Myocardial infarction and Cell therapy

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I. INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality worldwide. Myocardial infarction or heart attack is responsible for 13.7% of cardiovascular death in 2015 (1). An occlusion in the coronary artery decreases the blood flow to the nearby cardiomyocytes causing oxygen deprivation or ischemia. Prolonged deprivation of oxygen in the myocardium can lead to myocardial infarction. Cardiomyocyte proliferative capacity differs in species and life stages. The cardiomyocytes of adult mammals are terminally differentiated cells which can hardly regenerate after injury. Cardiomyocytes of axolotls, frogs, newts, and zebrafish, retain a lifelong capacity to proliferate. However, the neonatal mouse heart can regenerate within 7 days of neonatal period. Due to the lack of regenerative potential for cardiomyocytes, the cells in the infarct region undergo necrosis resulting in the formation of a fibrotic scar. Although there have been advancements in the management of acute myocardial infarction including fibrinolysis and extracellular matrix remodelling, the prognosis remains poor due to the lack of regenerative potential for the damaged myocardium which may eventually result in heart failure.

II. PATHOPHYSIOLOGY OF MYOCARDIAL INFARCTION

Coronary atherosclerosis constitutes about 80% of acute myocardial infarction and other causes include thrombosis, coronary spasm and coronary embolism. 60-90 % of Adenosine triphosphate (ATP) for cardiomyocytes is derived from fatty acid metabolism and 10-40% from glycolysis and lactate oxidation. Coronary occlusion causes a shift in aerobic metabolism to anaerobic glycolysis stimulating glucose uptake and glycogen breakdown. A decrease in ATP inhibits Na-K ATP ase and increases Na^+ and Cl^- in cells. This alters the transport system in sarcolemma and sarcoplasmic reticulum increasing cytosolic Ca^{2+} and a fall in intracellular pH. The severity of alterations depends on the size of the infarct. And these alterations are reversible upon restoration of the coronary flow if the duration of ischemia is <15-20 minutes. Whereas 20-30 minutes of severe coronary occlusion cause irreversible changes in cardiomyocytes of sub endothelial region. In experimental models of myocardial infarction post myocardial infarction remodelling also involves inflammatory alterations, cardiomyocyte hypertrophy and fibrotic alterations in the non-infarcted segments (2). Overload of the non-infarcted myocardium following myocardial infarction leads to hypertrophy and fibrosis.

III. DIAGNOSIS OF MYOCARDIAL INFARCTION

Fourth Universal Definition of Myocardial infarction (UDMI) categorized myocardial injury into acute and chronic myocardial injury based on cardiotroponin concentration as in Figure 1. Acute myocardial is manifested by dynamic changes in cardiotroponin concentrations during serial measurements. Whereas chronic myocardial injury is characterised by a stable or minimal change in cardiotroponin concentration. MI is further sub-classified by suspected pathophysiology. Type 1 myocardial infarction is attributed to atherothrombotic plaque rupture or erosion. Type 2 Myocardial infarction occurs is marked by an imbalance between oxygen supply and demand for example microvascular dysfunction, coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension etc. The first stage in the diagnosis of coronary heart disease is from the clinical history and interpretation of symptoms of ischemia. Cardiac ischemia can be assessed by the electrocardiogram (ECG) as shown in figure 2. Cardiac troponin T (cTnT) or cardiac troponin I (cTnI) measurement (99^{th} percentile) is also made along with the assessment of renal function. Troponin measurement is important in the differential diagnosis of non-ST segment elevation myocardial infarction (NSTEMI) which needs immediate intervention. Elevated troponin along with other clinical symptoms raises the possibility of NSTEMI. However high troponin level with a normal ECG is suspicious of an alternate diagnosis. Angiography of the heart and blood vessels is performed to check the narrowing of coronary arteries. Classical myocardial infarction can also be detected by creatine kinase –myocardial band (CK-MB) along with the existing cardiac biomarkers.

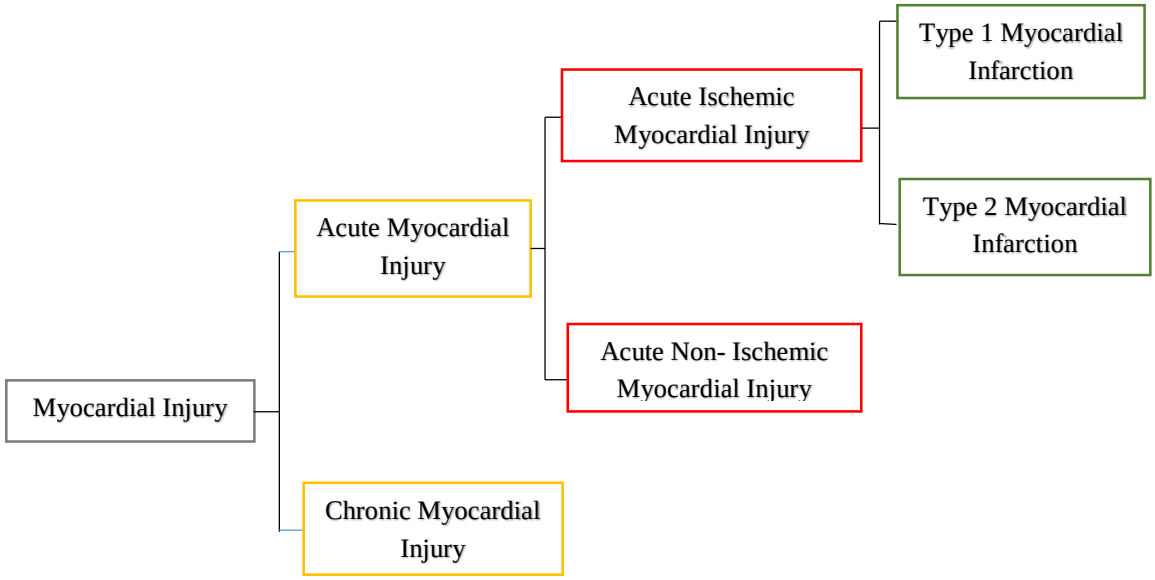

Figure 1: Classification of myocardial injury

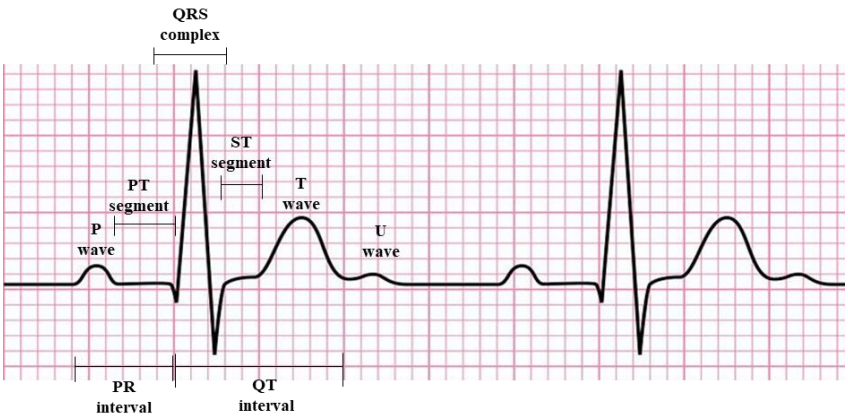

Figure 2: Normal ECG

Table 1. ECG interpretation

Segments	Indication	Disease condition
P wave	Atrial depolarization/contraction	Pulmonary valve stenosis, Increased pulmonary artery pressure, Right atrial enlargement (Hypertrophy)
PR segment Normal range (0.12 sec – 0.22 secs)	Impulse conduction through the atrioventricular node	PR interval exceeds 0.22 secs – First degree AV block (age related degenerative fibrosis) A short PR interval (<0.12 secs) indicates pre excitation
QRS complex Normal (<0.12 secs)	Depolarization of the ventricle/Ventricular contraction	Wide QRS complex – Bundle branch block, Hyperkalaemia, Drugs (Class I antiarrhythmic drugs, tricyclic antidepressants etc), Ventricular rhythm, ventricular tachycardia, external pacemaker, Wolf- Parkinson- White syndrome, Aberrant ventricular conduction
ST segment depression	Ventricular relaxation	Occurs during Physical exercise, Hyperventilation, Digoxin, Sympathetic tone, Hypokalaemia, Heart failure, Supra ventricular tachycardia, Pacemaker stimulation, Ischemia, hypertrophy
ST segment elevation	ST segment is displaced such that the level is above the PR segment	Ischemia
T- wave	Ventricular repolarisation	Inversion in myocardial ischemia
U wave	Occurs after T wave, one fourth of T wave	Inversion in ischemic heart disease and hypertension
QT duration	The Total duration of ventricular depolarization and repolarization	Inversely related to the rate of heartbeat, ventricular arrhythmia
Correction QT interval (QTc) (0.38 – 0.42 secs)	Heartbeat adjusted QT interval	Increases risk of ventricular arrhythmias, Psychiatric medications, hypocalcaemia, bradycardia, hypothyroidism, ischemia, cardiomyopathy

IV. MANAGEMENT STRATEGIES

In 2005, The European Resuscitation Council published guidelines on the emergency care of acute ST-elevation in myocardial infarction. Coronary artery occlusion by thrombus is responsible for 80% of hospitalization in cardiovascular diseases. The blood flow to the heart should be re-established as quickly as possible to protect heart muscles from further damage. Aspirin should be administered for the symptoms to dissolve the arterial blockage or thrombolytic clot. Treatment with thrombolytic drugs such as Urokinase or streptokinase within 3 hours of myocardial infarction has been reported to improve the condition in 30 % of patients of acute myocardial infarction and tissue plasminogen activator in 54% of patients. (3–7).

V. CELL THERAPY FOR MYOCARDIAL INFARCTION AND ITS BENEFITS

A wide variety of stem cells have been investigated over the past decades for cardiac repair in preclinical and clinical studies. This can be broadly categorised into pluripotent stem cells and adult stem cells.

A. PLURIPOTENT STEM CELLS

Pluripotent stem cells are cells that can proliferate and differentiate into other cells. There are namely two types of pluripotent stem cells – Embryonic stem cells and induced pluripotent stem cells. Embryonic stem cells (ESC) are derived from the embryo, specifically from the inner mass of the blastocyst. Whereas Induced Pluripotent Stem Cells (iPS) are derived from skin or blood cells which are reprogrammed to a pluripotent state by expressing pluripotent factors Oct3/4, Sox2, KLF4, cMyc. iPS are therapeutically equivalent to ESCs, ESC transplantation significantly improved cardiac function and structure in animal models. However, there is immune rejection after transplantation in patients and ethical issues in using ESC (8-10).

B. SOMATIC STEM CELLS

Somatic stem cells (SSCs) are the self-renewable undifferentiated population of cells seen in virtually all organs of the body. Endogenous stem cells expressing c-kit are Cardiac stem cells (CSC) which can differentiate into three cardiovascular cell types' namely cardiac myocytes, endothelial cells and smooth muscle. These are responsible for the formation of ≥ 1 % of new heart cells after birth in mammals through proliferation and dedifferentiation (11). New natal mice can completely regenerate lost myocardium until 7 days of the postnatal period. Whereas some vertebrates such as Zebrafish (12-15) newts (16-18), and neonatal mice (19), can regenerate lost myocardium through proliferation. Though cardiomyocytes are the ideal cells for cardiomyoplasty, finding a good source that can provide an efficient and enough population of cells for transplantation is challenging. Hence several different ESC lines have been manipulated to produce cardiomyocyte cells to date as shown in table 1. Personalized stem cell reprogramming seems to be a less explored area in stem cell research. A recent report also suggested the effect of age on the quantity and quality of cardiosphere-derived cells (20). The effect of ageing, food habits and epigenetics on stem cells needs to be addressed.

Table 2: Potential cell types for cardiac therapy

Cell Type	Advantages	Disadvantages
Cardiomyocytes (Adult/Foetal)	Multipotent, Cardiomyocyte Phenotype Electro-Physiologically Compatible	Immunosuppression Required Ethically Debatable Low Survival Rate Limited Supply
Haemopoietic Stem Cells (Bone Marrow/ Blood)	Autologous Transplantation, Multipotent, No Immunogenicity	Not Enough Population
Epithelial Progenitor Cells (Peripheral Blood And Bone Marrow)	Autologous Trans Plantation, No Immunogenicity	Need For Expansion
Mesenchymal Stem Cells (Bone Marrow, Skin, Adipose Tissue & Muscles)	Allogeneic or Autologous Transplantation, No Immunogenicity, Pluripotent	Need For Expansion
Skeletal Myoblast	Autologous Transplantation High Yield No Immunogenicity	Electro-Physiologically Incompatible, Arrhythmogenic No Gap Junction Formation

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