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Pathophysiology of Myocardial Reperfusion Injury after Ischemia

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Discovering the Pathophysiology of Reperfusion Injury After Myocardial Ischemia

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Introduction and Background

Myocardial infarction remains a leading cause of death in the United States. Lack of blood flow to the heart causes an imbalance between oxygen supply and demand resulting in damage to the myocardium. Timely restoration of blood flow is the first line treatment to prevent tissue injury. However, the process of reperfusion can itself induce cardiomyocyte death, known as myocardial reperfusion injury (Hausenloy & Yellon, 2013)

Sudden reintroduction of molecular oxygen to energy starved tissue results in a unique type of injury response that is not manifested during the period of hypoxic stress. The discovery of this reoxygenation-dependent injury response, which is now commonly called "reperfusion injury", opened a new field of research that, despite many therapeutic strategies, is just being translated to bedside care. (Granger & Kvietys, 2015).

I chose this topic because the pathophysiology of reperfusion injury can lead to extensive damage and poor clinical outcomes. According to Frank et al., 2012, myocardial ischemia reperfusion injury accounts for up to 50% of the final size of a myocardial infarct. Myocardial damage contributes to significant comorbidities and patient quality of life is dramatically influenced by the amount of preserved myocardial function after ischemia. The following information presented will outline the pathophysiology of myocardial reperfusion injury and the clinical implications for nursing care.

Significance of Reperfusion Injury

✧ Cardiomyocyte death
Reperfusion-induced death of cardiomyocytes that were viable at the end of the index ischemic event is defined as lethal myocardial reperfusion injury. The existence of lethal myocardial reperfusion injury has been inferred in both experimental MI models and in patients with STEMI by the observation that therapeutic interventions applied solely at the onset of myocardial reperfusion reduced infarct size significantly (Hausenloy & Yellon, 2013). One study demonstrated a 36% reduction in MI size in reperfused-STEMI patients randomized to receive ischaemic post-conditioning. (Frolich et al 2013).

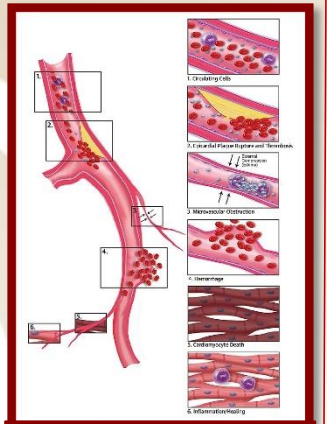

Illustration: Players involved in ischemia reperfusion injury (Ibanez et al, 2015)

✧ Ventricular Function
An increasing number of patients are developing heart failure. Understanding the implications of reperfusion injury to preserve LV systolic function and prevent the onset of heart failure may facilitate the discovery of new effective therapies for reducing MI size and preventing heart failure in patients presenting with reperfused STEMI (Bullock, Yellon and Hausenloy 2016). For this reason, therapeutic interventions for reducing reperfusion injury have be a viable target for cardioprotection in clinical practice

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Signs and Symptoms

✧ Reperfusion Arrythmia The most common reperfusion arrhythmia is accelerated idioventricular (AIVR), however ventricular premature contractions, sustained or non-sustained episodes of V-Tach, A-fib and V-fib are also observed (Tatli et al, 2013).

✧ Myocardial Stunning Reversible post-ischemic contractile dysfunction occurs on reperfusion of acute ischemic myocardium, resulting from the detrimental effects of oxidative stress and intracellular calcium overload on the myocardial contractile apparatus (Hausenloy & Yellon, 2013).

✧ Microvascular obstruction Occurs because of the vasculature's inability to reperfuse the previously ischemic area. (Hausenloy & Yellon, 2013). Contributing factors include capillary damage with impaired vasodilatation, external capillary compression by endothelial cell and cardiomyocyte swelling, embolization from the atherosclerotic plaque, micro-thrombi, the release of soluble vasomotor and thrombogenic substances, and neutrophil plugging. The presence of MVO is associated with a larger MI size, a lower LV ejection fraction, adverse ventricular remodeling, and worse clinical outcomes (Hausenloy & Yellon, 2013).

✧ Intramyocardial hemorrhage In severe cases of MVO extravasation of blood into the interstitium can produce intramyocardial hemorrhage within the area of infarction. It is a severe form of microvascular obstruction with a tendency to expand for several hours after percutaneous coronary intervention. According to Hamirani, Wong, Kramer and Salerno, 2015, the cause includes vascular endothelial damage and accumulation of red blood cells in the myocardial extracellular space. Vessels are injured by the initial ischemia but are reperfusable at the time of reflow. The result is a subsequent increase in intersitial pressure, again compromising tissue perfusion (Simonis, Strasser and Ebner 2012). Multiple factors contribute to the presence and severity of intramyocardial hemorrhage, including the amount of collateral flow, ischemic preconditioning, extent of necrosis, distal coronary microembolization, and patient risk factors.

Underlying Pathophysiology

What is actually happening?

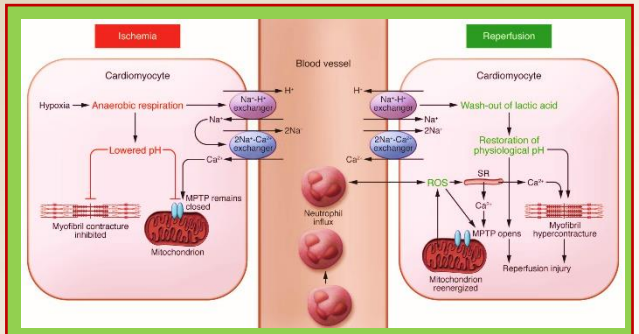

Figure: Schematic of main proponents of myocardia acute ischemic reperfusion injury (Hausenloy & Yellon, 2013)

✧ Inflammation Neutrophils block capillaries preventing reperfusion of the tissue, leading to tissue necrosis and an exacerbated immune response. Secretion of proinflammatory cytokines and chemokines recruite and activate neutrophils (Schofield, Woodruff, Halai, Chia-Lun Wu, & Cooper, 2013) This, as well as membrane expression of cell-adhesion molecules, induces leukocyte infiltration within the myocardial tissue. These leukocytes have the potential to release large amount of reactive oxygen species, contributing to further tissue damage. (Braunersreuther & Jaquet, 2012)

✧ Oxidative Stress. Influx of oxygen introduced during reperfusion. Unpaired electrons formed during the normal metabolism of oxygen accumulate due to an excessive reintroduction of oxygen. ROS overwhelm the endogenous elimination mechanism by antioxidants. This oxidative stress results in impairment of normal function of circulating molecules. (Braunersreuther & Jaquet, 2012).

✧ Intracellular pH changes
Interruption of oxygen supply leads to arrest of mitochondrial oxidative phosphorylation and loss of the major source of ATP generation for metabolic energy" (Braunersreuther & Jaquet, 2012). Anaerobic glycolysis takes over and produces hydrogen ions and lactate, leading to intracellular acidosis. At reperfusion, physiological pH is rapidly restored by the washout of lactate and the activation of the Na+-H+ exchange. This pH shift contributes to the MPTP opening and ultimately cardiomyocyte death (Hausenloy & Yellon, 2013).

✧ Calcium overload. The calcium overload is likely related to the effects of oxidative stress on the sarcolemmal Ca2+-pump ATPase, and Na+-K+ ATPase, leading to decreased efflux and increased influx of calcium. It also depresses the sarcoplasmic reticulum Ca2+-pump ATPase. These Ca2+ transport system dysfunctions ultimately lead to intracellular calcium overload. (Braunersreuther & Jaquet, 2012).

✧ Mitochondria transition pore opening Oxidative stress, calcium overload and intracellular change in pH all interact with each other to allow mitochondrial permeability transition pore (MPTP) opening. The MPTP is a nonselective channel of the inner mitochondrial membrane. Upon reperfusion, restoration of oxygen rapidly improves mitochondrial membrane potential, stimulating additional calcium influx, uncoupling of oxidative phosphorylation and the opening of the MPTP. (Shluter, 2016, p. 230). According to Simonis et al 2012 this phenomenon does not occur in ischemia but is a key determinant in the first few minutes of myocardial reperfusion. This ultimately contributes to uncontrolled activation of the contractile machinery leading to hypercontracture and cardiomyocyte death. (Hausenloy & Yellon, 2013).

Implications for Nursing Care

STEMI patients with a complete occlusion in a large artery with little coronary collateralization are most likely to benefit from a therapeutic intervention (Frolich et al. 2013).

✧ Ischemic post conditioning therapy. Four-60 second inflations/deflations of the angioplasty balloon with low pressure upstream from the stent following deployment has been shown to reduce MI size (Frolich et al 2013). The protocol for this therapy should be followed within 1 minute of stent deployment.

✧ Hyperoxemia and Hypothermia Hyperbaric oxygen reduces MI size by decreasing tissue edema, reducing formation of lipid peroxide radicals, altering NO synthase expression and inhibiting leucocyte adherence and plugging in the microcirculation. Lowering myocardial temperature during ischemia to 32–33°C can limit MI size in experimental studies by reducing metabolic demand, inflammatory response, platelet aggregation, and increasing myocardial efficiency. (Frolich et al, 2013).

✧ Remote Ischemic Conditioning. Applying three-5 min cycles of brief non-lethal ischemia and reperfusion using a blood pressure cuff applied to the upper arm. Applying this RIC protocol to STEMI patients immediately prior to reperfusion has demonstrated increased myocardial salvage (Simonis et al. 2012). The actual mechanisms, although unclear, have been attributed to a neuro-hormonal pathway conveying the cardioprotective signal from the limb to the heart.

✧ Pharmacologic intervention Is debated due to several therapies that have proven therapeutic in controlled laboratory settings but unsuccessful in clinical practice. The following offers insight into pharmacotherapies that have shown some positive outcome.

- Cyclosporin-A is an immunosuppressant drug that prevents the formation of the MPTP by binding with cyclo D (Sivaraman & Yellon, 2013).
- Atrial natriuretic peptide. Administering atrial natriuretic peptide (ANP) at reperfusion reduced MI size through the activation of pro-survival signaling pathways. Carperitide reduced MI size and preserved LV ejection fraction in reperfused-STEMI patients. (Frolich et al, 2013).
- Exenatide, a glucagon-like peptide-1 (GLP-1) agonist has demonstrated reduced MI size when administered at the time of reperfusion and has been successfully translated in the clinical setting. (Frolich et al, 2013).

Conclusion

Although the process of myocardial reperfusion has been optimized following a STEMI, the process of restoring coronary blood flow can induce cardiomyocyte death, thereby mitigating the full benefits of reperfusion in terms of MI size reduction. Therapeutic intervention administered solely at the time of myocardial reperfusion can reduce MI size by up to half, limiting incidence of LV remodeling and heart failure. Several molecular targets have been discussed in the influence of potential successful therapeutic management, however, standard clinical practice protocols are continuing to develop for optimal reperfusion injury prevention.

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