INTRODUCTION

Acute myocardial infarction remains a leading cause of morbidity and mortality worldwide. It occurs when irreversible myocardial cell damage or death occur ***(Bolooki and Askar, 2010)***.

ST segment elevation myocardial infarction is the most serious presentation of atherosclerotic coronary artery disease carrying the most hazardous consequences ***(Tosteson et al., 1996).***

ST segment elevation myocardial infarction is caused by occlusion of a major coronary artery and primary PCI is the preferred reperfusion strategy especially when performed by an experienced team within the shortest possible time from first medical contact ***(Werf et al., 2008).***

Despite early invasive strategies and optimal medical treatment, morbidity and mortality rates for STEMI continue to be high. Thus, further improvement of the initial therapy and procedural techniques necessary to improve patient outcome ***(deWaha et al., 2013)***.

The flow within the infarct-related artery will be assessed using the TIMI criteria and the corresponding myocardial blush grades ***(Liem et al., 1998; Cannon et al., 2001).***

Assessment of area with microvascular obstruction (MVO) has been shown to be a strong independent predictor for clinical outcome including mortality after acute coronary syndromes ***(Wu et al., 1998; deWaha et al., 2010)***. Assessment of MO by CMR, allows direct visualization and quantification of no-reflow and microcirculatory impairment ***(Nijveldt et al., 2007; Orn et al., 2009).***

Aim of the Work

To assess the microvascular obstruction (MVO) by cardiac MRI in comparison with Myocardial blush grading (MBG) post Primary Percutaneous Coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI) and TIMI-III flow after intervention.

Chapter 1

ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

Introduction

Acute coronary syndrome (ACS) refers to acute myocardial ischaemia caused by atherosclerotic coronary disease and includes ST-elevation myocardial infarction (STEMI), non ST-elevation MI (NSTEMI), and unstable angina (UA). These terms are used as a framework for guiding management. Patients with STEMI should be considered for immediate reperfusion therapy by thrombolytic agents or percutaneous coronary intervention (PCI) ***(Anderson et al., 2007).***

STEMI constitutes around 40% of acute myocardial infarction (AMI) and continues to be a major public health problem, both in developed as well as developing countries ***(Rogers et al., 2000)***.

Reperfusion therapy is the cornerstone of the treatment of patients with STEMI; it aims at reducing mortality and morbidity by achieving patency of the epicardial infarct-related artery (IRA) and by restoring myocardial tissue perfusion either pharmacologically or mechanically ***(Hellermann et al., 2002)***.

Definition and Diagnosis

STEMI is a clinical syndrome defined by characteristic symptoms of myocardial ischemia in association with persistent

electrocardiographic (ECG) ST segment elevation and subsequent release of biomarkers of myocardial necrosis ***(Thygesen et al., 2012).***

Acute myocardial infarction (AMI or MI), commonly known as a heart attack, is a disease state that occurs when the blood supply to a part of the heart is interrupted. The resulting ischemia or oxygen shortage causes damage and potential death of heart tissue. It is a medical emergency, and the leading cause of death for both men and women all over the world ***(Luepker et al., 2003).***

Definition of Denovo Myocardial Infarction:

Recent "Universal Definition of Myocardial Infarction" put by the recent 2012 ESC guidelines Criteria of acute myocardial infarction ***(Thygesen et al., 2012)*** as:

Criteria for Acute Denovo Myocardial Infarction (without prior PCI or CABG): The term myocardial infarction should be used when there is evidence of myocardial necrosis (myocardial cell death) in a clinical setting consistent with myocardial ischemia. Under these conditions, it is defined as:

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia;

- ECG changes indicative of new ischemia (new ST segment –T wave changes or new left bundle branch block [LBBB]);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of intracoronary thrombus by angiography or autopsy.

Universal Myocardial Infarction Classification of Type *(Thygesen et al., 2012)*

Type 1: Spontaneous Myocardial Infarction

Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries that leads to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial Infarction Secondary to Ischemic Imbalance

In instances of myocardial injury with necrosis in which a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/ordemand, e.g., coronary endothelial dysfunction, coronary artery spasm,

coronary embolism, tachyarrhythmias/bradyarrhythmias, anemia, respiratoryfailure, hypotension, and hypertension with or without LV hypertrophy.

Type 3: Myocardial Infarction Resulting in Death When Biomarker Values Are Unavailable

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic changes on the ECG or new LBBB but death occurring before blood samples could be obtained, before cardiac biomarkers could rise, or in rare cases, when cardiac biomarkers were not collected.

Type 4a: Myocardial Infarction Related to Percutaneous Coronary Intervention

MI associated with PCI is arbitrarily defined by elevation of cTn values to >5 ×the 99th percentile of the URL in patients with normal baseline values ($\leq 99^{th}$percentile of the URL) or a rise in cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (1) symptoms suggestiveof myocardial ischemia, (2) new ischemic changes on the ECG or new LBBB, (3) angiographic loss of patency of a major coronary artery or a side branch or persistent slow flow or no flow or embolization, or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.

Type 4b: Myocardial Infarction Related to Stent Thrombosis

MI associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall incardiac biomarkers values with at least one value above the 99th percentile of the URL.

Type 5: Myocardial Infarction Related to Coronary Artery Bypass Grafting

MI associated with CABG is arbitrarily defined by elevation of cardiac biomarker values to >10 ×the 99th percentile of the URL in patients with normalbaseline cTn values (<99th percentile of the URL). In addition, either (1) new pathologic Q waves or new LBBB, (2) angiographically documented new graft ornew native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality is required.

Pathogenesis of STEMI:

The pathogenesis of coronary atherosclerosis is multi-factorial ***(Libby et al., 2001)***

Broadly, endothelial injury and dysfunction result in the adhesion and transmigration of leukocytes from the circulation into the arterial intima as well as the migration of smooth-muscle cells from the media into the intima, thus initiating the formation of an atheroma or atherosclerotic plaque ***(Libby et al., 2005).***

Atherosclerotic plaques cause progressive narrowing of the coronary arteries and eventually can cause a coronary occlusion. However, myocardial infarctions with ST-segment elevation are more typically caused by the sudden thrombotic occlusion of a coronary artery that previously was not severely narrowed. When such an occlusion occurs, the abrupt rupture, erosion, or fissuring of a previously minimally obstructive plaque creates a potent stimulus for platelet aggregation and thrombus formation (see fig 1)***(Freedman et al., 2005).***

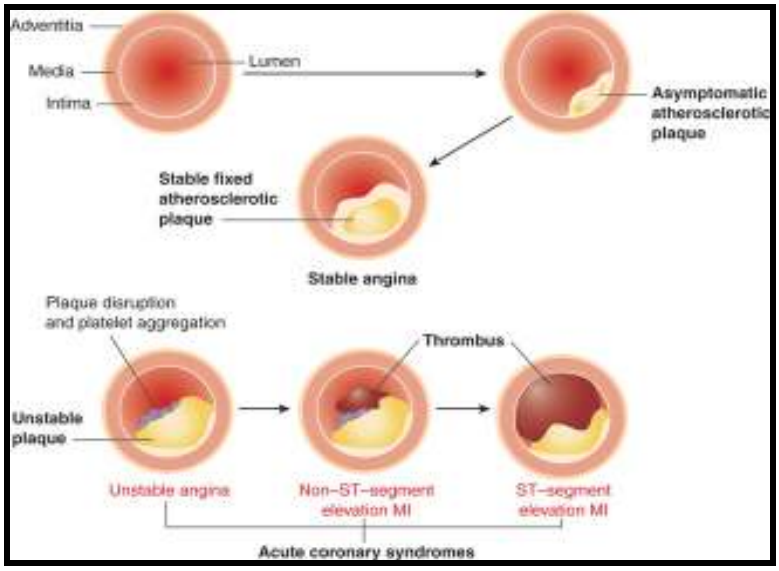

Fig. (1): Schematic diagram showing pathogenesis of myocardial infarct ***(Carol Mattson Porth et al., 2005).***

Although the mortality associated with ischemic heart disease (IHD) has declined in the recent decades, due to therapeutic improvements (e.g., thrombolytic agents, early revascularization, ACE inhibitors and beta-blockers) and to prevention campaigns reducing the incidence of myocardial

infarction (MI), IHD remains the leading cause of in adults in developed countries and the prevalence will continue to increase ***(Beller, 2001; Lloyd-Jones et al., 2010; Yeh et al., 2010).*** Worldwide, it is estimated that IHD will become the number one cause of death by 2020 ***(Fuster, 1999).***

Survivors of a first acute MI are thought to die of IHD at later ages due to heart failure and late cardiac deaths. Moreover, the increased life span will contribute to the increased incidence of cardiovascular disease and increased number of deaths from heart disease. Other contributing factors to an increased prevalence of IHD are an increasing prevalence of type II diabetes, physical inactivity and obesity. In times of constrained financial budgets ***(Escolano, 2010),*** the increasing prevalence of IHD will urge for the rational use of diagnostic and therapeutic means. One of the challenges is to define regularly updated appropriateness criteria for cardiac imaging techniques ***(Hendel et al., 2006; Hundley et al., 2010).***

Taking into account the short-lived capacity of the myocardium to sustain ischemia, coronary artery occlusion triggers an ‘‘ischemic cascade’’ in the perfusion territory distal to the occluded coronary artery (defined as the jeopardized myocardium or myocardium at risk), starting with metabolic disturbances shifting aerobic oxidative metabolisms almost immediately to anaerobic glycolysis, followed by diastolic and later systolic dysfunction and finally ECG changes and symptoms of angina (Fig. 2). The time frame of events is short,

for instance systolic contraction will cease within seconds after coronary occlusion ***(Jennings et al., 1978).***

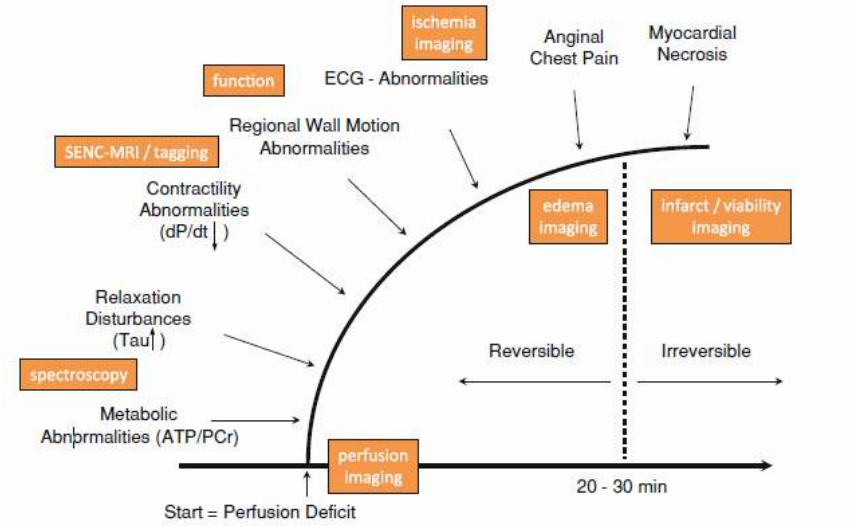

Fig. (2): Diagram of theIschemic Cascade and the roleof SENC-MRI (strain encoded-MRI) Techniques.MRI is of value to assess the ischemic cascade at different levels such as shown in the colored boxes.(Obtained from Clinical cardiac MRI , second edition, 2012, Ischemic Heart disease chapter, J. Bogaert and S. Dymarkowski, pages 203 - 273)

After approximately 20–30 minutes of sustained ischemia, the metabolic changes become irreversible causing intracellular edema together with accumulation of toxic metabolites, myocardial cell apoptosis, ultimately leading to myocyte necrosis. As the systolic wall stress and the resulting oxygen consumption are greater in the inner part of the myocardium, necrosis initiates in this part of the myocardium whereby the lateral boundaries of infarction closely correspond to the myocardium at risk. If ischemia persists, necrosis progresses in a transmural wave front taking 3–6 h to reach the subepicardium ***(Reimer and Jennings, 1970, 1979) (see fig.3).***

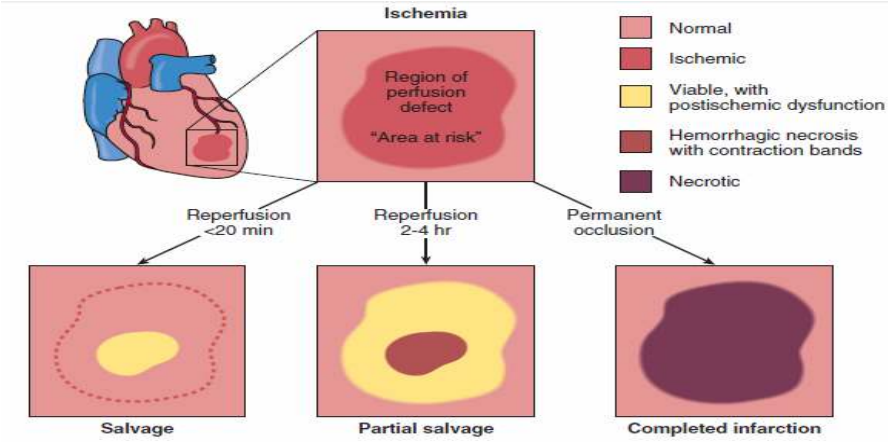

Fig. (3): Consequences of reperfusion at various times after coronary adhesion. In this example the midportion of the left anterior descending coronary artery is occluded and a large zone of ischemic myocardium develops—the "area at risk." Reperfusion in less than 20 minutes does not result in permanent loss of tissue, but there may be a period of contractile dysfunction of the reperfused myocardium—a condition referred to as "stunning." Later reperfusion results in hemorrhagic necrosis with contraction bands. Permanent occlusion results in necrosis of myocardium ***(From Schoen FJ: The heart.*** **In** ***Kumar V, Abbas AK, Fausto N [eds]: Robbins & Cotran Pathologic Basis of Disease. 8th ed. Philadelphia, WB Saunders, 2009).***

Whereas the initial extent of necrosis is determined by the extent of the myocardium at risk, the final extent of necrosis is largely determined by the degree of transmural progression ***(Lee et al., 1981)***. Viable tissue, mainly in the subepicardium, may survive the acute injury and show an improvement in the metabolism and function following reperfusion ***(Gropler et al., 1992; Bogaert et al., 1999).*** The extent of myocardial necrosis depends on many factors: (1) myocardium of risk, (2) residual blood flow to the ischemic territory, (3) myocardial oxygen consumption during ischemia and (4) duration of ischemia ***(Reimer et al., 1985) (see fig 4).***

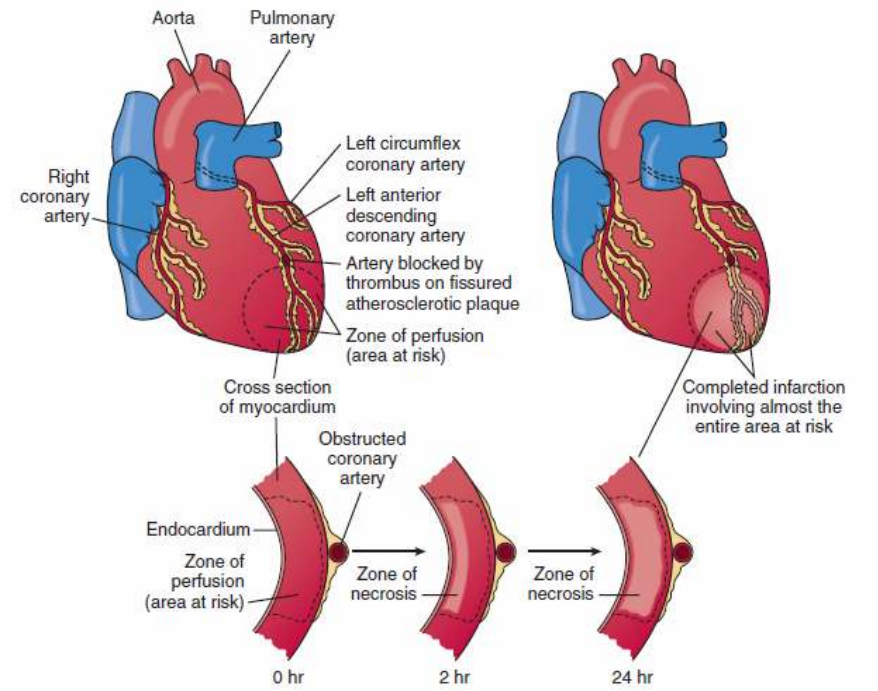

Fig. (4): Schematic representation of the progression of myocardial necrosis after coronary artery occlusion. Necrosis begins in a small zone of the myocardium beneath the endocardial surface in the center of the ischemic zone. This entire region of myocardium *(dashed outline)* depends on the occluded vessel for perfusion and is the area at risk. A narrow zone of myocardium immediately beneath the endocardium is spared from necrosis because it can be oxygenated by diffusion from the ventricle ***(From Schoen FJ: The heart.*** **In** ***Kumar V, Abbas AK, Fausto N [eds]: Robbins & CotranPathologic Basis of Disease. 8th ed. Philadelphia, WB Saunders, 2009.)***

The presence of a small fraction of perfusion to the infarct bed, from either antegrade or collateral flow, can significantly delay necrosis and limit the infarct size ***(Rivas et al., 1976).*** However, collateral circulation usually takes time to become functional ***(Patterson et al., 1993),*** and is often insufficiently developed in acute coronary syndrome patients

because of rupture of non- or minimally stenotic coronary plaques. Current therapeutic strategies are focused on urgent restoration of epicardial flow using mechanical or thrombolytic approaches. The aim is to salvage the jeopardized but viable myocardium in the myocardium at risk distal to the culprit lesion, to reduce adverse infarct and ventricular remodeling, and to improve patient outcome. The faster the restoration of myocardial perfusion, the lesser the transmural extent of necrosis, and the more the ischemically, jeopardized myocardium will be salvaged ***(Hochman and Choo, 1987; Francone et al., 2009)***.

In fact, the amount of myocardial salvage drastically decreases after the first 90 min and at 6 h myocardial salvage is nearly zero. Thus, the beneficial effects (in terms of short and long-term survival) of myocardial reperfusion in the golden hour(s) are largely due to myocardial salvage but any benefit obtained after the sixth hour is likely independent from the myocardial salvage ('open artery-theory'). Despite the beneficial effects of reperfusion, it has been shown that the process of cell death may continue during the first hours of reperfusion, a phenomenon called ''myocardial reperfusion injury'' ***(Matsumura et al., 1998; Becker et al., 1999; Gerber et al., 2000; Yellon and Hausenloy, 2007)*** (See Figure 5).

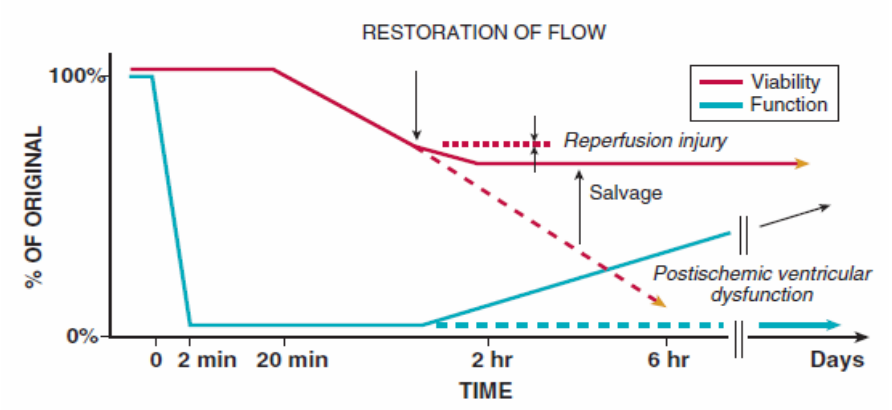

Fig. (5): Several potential outcomes of reversible and irreversible ischemic injury to the myocardium. The schematic diagram at the *bottom* depicts the timing of changes in function and viability. A key point is that although function drops dramatically after coronary occlusion, the tissue is still viable for a period. This is the basis for early aggressive efforts at reperfusion of patients with STEMI ***(From Schoen FJ: The heart.* In *Kumar V, Abbas AK, Fausto N [eds]: Robbins & Cotran Pathologic Basis of Disease. 8th ed. Philadelphia, WB Saunders, 2009).***

Coronary Anatomy and Location of Infarction

Angiographic studies performed in the earliest hours of STEMI have revealed an approximately 90% incidence of total occlusion of the infarct-related vessel. Recanalization as a result of spontaneous thrombolysis diminishes angiographic total occlusion in the period following the onset of MI. Pharmacologic fibrinolysis and PCI markedly increase the proportion of patients with a patent infarct-related artery early after STEMI.

A STEMI with transmural necrosis typically occurs distal to an acutely totally occluded coronary artery with thrombus superimposed on a ruptured plaque (see Fig. 6). Yet chronic total