INTRODUCTION

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values ***(Kristian et al., 2018).***

Coronary procedure-related myocardial infarction (MI) ≤ 48 hours after the index procedure is defined by an elevation of cTn values > 5 times for type 4a MI and > 10 times for type 5 MI of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a > 5 or > 10 fold increase and manifest a change from the baseline value of > 20%. In addition with at least one of the following:

- New ischaemic ECG changes (this criterion is related to type 4a MI only).
- Development of new pathological Q waves.
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology.
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major

epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization ***(Kristian et al., 2018; Tricoci et al., 2017; Thygesen et al., 2018).***

Regardless of the diabetic status of patients with coronary artery disease, both hyperglycemia and hypoglycemia are adversely associated with cardiovascular events ***(Nusca et al., 2012).***

In acute MI patients treated with primary percutaneous coronary intervention (PCI), there is a strong relationship between hyperglycemia and major adverse cardiac events (MACE) within 30 days of that treatment ***(van der Horst et al., 2007).*** Numerous studies have concluded that hyperglycemia is common in diabetic and non-diabetic patients with ST-elevation myocardial infarction (STEMI) and is associated with a higher risk of death and in-hospital complications ***(van der Horst et al., 2007; Kosiborod et al., 2009).*** In patients with STEMI who are undergoing primary PCI, diabetes mellitus is independently correlated with decreased myocardial reperfusion, larger infarct size, development of congestive heart failure and decreased length of survival ***(Marso et al., 2007).***

Because it is not clear whether cardiac events are more likely to be associated with hyperglycemia than with euglycemia, we set out to evaluate the relationship between elevated pre-procedural blood glucose levels and myocardial injury in patients who have undergone elective PCI.

AIM OF THE WORK

The aim of the study is to assess the relationship between elevated preprocedural random blood glucose level and peri-procedural myocardial injury in patients undergoing elective percutaneous coronary intervention.

Chapter 1

MYOCARDIAL INFARCTION AND MYOCARDIAL INJURY

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values ***(European Society of Cardiology, 2018).***

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia in the form of one of the following:

- Symptoms of myocardial ischaemia.
- New ischaemic ECG changes.
- Development of pathological Q waves.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.
- Identification of a coronary thrombus by angiography or autopsy ***(European Society of Cardiology, 2018)***

Types of myocardial infarction:

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI.

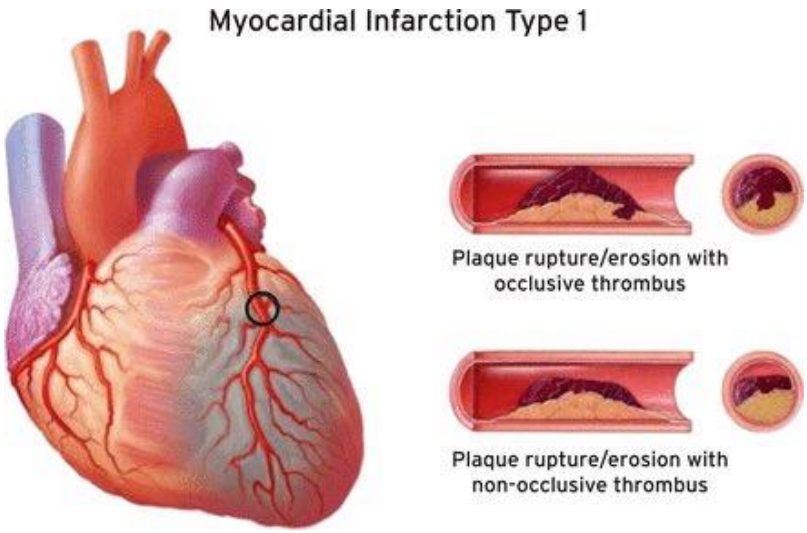

Figure 1: Myocardial infarction type 1 ***(European Heart Journal (2019).***

Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for type 2 MI.

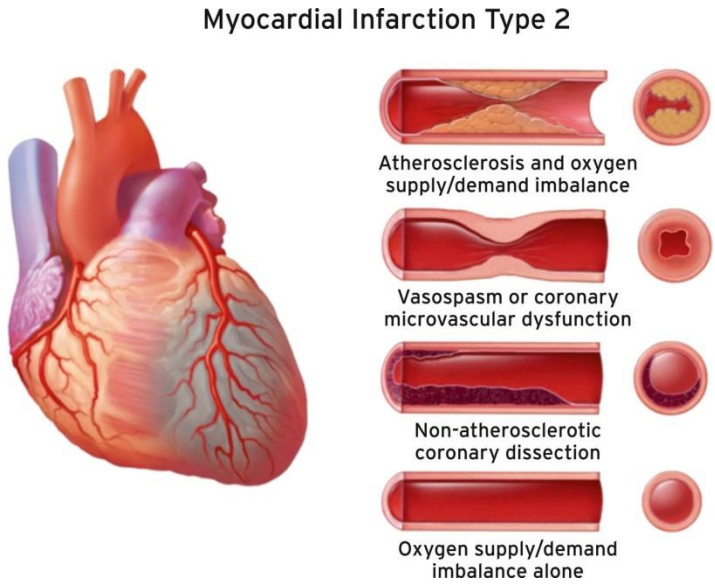

Figure 2: Myocardial infarction type 2 ***(European Heart Journal (2019)***

Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI.

Percutaneous coronary intervention (PCI) related MI is termed type 4a MI.

Other types of 4 MI include type 4b MI "stent thrombosis" and type 4c MI "stent restenosis".

Post-mortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

Coronary artery bypass grafting (CABG) related MI is termed type 5 MI.

Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for *type 4a MI* and > 10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a > 5 or > 10 fold increase and manifest a change from the baseline value of > 20% with clinical evidence of acute myocardial ischaemia ***(European Society of Cardiology, 2018).***

Pathological characteristics of myocardial ischaemia and infarction:

MI is defined pathologically as myocardial cell death due to prolonged ischaemia. Diminished cellular glycogen, relaxed myofibrils and sarcolemmal disruption are the first ultrastructural changes and are seen as early as 10–15 minutes after the onset of ischaemia ***(Jennings et al., 1974).***

Mitochondrial abnormalities are observed as early as 10 minutes after coronary occlusion by electron microscopy and are progressive. It can take hours before myocyte necrosis can be identified by postmortem examination in humans; this is in contrast to animal models, in which biochemical evidence of myocardial cell death due to apoptosis can be detected within 10 minutes of induced myocardial ischaemia in association with myocyte death ***(Ooi et al., 2000).***

Experimentally, necrosis progresses from the subendocardium to the subepicardium over several hours. The time course may be prolonged by increased collateral flow, reduced determinants of myocardial oxygen consumption and intermittent occlusion/reperfusion which can precondition the heart ***(Montecucco et al., 2016).***

Timely implementation of reperfusion therapy, when appropriate, reduces ischaemic injury of the myocardium ***(Montecucco et al., 2016).***

Biomarker detection of myocardial injury and infarction:

Cardiac troponin I (cTnI) and T (cTnT) are components of the contractile apparatus of myocardial cells and are expressed almost exclusively in the heart ***(Thygesen et al., 2012).***

Increase in cTnI values have not been reported to occur following injury to non-cardiac tissues. The situation is more complex for cTnT. Biochemical data indicate that injured skeletal muscle expresses proteins that are detected by the cTnT assay leading to some situations where elevations of cTnT could emanate from skeletal muscle ***(Mair et al., 2017).***

Recent data suggest that the frequency of such elevations in the absence of ischaemic heart disease may be higher than originally thought ***(Schmid et al., 2018).***

cTnI and cTnT are the preferred biomarkers for the evaluation of myocardial injury and high-sensitivity (hs)-cTn

assays are recommended for routine clinical use ***(Apple et al., 2015).***

Other biomarkers such as creatine kinase MB isoform (CK-MB) are less sensitive and less specific ***(European Society of Cardiology, 2020).***

Myocardial injury is defined as being present when blood levels of cTn are increased above the 99th percentile upper reference limit (URL). The injury may be acute, as evidenced by a newly detected dynamic rising and/or falling pattern of cTn values above the 99th percentile URL, or chronic, in the setting of persistently elevated cTn levels. Although elevated cTn values reflect injury to myocardial cells, they do not indicate the underlying pathophysiological mechanisms, and can arise following preload-induced mechanical stretch or physiological stresses in otherwise normal hearts ***(Weil et al., 2018).***

Various causes have been suggested for the release of structural proteins from the myocardium, including normal turnover of myocardial cells, apoptosis, cellular release of cTn degradation products, increased cellular wall permeability, the formation and release of membranous blebs and myocyte necrosis ***(White, 2011).***

Myocardial ischaemic or non-ischaemic conditions associated with increased cTn values are presented in **Table 1**. The complexity of clinical circumstances may sometimes make it difficult to discriminate specific individual mechanism(s) of

myocardial injury. In this situation, the multifactorial contributions resulting in myocardial injury should be described in the patient record.

Table 1: Reasons for the elevation of cardiac troponin values because of myocardial injury ***(European Society of Cardiology, 2018)***

Myocardial injury related to acute myocardial ischaemia
Atherosclerotic plaque disruption with thrombosis.
Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance
Reduced myocardial perfusion, e.g. • Coronary artery spasm, microvascular dysfunction • Coronary embolism • Coronary artery dissection • Sustained bradyarrhythmia • Hypotension or shock • Respiratory failure • Severe anaemia
Increased myocardial oxygen demand, e.g. • Sustained tachyarrhythmia • Severe hypertension with or without left ventricular hypertrophy
Other causes of myocardial injury
Cardiac conditions, e.g. • Heart failure • Myocarditis • Cardiomyopathy (any type) • Takotsubo syndrome • Coronary revascularization procedure • Cardiac procedure other than revascularization • Catheter ablation • Defibrillator shocks • Cardiac contusion
Systemic conditions, e.g. • Sepsis, infectious disease • Chronic kidney disease • Stroke, subarachnoid haemorrhage • Pulmonary embolism, pulmonary hypertension • Infiltrative diseases, e.g. amyloidosis, sarcoidosis • Chemotherapeutic agents • Critically ill patients • Strenuous exercise

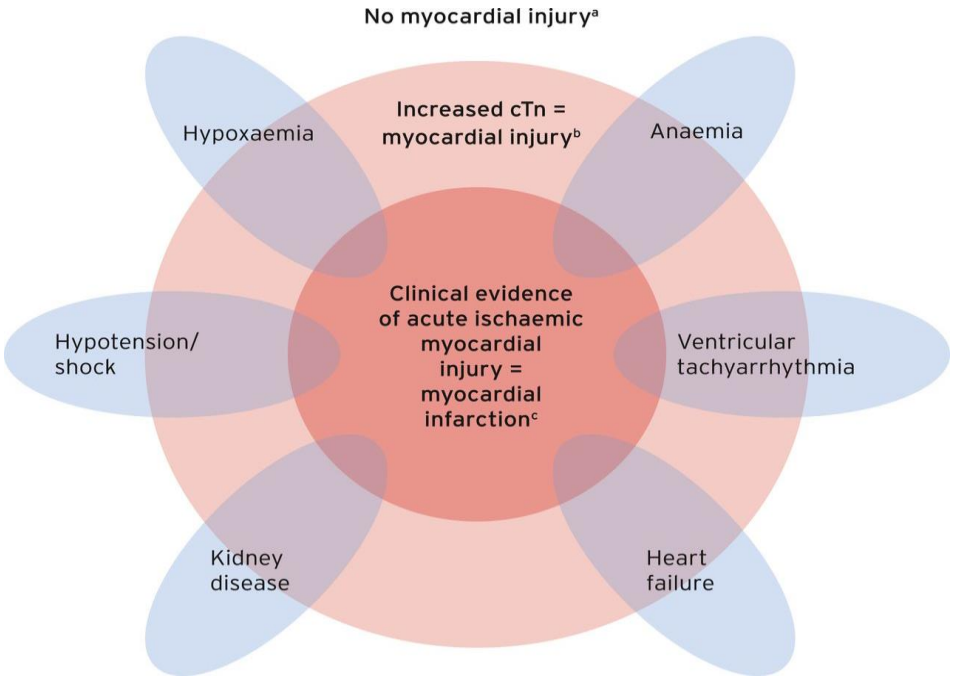

Figure 3: Spectrum ofmyocardial injury, ranging from no injury to myocardial infarction ***(European Society of Cardiology, 2018)***

Factors Affecting Peri-procedural Myocardial Injury.

Revascularization procedures resulting in direct instrumentation and manipulation of the coronary arterial vasculature (whether CABG or PCI) predispose patients to ischemic events that can lead to myocardial necrosis.

After PCI, a number of factors have been associated with periprocedural MI, which can broadly be categorized as

(1) Patient-related factors: ***(Roe, 2004; Zairis, 2005)***

- Multivessel disease.
- Evidence of systemic atherosclerosis.

- Reduced left ventricular ejection fraction.
- Diabetes mellitus.
- Older age.
- Chronic kidney disease.
- Systemic inflammation on presentation including
- Elevated C-reactive protein.
- Smoking

(2) Lesion-related factors:

- Calcification.
- Lesion eccentricity.

(3) Procedure-related factors:

- Device selection, in particular, atherectomy ***(Gruberg, 2002).***
- Aggressive stent expansion resulting in plaque extrusion ***(Iakovou, 2003).***
- Side branch occlusion ***(Ricciardi, 2003)***
- Side branch stenting ***(Steigen, 2006)***
- Angiographic complications including distal emolization.

- Coronary dissection.
- No-reflow.
- Vasospasm.

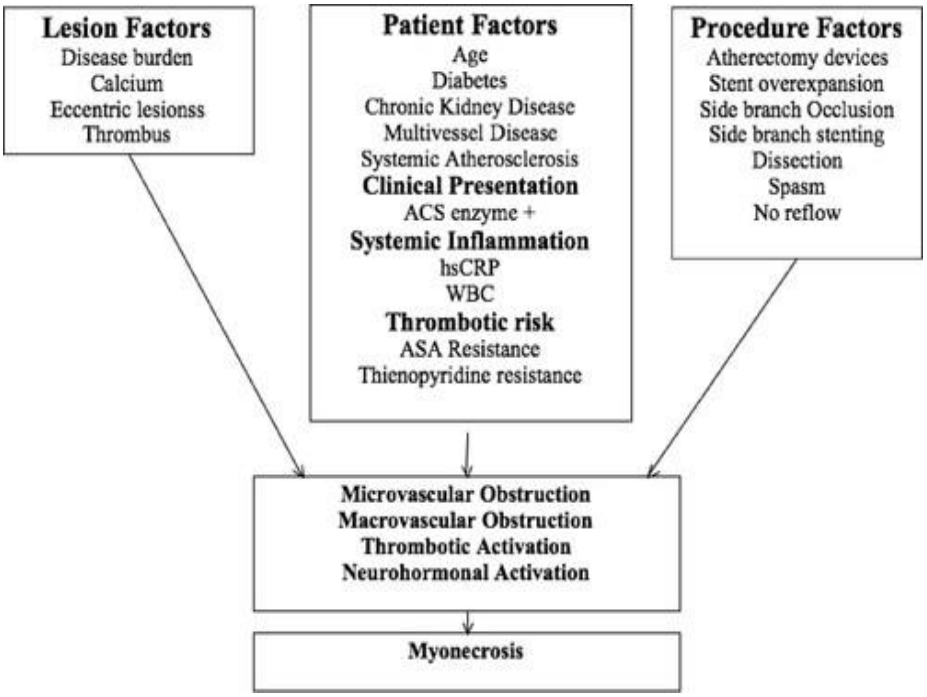

Figure 4: Risk factors and mechanisms of biomarker release after PCI ***(Herrmann, 2005).***

These risk factors identify patients with increasing atherosclerotic disease burden, increased thrombotic risk and with neurohormonal activation that predisposes to either macrovascular complications (side branch occlusion or macroembolization) or microvascular obstruction (distal embolization of microparticles) unifying the pathophysiologic basis of myocardial necrosis after PCI ***(Leosco, 1999).***

Chapter 2

HYPERGLYCEMIA AND ATHEROSCLEROSIS

Data from human and animal studies supporting a direct pro-atherogenic role of hyperglycemia in vascular cells are not as strong as those for insulin resistance, but there is suggestive evidence that high glucose is atherogenic, particularly at the level of the arterial endothelium. Hyperglycemia induces a large number of alterations at the cellular level of vascular tissue that potentially accelerate the atherosclerotic process ***(Mazzone, 2010).***

Oxidative stress is widely invoked as a pathogenic mechanism for atherosclerosis. Among the sequelae of hyperglycemia, oxidative stress has been suggested as a potential mechanism for accelerated atherosclerosis ***(Nishikawa, 2000).*** Hyperglycemia can increase oxidative stress through several pathways. A major mechanism appears to be the hyperglycemia-induced intracellular reactive oxygen species (ROS), produced by the proton electromechanical gradient generated by the mitochondrial electron transport chain and resulting in increased production of superoxide ***(Nishikawa et al., 2000).***

Two other mechanisms have been proposed that may explain how hyperglycemia causes increased ROS formation. One mechanism involves the transition metal-catalyzed autoxidation of free glucose, as described in cell-free systems.

Through this mechanism, glucose itself initiates autoxidative reaction and free radical production yielding superoxide anion (O_2-) and hydrogen peroxide (H_2O_2). The other mechanism involves the transition metalcatalyzed autoxidation of protein-bound Amadori products, which yields superoxide and hydroxyl radicals and highly reactive dicarbonyl compounds ***(Wolff, 1993; Aronson et al., 2002).***

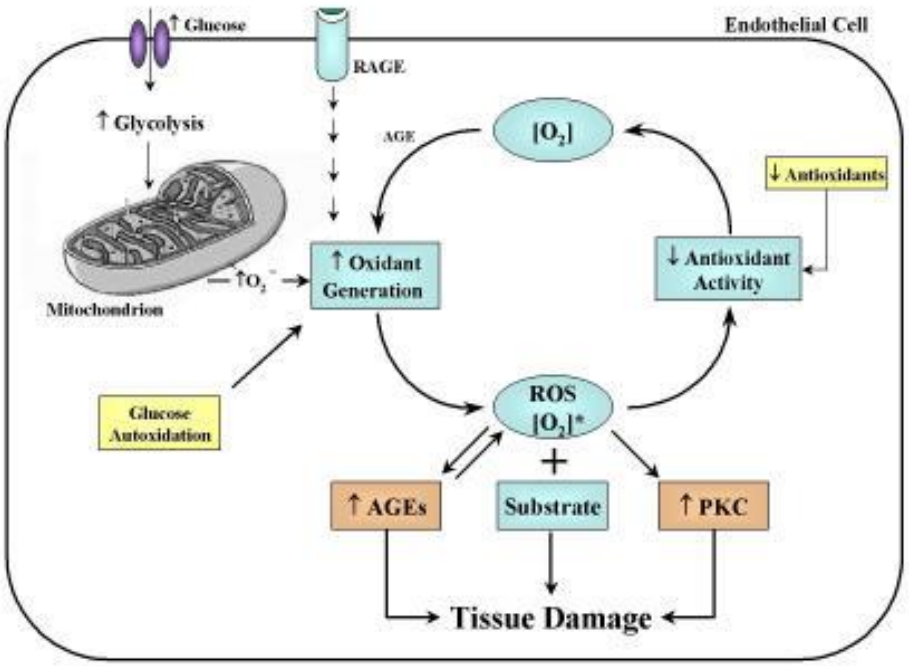

Figure 5: Relationship between hyperglycemia and rates of oxidant generation