INTRODUCTION

The synergy between percutaneous coronary intervention (PCI) with Taxus and Cardiac Surgery (SYNTAX) score has been developed to characterize coronary anatomy based on 11 step approach, such as lesion location and complexity, and in connection with the SYNTAX trial ***(Sianos et al., 2005 and Serruys et al., 2009).***

Based on the outcome of the SYNTAX trial the ESC has produced guidelines for coronary revascularization to determine when to perform PCI or CABG ***(Wijns et al., 2010).***

The SYNTAX trail was designed as an all corners study. Meaning that a real world patient population was tested instead of a highly selective population. The goal of the trial was to develop a semi-quantitative, visual score to help guide cardiologist as well as cardiothoracic surgeons for the best plan of revascularization. It is an important landmark study, that provided evidence-based, contemporary, objective randomized data about revascularization of 3 vessel disease and left main patients ***(Sianos et al., 2007).***

The syntax score can guide the selection of revascularization in whether it be percutaneous or surgical to best suit each individual. In recent years the SYNTAX score has been the most widely used angiographic score ***(Margo et al., 2014).*** Since the SYNTAX score is a diagnostic tool that

assess anatomical variability, which limits its accuracy ***(Garg et al., 2010).***

The 3-year SYNTAX study results suggest that CABG remains the standard of care for patients with complex disease; PCI may be an acceptable alternative revascularization method to CABG when treating patients with less complex disease ***(Kappetein et al., 2011).*** The results of the trial also indicated that, for more severe CAD (SYNTAX scores >22 for three-vessel or left main coronary disease), CABG offered a survival advantage, and it reduced the need for a repeat intervention and overall adverse cardiovascular events up to 4 years after revascularization ***(Serruys et al., 2009).***

On the other hand, Single Photoemission Computed Tomography (SPECT) Myocardial Perfusion Imaging (MPI) is a widely available method and has been validated extensively. Even though it does not reveal morphological changes in the vascular wall, it can be used to assess the functional capacity of the vessels and to diagnose changes in the myocardial perfusion.

The nature of the relationship between SYNTAX score and myocardial ischemia, however, has not yet been extensively evaluated. Thus, the aim of the present study was to examine whether SYNTAX score had a significant relationship with myocardial ischemia as assessed on myocardial perfusion imaging.

Transient ischemic dilation (TID) of the left ventricle on a stress single-photon emission computed tomography (SPECT) radionuclide myocardial perfusion imaging (MPI) study is thought to reflect myocardial ischemia that is sufficiently severe and extensive to cause visually apparent LV enlargement on the post-stress relative to the post-rest images. Several pathophysiologic mechanisms have been proposed, including actual stress-induced transient cavity dilation, a lack of subendocardial tracer uptake in the setting of extensive subendocardial ischemia without true anatomic cavity enlargement, a stress induced decrease in LV systolic function from stunning that appears as TID in the summed SPECT images, or perhaps various combinations of these. Regardless of the mechanism of the phenomenon, the presence of TID in patients with an abnormal MPI study has been shown to be a marker of severe and extensive CAD and in a few studies to confer increased risk for cardiovascular events. **(Abidov et al., 2004)**

AIM OF THE WORK

This study compared the relationship between myocardial ischemia, as assessed by SPECT, with the severity of the coronary artery disease. The severity of CAD was assessed by the SYNTAX score with coronary angiography, in patients with stress induced LV (left ventricle) cavity dilatation by SPECT and those without exercise induced LV dilatation.

ISCHEMIC HEART DISEASE

Myocardial ischemia is a consequence of reduced blood flow in coronary arteries, due to a combination of fixed vessel narrowing and abnormal vascular tone as a result of atherosclerosis and endothelial dysfunction. This leads to an imbalance between myocardial oxygen supply and demand ***(Lilly et al., 2005).***

The imbalance of oxygen supply and demand may lead to myocardial cells dying from the lack of oxygen and this is called a myocardial infarction (commonly called a heart attack). This leads to heart muscle damage, heart muscle death and later myocardial scarring without heart muscle regrowth. Transient ischemia can be induced from chronic high grade coronary artery stenosis which can lead to the induction of a ventricular arrhythmia, that might also complicate to ventricular fibrillation leading to death ***(Lilly et al., 2005).***

Pathophysiology

Ischemia occurs when the amount of blood that goes to the myocardial cells is limited. This process can lead to the death of the myocardium due to the lack of oxygen which in turn is called myocardial infarction. This results in heart muscle damage, death, and myocardial scarring without heart muscle regrowth. This process may then lead to heart failure, ventricular arrhythmias that can progress to ventricular fibrillation and eventually death ***(Ambrose and Singh, 2015).***

As the blood concentrations of apolipoprotein B-containing lipoproteins, of which the most prevalent form usually is low density lipoprotein (LDL), the chances of developing atherosclerosis increases as is the case of familial hypercholesterolemia (FH) ***(Yusuf et al., 2004; Lim et al., 2012).***

Myocardial ischemia is a sequela to reduced blood flow in the coronary arteries. This is mainly due to fixed vessel narrowing and abnormal vascular tone as a result of atherosclerosis and endothelial dysfunction. After which imbalance between oxygen supply and demand ***(Lilly et al., 2005).***

Stages of Atherosclerosis

Intimal thickening and fatty streaks

The first vascular changes that occur that can be described microscopically is intimal thickening, it consists of layers of smooth muscle and extracellular matrix (American Heart Association AHA type I lesion). It is noteworthy to know that intimal thickening is a lot more common in atherosclerotic –prone arteries such as carotid, coronary, iliac artery abdominal and descending aorta ***(Nakashima et al., 2002)***. However, since this type of change is considered adaptive because the smooth muscle cells (SMC) exhibit very low proliferative activity the older a person becomes and have an anti-apoptotic phenotype ***(Orekhov et al., 1998; Imanishi et al., 2000).***

Fatty streak or intimal xanthoma (AHA type II lesion) is mainly composed of abundant macrophage foam cells mixed within the smooth muscle cells and proteoglycan rich intima. Even though this lesion is recognized by the AHA classification as the earliest form of atherosclerosis, reports of human and animal studies ***(Fan et al., 2003; Aikawa et al., 1998)***, show that this lesion is a reversible process (with a few chances of progression). Also as we know from the Path biologic Determinants of Atherosclerosis in Youth (PDAY) study it is clear lesions in the abdominal ventral aorta, thoracic aorta and right coronary lesions may regress with the advancing of age ***(Fan et al., 2003; Jack, 1993).*** Elegant studies have also shown that foamy macrophages may desert the wall by passage between the endothelial cells and into the lumen ***(Ley et al., 2007)***.

Pathologic Intimal Thickening

This is known to be as the earliest progressive lesion (AHA type III lesion). It is mainly composed of layers of smooth muscle cells in proteoglycan matrix that is aggregated close to the lumen. Underneath it an acellular area of lipid pool, rich in hyaluronan and proteoglycans ***(Virmani et al., 2000)***. Structural changes in the glucosamine chains in the proteoglycans may represent an initial proatherogenic step that later on eases the binding of atherogenic lipoproteins ***(Nakashima et al., 2008; Nakashima et al., 2007).***

A hallmark of pathologic intimal thickening is the accumulation of macrophages on the luminal aspect of the plaque (outside the lipid pool), although they are not always observed in lesions of pathologic intimal thickening. Lesions with macrophages are considered at a more advanced stage of plaque development ***(Nakashima et al., 2007).***

The precise reason for why macrophages accumulate in the lesions of the pathologic intimal thickening is not fully understood but it is accepted that certain lipoproteins in the lipid pool play an important role. Also some lesions show varying levels of small free cholesterol clefts. This is believed to have been derived from dying smooth muscle cells but it still remains to be proven. Microclacification may also be present and are likely as a result of calcifying matrix vesicles ***(Kockx et al., 1998; Kolodgie et al., 2007).***

Fibroatheroma

Fibrous cap atheroma is the first of the advanced lesions of coronary atherosclerosis by the AHA classification scheme. One of its defining features is the presence of a lipid-rich necrotic core surrounded by collagen rich fibrous tissue. The fibrous cap atheroma may result in significant luminal narrowing and is also prone to complications of surface disruption, thrombosis, and calcification. The origin and development of the core is fundamental to understanding the progression of coronary artery disease. The fibrous cap consists

of collagen, smooth muscle cells, and proteoglycan with varying degrees of inflammatory cells—mostly macrophages and lymphocytes. The thickness of the fibrous cap is what differentiates the fibroatheroma (relatively thick) from the thin fibrous cap atheroma (classic "vulnerable" plaque) ***(Virmai et al., 2000; Stary et al., 1995).***

Recognition of early necrosis is identified by macrophage infiltration within lipid pools associated with a substantial increase in free cholesterol and breakdown of extracellular matrix, presumably by matrix metalloproteinase (MMP) activity. This, together with the death of macrophages in the setting of defective phagocytic clearance of apoptotic cells, is thought to contribute to the development of late plaque necrosis. Ultimately, the size of the necrotic core is a strong predictor of lesion vulnerability ***(Nakashima et al., 2007; Ohayon et al., 2008).***

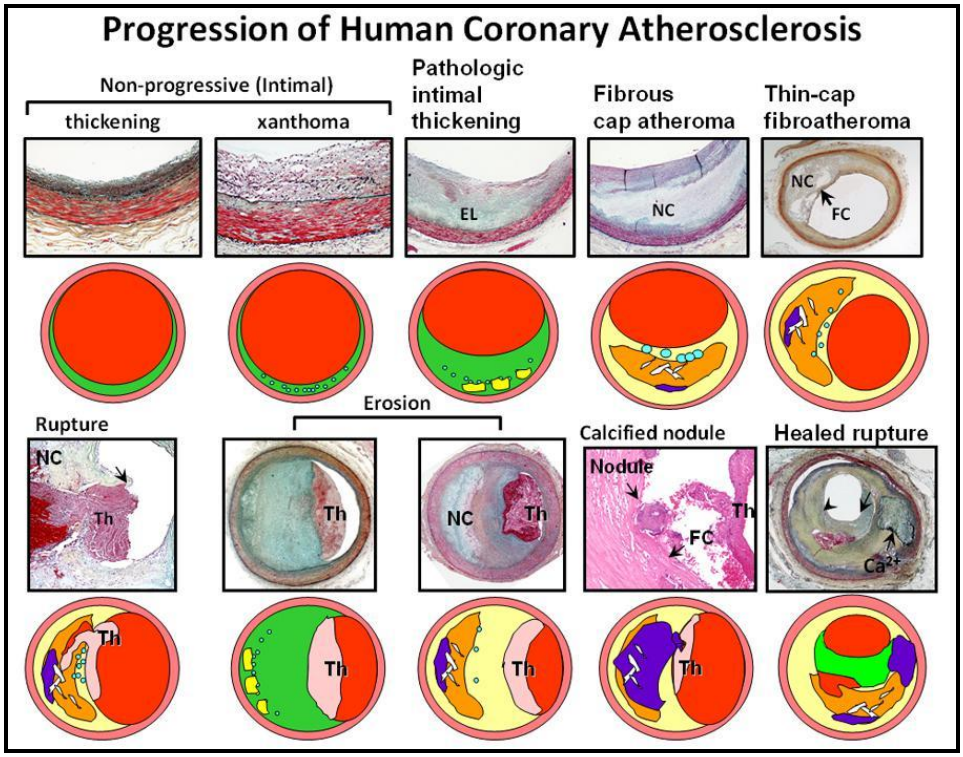

Figure (1): Processes involved in atherosclerosis include coagulation, inflammation, lipid metabolism, intimal injury, and smooth muscle cell proliferation ***(Nakashima et al., 2007).***

Plaque angiogenesis and intraplaque hemorrhage

Neovessels, originating from the adventitial vasa vasorum, grow to the base of progressive atherosclerotic lesions and provide a different entry pathway for monocytes and immune cells of unknown importance ***(Kumamoto et al., 1995).*** The plaque neovessels lack supporting cells and are fragile and leaky, giving rise to local extravasation of plasma proteins and erythrocytes ***(Sluimer et al., 2009).*** Such intraplaque bleedings are common in fibroatheromas and may expand the necrotic core and promote inflammation. Another common source of

plaque hemorrhage is extravasation of blood through a ruptured fibrous cap.

Plaque hemorrhage is associated with macrophages of the hemoglobin-induced phenotype (M(Hb)) that express CD163, a scavenger receptor that takes up haptoglobin-bound hemoglobin and thereby protect against the cytotoxic effects of free hemoglobin. These macrophages lack typical markers of M1 macrophages (tumor necrosis factor-α and inducible nitric oxide synthase), express the mannose receptor typical of M2-like macrophage differentiation, and are resistant to foam cell formation ***(Finn et al., 2012)***.

New data show that the inflammatory response to intraplaque hemorrhage is accentuated in patients with impaired haptoglobin function caused by the common Hp2-2 genotype, including particularly patients with diabetes mellitus, and this may contribute to the increased risk of Coronary heart disease CHD in individuals with high glycosylated hemoglobin ***(Finn et al., 2012).***

Mechanisms of plaque rupture, erosion, and thrombosis

Atherosclerosis alone may cause the obstruction of coronary blood flow and cause stable angina pectoris, but this is usually nonfatal in the absence of scarring of the myocardium, which may in turn cause an arrhythmia presenting as sudden cardiac death. ACS are usually always caused by a luminal

thrombus or a sudden plaque hemorrhage on an atherosclerotic plaque with or without vasospasm ***(Davies et al., 2000).*** In ST-segment elevation myocardial infarction, the thrombus is usually occlusive and maintained, whereas in unstable angina and non–ST-segment elevation myocardial infarction, the thrombus is usually partial and dynamic, or even absent to begin with. Also in patients who suffer from sudden coronary death, acute or organized thrombus is usually found; others die with severe coronary disease in the absence of thrombosis with or without myocardial scarring ***(Davies et al., 2000).*** Few cases of ACS occur due to emboli, artery dissection, vasculitis, cocaine abuse, tunnel coronary arteries, and trauma ***(Jacob et al., 2014).***

The most frequent cause of thrombosis is plaque rupture. In plaque rupture, there happens to be a structural defect in the fibrous cap which exposes the highly thrombogenic core to the blood. Dislodged plaque material can be seen within the thrombus, indicating that rupture and thrombosis occur side by side and thereby supporting its causal relationship. Plaque rupture is a well-defined term, described in a consensus statement from 2004, whereas other terms, such as plaque disruption and fissuring, are used ambiguously in the literature ***(Schaar et al., 2004).***

In some cases, nodular calcifications are found bulging into the lumen through a ruptured fibrous cap, and this is considered a separate precipitating mechanism of thrombosis.

When no plaque rupture can be found despite a thorough microscopic search, then the term plaque erosion is used. The reason why is because the endothelium is typically not present beneath the thrombus, but whether this is the precipitating mechanism still needs to be researched ***(Hansson et al., 2009)*** whether it be intimal thickening or fibroatheromas either one can be complicated by plaque erosion.

In a recent researches from autopsy studies from around the world, most of the fatal coronary thrombi was associated with plaque rupture whether or not there was a clinical manifestation (MI, 79%; sudden coronary death, 65%), age (>60 years, 77%; <60 years, 64%; unknown, 73%), sex (men, 76%; women, 55%), and continent (Europe, 72%; United States, 68%; Asia, 81%) (39) Plaque rupture is also one of the most common substrate for thrombi causing MI in patients who survive ***(Lakka et al., 2002).***

The sex differences seem noteworthy and, interestingly, plaque rupture has been found to be particularly infrequent in premenopausal women, who however constitute an extremely small group of heart attack victims. Some studies have reported that diabetes mellitus, smoking, and the level of hyperlipidemia are associated with the mechanism of thrombosis in ACS but, except for sex and menopause, no consistent relationships have been demonstrated ***(Falk et al., 2013).*** Smoking seems to aggravate the process of coronary thrombosis, regardless of plaque type ***(Burke et al., 1998).*** A study using intravascular

optical coherence tomography showed that the incidence of plaque ruptures may be higher in ST-segment elevation myocardial infarction when compared to that of non–ST-segment elevation myocardial infarction ***(Yasushi et al., 2011).***

Mechanisms of Plaque Rupture

Plaque rupture occurs where the cap is thinnest and most infiltrated by foam cells (macrophages). In eccentric plaques, the cap margin is often the weakest spot or shoulder region might also be the culprit, ***(Falk et al., 1995)*** and the only fibrous caps that are at the risk of rupturing are the extremely thin ones. When examined by microscopic examination in an autopsy study for sudden cardiac death, the average thickness of ruptured caps measured was found to be only 23 μm and nearly all of them from ruptured fibrous caps were below 65 μm [(41)] According to this data, ***(Virmani et al., 2000)*** introduced the term thin-cap fibroatheromas (TCFAs) for coronary fibroatheromas in which the defining thickness was <65 μm, this number can be used to identify the majority of plaques at risk for rupture.

The image below shows a thin cap fibroatheroma with inflammation in the cap(A-B).

Images show staining of the macrophages red and image D is a higher magnification showing SMCs ***(Falk et al., 2013).***

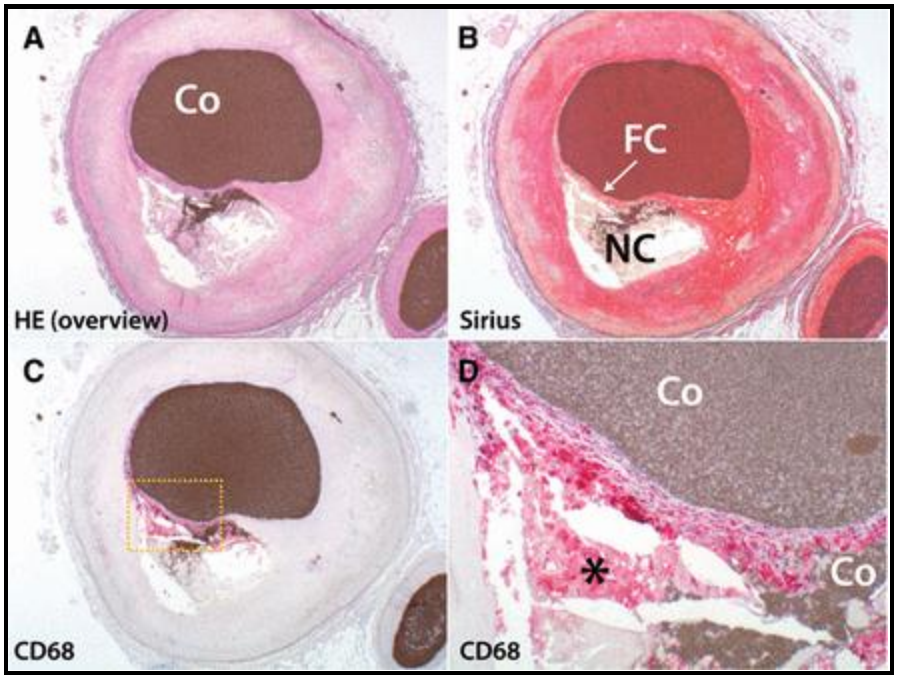

Figure (2): Microscope view of atherosclerotic stages ***(Falk et al., 2013)*** (Images show staining of the macrophages red with different dyes and higher magnification showing SMC).(FC fibrous cap, NC necrotic core and Co compartment)

Rupture of a thin cap and subsequent thrombosis can occur spontaneously, but in a few cases, a temporary increase in emotional or physical stress provides the final trigger for the event. Recognized triggers include any form of physical activity including sex, or other forms such as, anger, anxiety, work stress, earthquakes, and terror attacks, temperature changes, infections, and cocaine use ***(Mittleman et al., 2011).*** Some simple daily activities or the circadian rhythm of biological pathways may cause the onset of ACS, which are most frequent in the morning ***(Muller et al., 1985).*** The pathways that trigger such events may include activation of the