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PATHOPHYSIOLOGY OF MYOCARDIAL ISCHEMIA/REPERFUSION INJURY AND THE THERAPEUTIC FUNCTION OF NATURAL MEDICINES

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ABSTRACT

Heart is a dynamic electrical and mechanical machine in our body that starts working from fetus to till death. The disease to heart and/or blood vessels are known as cardiovascular diseases (CVDs). Aging gradually declines metabolic and physiological process that increases the risk factors of the disease. Pathological alterations in heart and blood vessels during aging increase the incidence of myocardial infarction. There are several risk factors such as hyperlipidemia, hypertension, diabetes, obesity, sedentary lifestyle, smoking and poor nutrition. These comorbidities and comedication during aging enhances the progression and severity of the disease. Complete understanding of pathophysiology of disease may help in increasing life expectancy and better treatment. The current review focuses on pathophysiology of myocardial ischemia/reperfusion injury and the role of natural medicines.

KEY WORDS

Myocardial infarction, myocardial ischemia/reperfusion injury, metabolic shift, homeostasis and natural medicines

INTRODUCTION

Myocardial ischemia/reperfusion

Coronary artery supplies blood to the heart. Occlusion in coronary artery due to atherosclerosis, narrow downs the vascular lumen and activates clotting cascade. Early stages of narrowing of arteries elicit hypoxia and eventually complete blockade due to formation of thrombus in the intracoronary leads to ischemia. During these periods the demand and supply of oxygen and other nutrients will not be in equilibrium, there by alters cellular homeostasis and leads to cell death [1,2]. This causes acute myocardial infarction (MI). Initiation and progression of atherosclerosis plays a crucial role in the development of MI. Mainstay therapy is reperfusion through percutaneous coronary intervention and thrombolytic therapy. Reperfusion has a dual role where, on one side it salvages the diseased myocardium and on the other side it leads to reperfusion injury which aggravates the severity of myocardial infarction. Thus, causes myocardial ischemia/reperfusion (M-I/R) injury

Prevalence of the disease

In India, 4 deaths per minute and 2.5 million deaths every year is due to cardiovascular diseases (CVDs) [3,4]. By 2030, mortality due to CVD reaches to 35.9% compared to 2008 where it was 24% in India [5]. The occurrences of CVDs are either congenital or acquired. According to fact sheets of world heart federation 2017, 46% and 38% deaths due to CVD are caused by ischemic heart diseases (IHD) in male and female respectively. Among IHD, MI and stroke are epidemic globally. Though there are several advancements in the treatment, yet the number of people suffering with MI is rising due to increase in older population. The cost of

treatment will be tripled by 2030, where it will be an alarming economic concern worldwide [6].

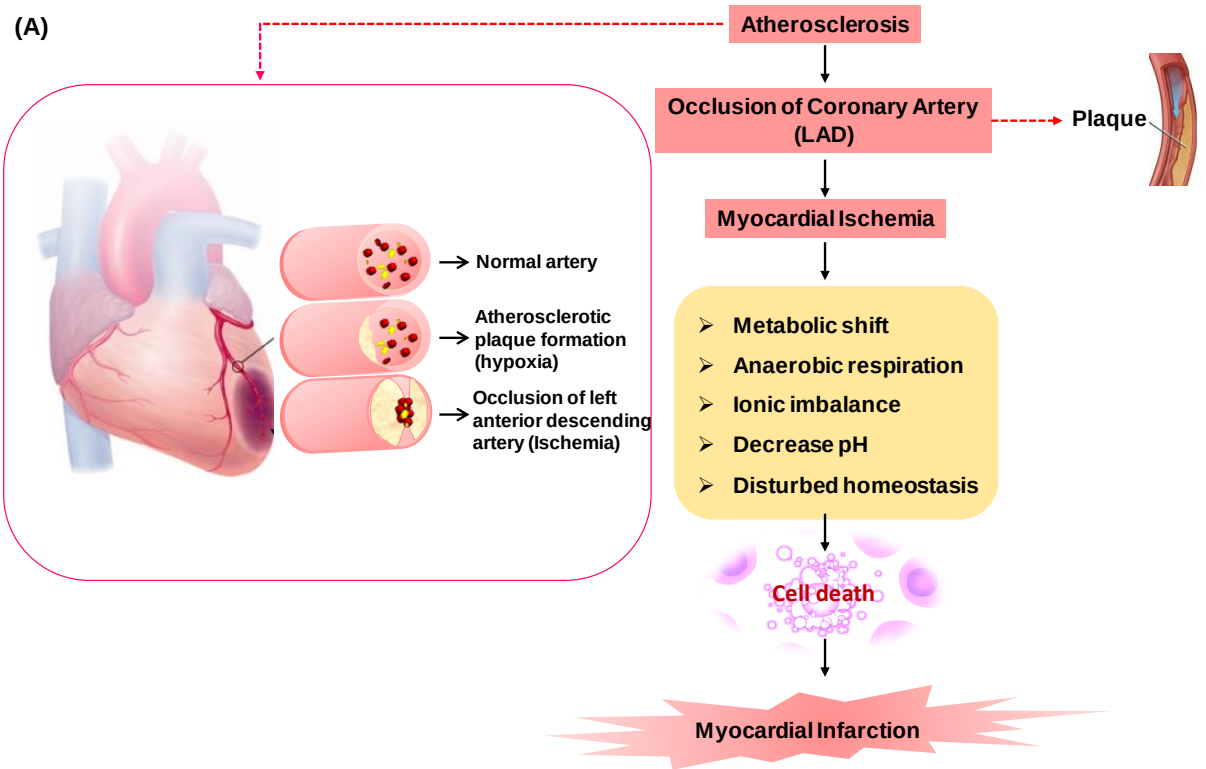
Risk factors

Inevitable risk factors such as aging, family history and genetic factors; controllable risk factors such as diabetes, hypertension, hyperlipidemia, smoking, alcohol consumption, stress, obesity and life style modifications are the major risk factors of MI [5,7–9]. Altered cellular morphology, homeostasis and metabolism causes endothelial dysfunction, chronic inflammation and tissue remodeling. "Atherosclerosis is the underlying factor for the occurrence of MI".

Pathophysiology of myocardial infarction

Coronary vasculature majorly controls the function of heart as it supplies oxygen and nutrients to the myocardium. Around 80% of myocardial ischemia is due to atherosclerosis in coronary artery (left anterior descending artery) and the other causes are coronary spasm, embolism and thrombosis in nonatherosclerotic arteries [10]. This leads to death of cardiomyocytes and the severity of infarction depends on the localization of plaque, age and comorbidities. Myocardium can tolerate brief period of ischemic episodes, but ischemia for more than 15 minutes causes irreversible damage [11]. MI eventually leads to cardiac failure based on the severity of loss of cardiomyocytes, hibernating myocardium, ventricular remodeling and myocardial stunning. These complications can be observed during hospitalization or discharge. Therefore, proper diagnosis and analyses are important while treating the patient.

Fatty acids are the primary source of energy for myocardium and 60-80% of ATP required is generated from β-oxidation and the remaining is from oxidation of glucose/ lactate and ketones. In early ischemic condition, cardiomyocytes tries to survive by undergoing profound changes, a metabolic shift towards glucose uptake is seen as fatty acid breakdown requires sufficient oxygen and leads to energy imbalance[12]. After ischemia, cell shifts from aerobic respiration to anaerobic glycolysis and continues during prolonged ischemia. Production of ATP is decreased, accumulation of byproducts of cellular metabolism and intracellular levels of protons, calcium ions are elevated [13]. This leads to disturbance in cellular homeostasis due to improper function of ion channels such as Na^+/K^+ ATPases, Ca^+ ATPases and altered pH (acidic) which inturn alters pathology and physiology of heart [14]. All these variations together cause improper functioning of heart and increases the severity of infarcted area.



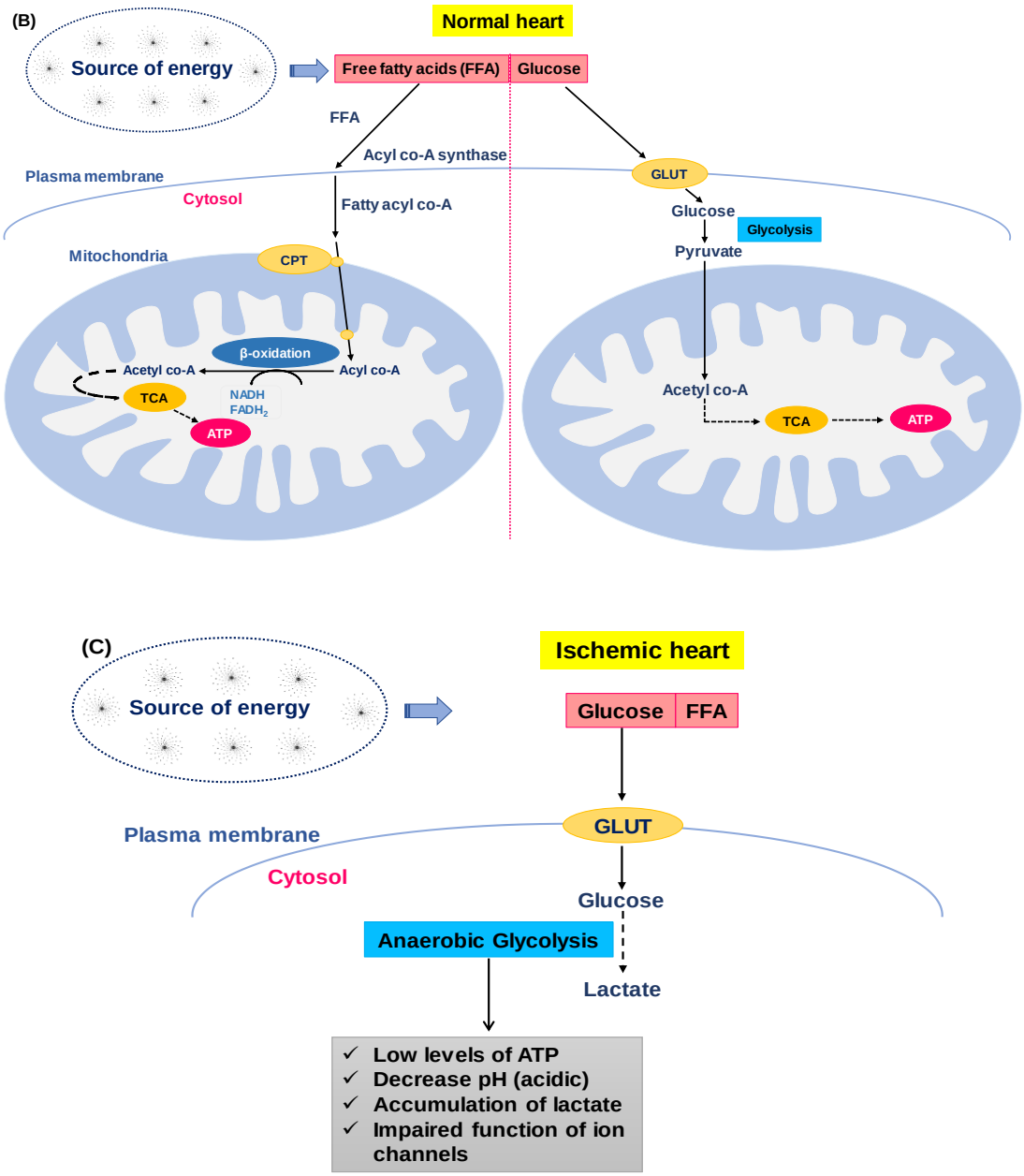


Figure 1. (A) Schematic representation of pathophysiological changes during myocardial infarction. (B) Regular metabolism for energy production in normal heart. (C) Altered metabolism for energy production in ischemic heart

Therapies to treat MI and challenges

Early diagnosis of MI is needed to protect from death by avoiding myocardial rupture. Reperfusion of blood flow in the coronary artery is only available therapy to protect ischemic myocardium. Thrombolytic therapy by anticoagulant streptokinase, plasminogen activator inhibitors and primary percutaneous coronary angioplasty (PCI) are the successful methods for reperfusion; thereby decreases the severity of infarction and mortality rate. Timely reperfusion with comedication such as antiplatelet therapy, beta blockers will bring back normal hemodynamic factors and maintains proper electrical and mechanical activities of heart [15]. Reperfusion treatment is beneficial when it is done within 3 h of onset of symptoms.

Thrombolytic treatment is the mainstay of reperfusion incase where immediate PCI cannot be performed[16]. Compared to thrombolysis, PCI is the best method as ischemic attack, cardiopulmonary resuscitation, trauma persistent hypertension were observed in 10.3% of patients who had undergone the thrombolytic

treatment [17]. Stent-based reperfusion therapy is the advanced method of treatment. Drug eluting stents are highly efficient without any thrombotic complications [18]. Besides interventional therapy, the patients will be under medication for cardiac protection to prevent recurrent cardiac episodes [19].

Pathophysiology of myocardial ischemia/reperfusion injury (M-I/R)

M-I/R was first described in 1960 by Jennings et al., in canine heart. Comorbidities and comedication are thriving factors influence the efficacy of treatment during MI. Reperfusion of coronary blood flow paradoxically induces myocardial damage known as M-I/R injury, a serious clinical problem. Restoration of blood flow generates reactive oxygen species in larger quantities because of oxidative stress; series of intracellular changes such as massive calcium overload and dysfunction of mitochondria due to dissipation of mitochondrial membrane potential; cardiomyocytes tries to acquire normal pH immediately; altered nitric oxide (NO) metabolism; all these stimulate necrosis or apoptotic cell death [20,21]. Pathological changes in cardiomyocytes due to reperfusion, occurs simultaneously and are interconnected to elevate myocardial damage.

Early restoration of blood flow, the cells restart aerobic respiration as of normal cells within few seconds of reflow. This cause oxidative stress and release free radicals. Free radicals such as reactive oxygen species (ROS), Superoxide(O_2^-) and hydroxyl (OH^-) ions are a major culprit of M-I/R injury. At this instance antioxidants such as superoxide dismutase (SOD), glutathione-s-transferase (GST) cannot completely scavenge free radicals as their levels are comparatively lower than outburst of free radicals. ROS in mitochondria opens mitochondrial permeability transition pore (mPTP), a channel of inner membrane of mitochondria that alters membrane potential and depletes ATP production by disconnecting oxidative phosphorylation. Opening of mPTP releases cytochrome-C to the cytosol there by activates apoptotic cell death. mPTP acts as best target for cardio protection [22].

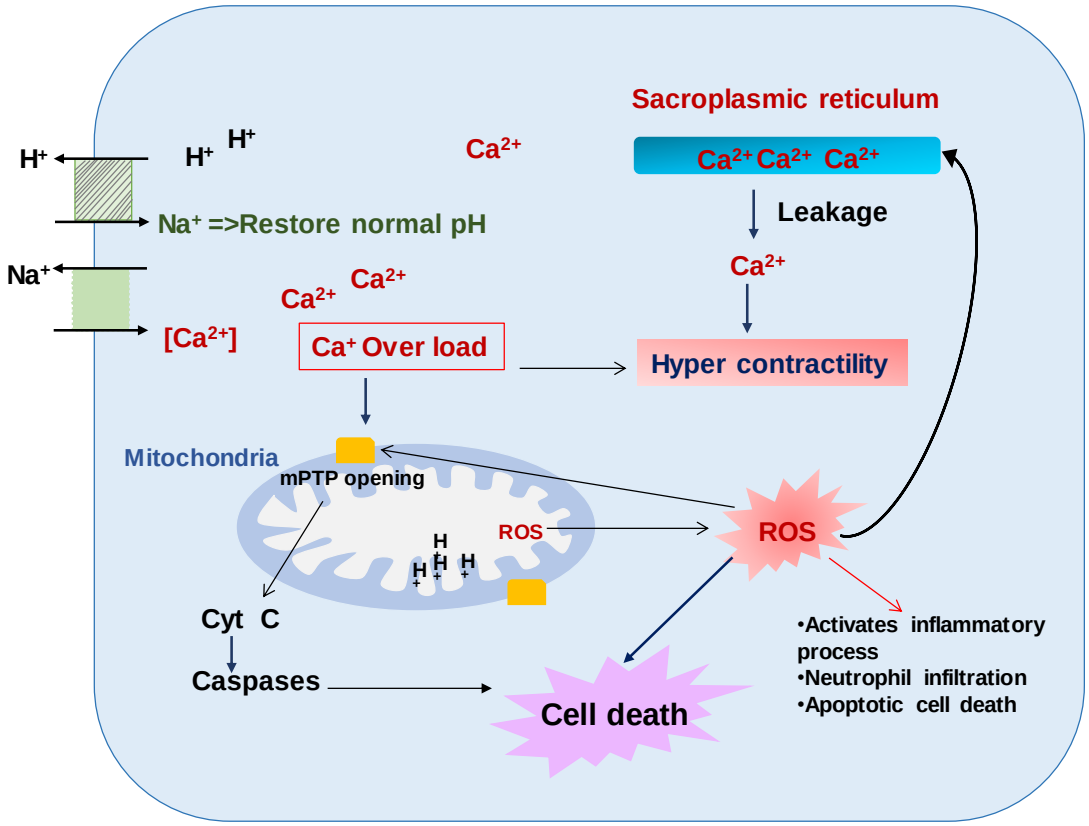


Figure 2. Schematic illustration of consequences of ischemia/reperfusion injury that triggers cell death due to altered homeostasis, reactive oxygen species and calcium overload.

On the other hand, free radicals shoot up inflammatory reactions that adverse the severity of injury. Several reports have stated that proinflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, NF-κB and IFN-Ɣ are upregulated during reperfusion that leads to cell death [23–25]. M-I/R injury also directs to endothelial dysfunction where the permeability of endothelial cells is increased. This further leads to activation and infiltration of immune cells. Integration of endothelial cells acts as best barrier to reduce inflammation [26]. During inflammatory process, macrophages secretes cytokines that evokes infiltration of neutrophils that orchestrate tissue damage by releasing free radicals [27].

Reperfusion may sometimes cause myocardial stunning as contractile function of cardiomyocytes cannot revert back to normal levels easily. Stunned myocardium requires abundant amount of oxygen to perform the mechanical function and thus decreases its efficiency.

By restoration of blood flow, the ischemic cell tries to stabilize homeostasis by attaining normal pH. During this process, intracellular H^+ ions are transported to extracellular space by exchanging Na^+ ions by Na^+/ H^+ exchanger and Na^+/HCO_3^- cotransporters. The Na^+ levels will be increased inside the cell which will be further exchanged with Ca^{+2} levels by Na^+/ Ca^{+2}. Increased cytosalic Ca^{+2} concentration depolarize membrane potential that permits L-type calcium channels to open and further increases calcium over load. This will in turn activates opening of mPTP channel and release ROS in cytosol that destroy sarcoplasmic reticulum (SR). Calcium from SR also leaks out to the cytosol and causes Ca^{+2} overload in cardiomyocytes [28]. Opening of mPTP leads to leakage of cytochrome C in cytosol that activates caspases and apoptotic cell death [29].

The other ticking problem in M-I/R injury is invasion of myofibroblast at the damaged site. The place where the cardiomyocytes death is observed will be eventually cleared by phagocytosis and will be occupied by myofibroblast. These are the spindle shaped cells that synthesize extracellular matrix proteins such as collagen that control contractile function of heart. But upon wound healing, myofibroblast at the infarcted area will be cleared and forms a scar that leads to ventricular remodeling [30]. This pathological process causes ventricular fibrillation and heart failure.

Numerous drugs to protect from M-I/R injury were validated in animal trials but translational to clinical setting is failed. Hence, a serious need in understanding multiple pathways involved in the disease is required. Novel discovery of potential targets to salvage disease myocardium is necessary to protect from M-I/R injury. It is hypothesized that combined targeting of multiple factors such as inflammation, ROS generation, calcium overload and endothelial dysfunction may salvage myocardium from I/R injury. The alternative therapy with minimal complications can be achieved by using traditional medicines.

"Cardiac regeneration is the best way to treat damage myocardium to avoid the complications involved in treatment of MI". But the cardiac regeneration is highly challenging. Cardiomyocytes are post-mitotic cells and very few resident stem cells makes poor regenerative capacity to resuscitate damaged myocardium. Cellular plasticity is compromised in adult heart. Eliciting cardiac regeneration either by reprogramming cardiomyocytes proliferation or activating c-kit stem cells of heart by regulating upstream and downstream signaling pathways holds mainstay to treat MI [31].

Role of natural products in treating myocardial ischemia/reperfusion injury

Herbal products are highly effective to protect myocardial damage and are emphasizing method to treat M-I/R injury with very minimal side effects. It was estimated that 80% of the population from developing countries depends on natural medicine from plants and animals. Medicinal plant have potent antioxidant, anti-inflammatory, anti-apoptotic, anti-atherosclerotic, antihypertensive and antithrombotic activity due to presence of wide varieties of flavonoids (functional foods), terpenes, polyphenols and cardioprotective amines [32–34]. The herbal medicines are used in the form crude extracts, decoctions or mixed compounds as it has synergistic effect [35].

Recent study on mangiferein, a natural compound extracted from the bark of *Mangifera indicia* proved to have cardioprotective activity by controlling inflammation and oxidative stress by acting as an inhibitor for advanced glycation end products – receptor for advanced glycation end products *in vivo* model of M-I/R injury [36]. Tanshinone IIA, a component of *Salvia miltiorrhiza,* proven to stabilize atherosclerotic plaques with antioxidant and anti-inflammatory activity [37]. Several medicinal compounds are under clinical trials that can be further used as magic bullets. Advancements in using herbal medicine in recent years

have growing attention to use as an alternative medicine to treat cardiovascular diseases. India and Chain are the goldmines for these medicinal plants. Wider usage of these can be done when the mode of action of these are completely understood. In addition to this the type of components, activity, safety and stability are required for clinical use [38]. Pharmacological evaluation of medicinal plants can either act as a leading drugs or gives a clue for drug structures as it helps in analyzing interactions between target and the compound [39] to develop better therapeutics.

CONCLUSION

Timely restoration of blood flow, targeting and treating reperfusion injury is inversely related to death of cardiomyocytes. This reduces the size of infarct due to M-I/R injury. Translation of therapeutic strategies from bench to bed side is possible by better understanding of timely changes in physiology and pathology of the myocardial injury.

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