INTRODUCTION

Acute myocardial infarction (AMI) remains a public health problem of epidemic proportions. Recent data from the American Heart Association (AHA) reveal a prevalence of myocardial infarction (MI) of 1.9-5.2%, which varies by age, sex, and ethnicity.[(1)] Annually, there are 565,000 first-time, and 300,000 recurrent, myocardial infarctions In the United States annually.[(1)]

Interestingly, in the last decade the National Registry of Myocardial Infarction (NRMI) have recorded a decrease in the percentage of patients with myocardial infarction who present with ST segment elevation (from 36% to 27%, $P \leq 0.001$), while the percentage presenting without ST segment elevation has increased (from 45% to 63%, $P \leq 0.001$).

Primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) has been shown to be preferable to thrombolytic therapy in terms of patient survival, higher rates of patency in the infarcted arteries, and lower rates of reinfarction and stroke **(154).**Thus, PCI has become the standard therapy for AMI. However, in some patients, after the epicardial coronary occlusion has been resolved, the blood flow may cease or

slow down dramatically. This phenomenon is called no reflow or slow reflows.

Defined angiographically, no-reflow manifests as an acute reduction in coronary flow (TIMI grade 0-1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion. Lesser degrees of flow impairment (TIMI grade 2) are generally referred to as “slow-flow.” However, studies of acute MI patients have reported that scintigraphic evidence for no-reflow may occur in the *absence* of angiographic slow-flow, suggesting that microvascular injury may be angiographically inapparent in some patients.[63]

No/slow reflow is a serious complication of PCI performed for AMI that increases mortality and decreases left ventricular functional recovery. Furthermore, this phenomenon is also linked to ventricular arrhythmias, early congestive heart failure, ventricular remodeling and even cardiac rupture.[80] For these reasons, it is very important to prevent no reflow or slow reflow during PCI for AMI.

The exact mechanisms that underlie the no reflow or slow reflow phenomena are not known. The main pathogenic mechanisms causing this phenomena were thought to be distal embolization and ischemia-reperfusion injury.However, there is considerable evidence suggesting

that these phenomena are mainly due to dysfunction of the microcirculation and the presence of vasospasm at the level of the resistance arterioles.[102] Therefore, it is thought that improving the microcirculation would be a very useful strategy for dealing with these phenomena.

Nitroprusside is a nitric oxide donors that vasodilate conductance vessels and has been shown that intracoronary nitroprusside injection is a safe and effective technique for managing the slow reflow phenomenon once it occurs during coronary intervention. Also, calcium channel blockade has several potentially beneficial effects in the setting of no reflow in addition to attenuation of microvascular spasm. Reduction of heart rate and blood pressure may reduce myocardial ischemia and infarct size.

Verapamil may inhibit platelet aggregation and thrombus formation in the microvasculature and may have a direct effect on calcium flux across the sarcolemmal membrane or within intracellular compartments that could protect reversibly injured myocytes.[109]

AIM OF THE WORK

To compare the effect of intracoronary verapamil with and without sodium nitroprusside on the prevention of the no/slow reflow phenomenon in patients with acute anterior ST segment elevation myocardial infarction undergoing primary percutaneous intervention.

ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION - DEFINITION AND PATHOGENESIS

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 oxygen0 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.[(78)]

Definition of Denovo Myocardial Infarction:

Recent "Universal Definition of Myocardial Infarction" put by the recent 2012 ESC guidelines [(140)] 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 ischaemia. 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:

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

Types of Myocardial Infarction:

1) ST-elevation myocardial infarction: • ECG criteria:

* ≥2 mm of ST segment elevation in 2 contiguous precordial leads in men (1.5 mm for women)
* ≥1mm in other leads (2 contiguous)
* An initial Q wave or abnormal R wave develops over a period of several hours to days.

• Within the first 1-2 weeks (or less), the ST segment gradually returns to the isoelectric baseline, the R wave amplitude becomes markedly reduced, and the Q wave deepens. In addition, the T wave becomes inverted.

• In addition to patients with ST elevation on the ECG, two other groups of patients with an acute coronary syndrome are considered to have an STEMI: those with

new or presumably new left bundle branch block and those with a true posterior MI.

- An elevation in the concentration of troponin or CK-MB is *required* for the diagnosis of acute MI.

- Anterior STEMI: ST elevation in the precordial leads + I and aVL (Left anterior descending artery territory) i.e LAD territory

- Posterior STEMI: reciprocal ST depressions in V1-V3 (ST elevation in post leads), may have component of inferior ischemia as well (ST elevations in II, III and aVF) Often occurs with inferior MI (Left circumflex artery)

- Inferior STEMI: ST elevation in II. III and aVF (+ ST elevation in R-sided precordial leads), reciprocal changes in I and aVL (Right coronary artery or left circumflex artery).[25]

2) Non ST elevation myocardial infarction:

Non-ST-elevation myocardial infarction (NSTEMI) is an acute ischemic event causing myocyte necrosis. The initial ECG may be normal or show nonspecific ischemic changes. It does not show ST elevation, evidence of posterior MI, or a new left bundle-branch block. In most patients the ECG does not show new Q waves, and a non-Q-wave MI is ultimately diagnosed. NSTEMI encompasses

a broad spectrum of ischemic injury to the myocardium, which is detected by elevation of serum cardiac biomarkers. It can be distinguished from unstable angina pectoris, which presents with normal or nonspecific ECG changes and normal serial cardiac biomarkers.[(140)]

Risk Factors:

1- Non-modifiable risk factors:

- Older age
- Male gender[(144)]
- Family history of an early heart attack (before the age of 60), which is thought of as reflecting a genetic predisposition.[(144)]

2- Modifiable risk factors:

- Cigarette smoking
- Dyslipidemia (especially high Low Density Lipoprotein and low High Density Lipoprotein)
- Diabetes (with or without insulin resistance)
- High blood pressure
- Obesity (defined by a body mass index of more than 30 kg/m^2, or alternatively by waist circumference (>120 cm in men and >88 cm in women
- Women using combined oral contraceptive pills

Some novel biochemical markers have been shown to be independent predictors of risk in ACS and in developing atherosclerosis especially in patients who experience life threatening ACS with few traditional risk factors.[15] These biochemical markers fall into one of the following categories:

- Markers of necrosis: Troponin, CK-MB mass
- Markers of inflammation: High sensitivity C-reactive protein (hs-CRP), myeloperoxidase, pregnancy associated plasma proteins A, soluble CD-40 ligand, interleukin-6 and tumor necrosis factor (TNF).
- Markers of hemodynamic stress or neurohormonal activation: Brain natriuretic peptide (BNP) and N-terminal fragment of pro-brain natriuretic peptide (NT-pro BNP).
- Markers of coagulation: fibrinogen.
- Markers of vascular damage: Creatinin clearance and Cystatin C.
- Markers of accelerated atherosclerosis: hemoglobin A1c (HbA1c), proteogenomics. Others: lipoprotien a Lp(a) and homocysteine.

Pathophysiology:

Rupture of the lipid-rich atheromatous plaque, intraplaque hemorrhage, and intraluminal thrombus are three pathological hallmarks most commonly recognized in

the infarct-related coronary artery at the site of acute myocardial infarction.[62]

Plaque Structure:

Mature atherosclerotic plaques are composed of a variable amount of lipid core and a connective tissue matrix cap. The lipid core is created by the necrosis of lipid-rich macrophages (foam cells) and blood-borne lipoproteins trapped within the sub-endothelial, extracellular space.[148] The core is a soft, hypo-cellular, and vascular "gruel" containing cholesterol and its esters. The composition of the gruel determines its consistency.

The fibrous connective tissue matrix cap is formed of collagen, elastin, proteoglycans, and glycosaminoglycans, and constitutes more than 70% of a typical coronary plaque. Vascular smooth muscle cells are the major sources of the elements of this connective tissue matrix.

Focal areas of endothelial denudation occur over the plaque, exposing the underlying connective tissue matrix and allowing a monolayer of platelets to adhere at the site. Such ultramicroscopic thrombi are far too small to be visible on angiography or to impede flow, but may contribute to smooth cell growth by release of platelet derived growth factor.[132]

The Vulnerable Plaque Concept:

Analysis of plaques which have undergone disruption has been used to determine characteristics which may indicate currently stable plaques whose structure and cell content makes them likely to undergo an episode of thrombosis in the future (vulnerable plaque).

Vulnerable plaques are characterized by:

1. Large lipid-rich core that often fills more than 40% of the plaque volume.
2. Increased neovascularization.
3. Thin fibrous cap with thinned-out areas.
4. Active inflammatory cell infiltrate that accumulates in greatest concentration underneath thinned or disrupted portions of the cap, and at the rupture-prone shoulder regions of the plaque.[24] *Figure (1) ilustrates the structure of vulnerable plaque and plaque discruption.*

Pathological hallmarks:

1. Plaque discruption:

Types of Plaque Disruption:

a- Passive plaque disruption:

A variety of local, mechanical, and hemodynamic forces (such as bending, compression, stretching, shear, or fluctuations in pressure) subject coronary plaques to constant stresses that may trigger disruption of vulnerable plaques, particularly at the shoulder region of the fibrous cap, which is the point of greatest vulnerability, a phenomenon known as "Cap fatigue". **(24)**

Another potential mechanical trigger of plaque disruption could be “Cap tension”, which is a function of circumferential wall tension caused by the blood pressure. According to Laplace's law, tensile stress is positively correlated with both blood pressure and luminal diameter. Consequently, plaques located in an artery with a larger lumen (e.g. those that are only mildly or moderately stenosed) may be subjected to a greater stress.**(70)**

b- Active plaque disruption:

An active phenomenon of plaque disruption is probably important. The evolution of a stable plaque to

rupture may be described in 5 steps: i) Endothelial activation, ii) Low-density lipoprotein (LDL) transport and trapping, iii) LDL oxidation, iv) Cytokine and protease expression, and v) Rupture of the fibrous cap[24]:

i- Role of Endothelial Activation:

Endothelial dysfunction is present at the earliest as well as later stages of coronary heart disease. Specific coronary heart disease risk factors linked to endothelial dysfunction include dyslipidemia, hypertension, smoking, aging, diabetes mellitus, positive family history of premature atherosclerosis, and elevated levels of plasma homocysteine.

Endothelial dysfunction initiates the formation of atherosclerotic plaques. Endothelium responds to flow disturbances by secreting proinflammatory cytokines and chemokines that encourage leukocyte activation. Endothelial dysfunction also permits smooth muscle proliferation to proceed unchecked in the media and subintima and creates conditions favorable for intravascular platelet aggregation.[24] Furthermore, endothelial dysfunction enhances permeability to lipoproteins and other plasma constituents.

ii- Low-density lipoprotein (LDL) transport and trapping:

As inflammatory cells enter the vessel wall, LDL is transported back and forth across the wall. Transport of

cholesterol from the cells of the vessel wall back into the blood (Reverse cholesterol transport) is mediated by several specific transport proteins and by high-density lipoprotein and its carrier Apo lipoprotein A-I.

Cholesterol is then transported to the liver, where it is excreted into the bile. Increasing high-density lipoprotein (HDL) levels has other potential plaque stabilizing effects: It inhibits adhesion molecule expression, is an antioxidant, and blocks expression of matrix metalloproteases.**(70)**

iii- LDL oxidation:

In unstable plaques, the native LDL oxidation occurs in the presence of free oxygen radicals. In humans, the level of plasma-oxidized LDL increases with age and substantially higher in patients with coronary artery disease. Tissue macrophages that have been taken up the cholesterol from Apo lipoprotein-B-containing lipoproteins become trapped in the extracellular matrix of the sub endothelium. Uptake of oxidized LDL is a powerful stimulus to macrophage activation. Native LDL has no effect on expressions of cytokines and proteolytic enzymes, whereas oxidized LDL first activates the cells and then, at high levels, it becomes toxic.**(43)**

iv- Cytokine and protease expression:

At the cellular level, atherosclerosis may be considered a chronic inflammatory process as applied to the vessel wall

and plaque rupture to be an acute exacerbation of the chronic inflammatory process. Activated T-lymphocytes and degranulated mast cells localize at the site of plaque rupture.

TNF-α from mast cells activates endothelial cell. Tumor growth factor-β from smooth-muscle cells and macrophages stimulates expression of proteoglycans. Interferon-γ suppresses smooth-muscle cell replication and promotes macrophage activation and replication. **(19)**

One extracellular protein, tenascin-C, is not present in the normal vessel wall but is strongly expressed in unstable plaques. In these plaques, tenascin-C expression localizes to the tissue macrophages. Both matrix metalloprotease expression and smooth-muscle cell apoptosis are induced by tenascin.

Vascular thrombosis: Over a century ago, Rudolf Virchow presented a hypothesis that three factors - vessel injury, altered blood flow, and changes in blood coagulability - were responsible for vascular thrombosis (Virchow's triad). After the rupture of the fibrous cap, the thrombogenic components of the atheromatous core are abruptly exposed to the intraluminal blood where they stimulate platelet adhesion and aggregation, thrombin generation, and fibrin accretion - events that lead to formation of a thrombus.**(30)**