in the form of an intracoronary injection before reperfusion.[29]

Beta-blockers:

Beta-blockers provide protection against free radical mediated sarcolemmal lipid peroxidation. The antioxidant effect of the β-blockers results not only from their beta blocking properties, but also from their interaction with membrane lipids, resulting in the formation of the drugphospholipid complex.[30] Beta-blockers also decrease the saturated fatty acids in the membrane phospholipids. These effects retain the membrane integrity of the myocyte and reduce the susceptibility of the membrane to free radical attack.[31] Thus it is possible thatβ-blockers reduced the myocardial energy demand as well as the energy utilization during ischemia, which may in part account for the reduced cellular injury.[32]

Erythropoietin:

Erythropoietin (EPO) has been shown in experimental studies to have cardio protective effects.[33] There are two proposed mechanisms of cardio protection with Erythropoietin. First, stimulation of the Erythropoietin receptor in the heart increases neovascularization[34] and secondly, in ischemia–reperfusion models with Erythropoietin, there is a decrease in apoptosis which could possibly limit the infarct size.[35]

Anti-platelets:

A better understanding of the mechanisms leading to platelet activation in the context of myocardial reperfusion injury might help identify new therapeutic targets to limit plateletinduced reperfusion injury without further increasing the risk for clinically relevant bleeding and we aimed to identify targets that reduce ischemia–reperfusion (IR) injury with minimal or comparable risk of bleeding to the current therapeutic standards.[36] The ability of P2Y12 inhibitors to ameliorate myocardial response to ischemia/reperfusion challenging, which are part of the so-called pleiotropic properties of anti-platelet therapies investigated by Cohen and Downey group. It is likely that nowadays all patients with ACSs are treated with platelet P2Y12 receptor antagonists. It has been proposed that those patients receiving P2Y12 receptor antagonists are already cardioprotected, whether this cardioprotective effect is due to an amelioration of platelet function or is due to a direct effect on myocardium, is under investigation.[37] Blockade of platelet aggregation during primary PCI for AMI is a standard care to inhibit intravascular coagulation and to minimize stent re-thrombosis. Indeed, anticoagulant therapy during primary PCI for AMI is routinely applied.[38]

CONCLUSION

Protection against myocardial ischemia-reperfusion injury is a promising strategy for ameliorating the consequences of coronary disease for individual and societal health. During the coming years, it will be necessary to focus on studying the molecular mechanisms of cell death during myocardial reperfusion and on developing new therapies to prevent cell death and to establish the best way to use these treatments in clinical practice. Great progress has been made in deciphering the cellular mechanisms that lead to ischemia reperfusion and further studies will provide us with better understanding of the processes involved and with new therapeutic targets to tackle the challenge of ischemia reperfusion injury.

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