Chapter 8
Myocardial Infarction: Disease Mechanisms and Therapeutic Perspectives

Kalyan C. Chapalamadugu
University of South Florida, USA

Rakesh Kukreja
Virginia Commonwealth University, USA

Samhitha Gudla
University of South Florida, USA

Srinivas M. Tipparaju
University of South Florida, USA

ABSTRACT

Myocardial infarction (MI) is a major cardiovascular disease (CVD) and ranks among the leading causes of morbidity and mortality in humans, worldwide. Despite advances in disease prevention and treatment strategies, majority of the developed and developing world's suffer higher disease burden from MI, and incur billions of dollars in healthcare costs (Murray et al., 2015). Global estimates from 2013 show that MI is the major cardiovascular disease (CVD), and that deaths due to MI accounted for nearly half of the 17 million CVD mortalities (GBD, 2013; Mortality and Causes of Death Collaborators, 2015). Within the United States, MI top's the chart of both communicable and non-communicable diseases in terms of health loss that it is estimated to have inflicted in the population (Murray, et al., 2015). It has been estimated that every 2 minutes, three Americans suffer from myocardial infarction (MI), primary cause of MI being coronary blood flow obstruction and myocardial damage. The annual estimates of MI incidence in USA are approximately three quarter million a year while almost two-thirds of these cases represent new attacks (Mozaffarian, et al., 2015). Collectively, MI continues to lead the charts for CVD incidence rates, health loss, mortalities thereby putting enormous strain on healthcare system.

MULTI-ETIOLOGICAL DISORDER

MI primarily arise due to obstruction in the coronary blood flow to one or multiple regions of heart causing subsequent tissue hypoxegenation, metabolic modifications in the myocardium, cell death and decreased contractility. A major condition that leads to this obstruction is coronary artery diseases such as atherosclerosis, which involves plaque build-up (an intimal and/or sub-intimal deposition of lipids,

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inflammatory cells and fibrous tissue) at the branching portions or in the narrow regions of the larger arteries. While a potential of the plaque to directly block the arterial lumen causing reduced blood flow always exists, atherosclerotic complications primarily arise due to the plaque rupture providing a foci for platelet aggregation and eventual thrombosis in the blood vessels, thereby effectively decreasing or altogether blocking the blood and oxygen supply to the dependent portions of the myocardium (Libby & Theroux, 2005; Naghavi et al., 2003). Plaque rupture leading to MI contributes to almost 70% of the total acute myocardial fatalities (Naghavi, et al., 2003). However, coronary artery diseases and therefore MI is always considered a multi-etiological disease as several factors contribute to atherosclerosis. One retrospective study in a select white male population revealed positive correlations between plaque lesions in aorta or coronary arteries and serum low-density lipoprotein (LDL), total cholesterol, triglycerides, systolic and diastolic blood pressure, and ponderal index (Berenson, Wattigney, Bao, Srinivasan, & Radhakrishnamurthy, 1995). Similar studies in the United Kingdom (Turner et al., 1998) revealed that type-2 diabetes is also a major risk factor for atherosclerosis as not only that hemoglobinA_{1c} and fasting blood glucose levels positively correlate with higher incidence of coronary disease and myocardial infarction, but diabetes can enhance the risk of MI through increasing the predisposition for atherosclerosis to perturbed serum lipid profile (Turner, et al., 1998). Further, life style factors, which include diet, physical activity, smoking, can significantly influence MI incidence (Ambrose & Barua, 2004; Oliveira, Barros, & Lopes, 2009). Epidemiological studies indicate that hypertension is perhaps, one single most risk factor for MI incidence, and estimates suggest that mortality due to coronary heart diseases doubles with every increment of a 20 mm Hg systolic or 10 mm Hg diastolic blood pressure (Cífková, 2008; McAreavey et al., 2016). Hence, conditions that can significantly contribute to hyperlipidemia, inflammation, aberrant vascular tone and hyperglycemia can all contribute to pathogenesis of plaque buildup in the arteries leading to atherosclerosis and associated cardiac complications such as MI.

Pathogenesis of Myocardial Infarction

Heart is one of the high energy demanding contractile tissue, and primarily relies on aerobic metabolism for unabated supply of high energy Adenosine triphosphate (ATP) to meet its energy requirements. Approximately two-third of ATP supply in normal healthy hearts comes through β-oxidation of long chain fatty acids in the mitochondria, while the rest summoned through catabolism of other substrates such as glucose, lactate, ketones and amino acids (Lopaschuk, Ussher, Folmes, Jaswal, & Stanley, 2010). Given that oxygen supply is essential to oxidative metabolism in all cells; it is inevitable that conditions that limit oxygen supply to the tissue would adversely affect the metabolism and energy supply compromising the structural and functional integrity of the heart. Immediate to the onset of ischemia, myocardium switches its reliance on fatty acids for ATP to anaerobic glycolysis, and depending on the severity of ischemia, this shift in metabolism leads to a moderate to severe fall in myocardial ATP and phosphocreatine concentrations and increases in net lactate, NADH, cellular acidosis, which can disrupt the ionic homeostasis in the cell resulting in Ca^{2+} overload. Simultaneously, inhibition of oxidative phosphorylation (OXPHOS) and accumulation of NADH in the mitochondria enhances ROS production. Further deprivation of oxygen and low energy state also affects endoplasmic reticulum leading to UPR and ER stress. These endogenous stress responses combined with energy shortage eventually leads to cell death and infarct formation (Kajstura et al., 1996; Yu et al., 2014). Accumulation of dead cells combined with modified extracellular milieu can signal inflammatory response, which attracts leukocytes to the infarct zone (Frangogiannis, 2008). Establishing blood flow and thereby renewing oxygen and nutrient supply