INTRODUCTION

Surgical revascularization of the coronary arteries is one of the most frequent surgical procedures performed worldwide. The reduction or disappearance of angina, the improved tolerability of physical exercise and the overall improvement in quality of life and life expectancy have been the motivations underlying its use since the first the procedure was performed in the 1950. Although the procedure is one of the major successes of modern medicine, it doesn't treat the disease underlying the symptoms (atherosclerosis) only the clinical presentation of coronary artery disease ***(Riccardo et al., 2012).***

The prognosis of patients who have undergone surgical revascularization depends not only on the outcome of the procedure but also on the progression of the disease in the native coronary arteries and in conduits used to bypass ***(American Journal of Cardiology, 2009)***. The large number of patients suffering a recurrence of angina after surgical revasculization represents a significant issue in clinical cardiology. Recurrence of angina can be present in association with myocardial ischemia both in previously reperfused and non reperfused regions. These patients should therefore undergo clinical and instrumental monitoring and some cases a repeat procedure is required, which unfortunately is

encumbered by a higher percentage of post procedure complications ***(Lorenzo, 2011)***.

Diabetes mellitus is associated with a tendency toward higher platelet reactivity, higher levels of coagulation factors, greater systemic inflammation, and reduced efficacy of aspirin, and consequently some signal of increased graft failure in diabetic individuals may be expected. The lack of such a signal to date suggests a complexity to the pathbiology of graft disease or perhaps a beneficial effect of hypoglycemic medication ***(American Journal of Cardiology, 2011)***.

Non-invasive imaging of coronary artery bypass grafts by computed tomography was first described in the early 1980s. Meanwhile, multi-slice computed tomography (MSCT) is now available. This new technique allows detection of coronary lesions with good sensitivity and specificity due to continuous improvement and modification of this method. The aim of this study was to investigate whether stenosis or occlusion of CABG can be detected by MSCT ***(Christof, 2003).***

Conventional coronary angiography however is expensive and has a small risk of potentially life-threatening complications, including arrhythmia, stroke, coronary artery or graft dissection, embolic events and myocardial infarction. Therefore a reliable non-invasive imaging modality is

preferable for evaluation of patients suspected of having graft stenosis or occlusion ***(Said et al., 2012).***

Multislice computed tomography (MDCT) is a result of progress in the scanner technology which led to improved spatial resolution through thinner slice collimation and to increased temporal resolution through faster gantry rotation. MDCT angiography is a non-invasive imaging technique that can be performed on ambulatory patients ***(Hamon, 2008).***

MDCT has promising results in the assessment of bypass graft patency than 16-MDCT. Several studies have shown high diagnostic accuracy of 16-MDCT in the detection of complete graft occlusion; however those studies yielded limited data on the accuracy of 16-MDCT in the detection of greater than 50% bypass graft stenosis ***(Levent, 2012)***. Dual source CT provides significantly better diagnostic image quality than single source CT despite higher heart rates with diagnostic accuracy of 100% for the detection or exclusion of significant stenosis in arterial and venous grafts using dual source MDCT ***(Robert, 2009).***

AIM OF THE WORK

Evaluation the effect of diabetes mellitus on the patency of arterial and venous grafts after coronary artery bypass surgery assessed by multi-slice CT coronary angiography.

DIABETES MELLITUS AND CORONARY ARTERY DISEASE

Cardiovascular disease is the major cause of mortality for individuals with diabetes. Type 2diabetes is an independent risk factor for macrovascular disease, and its common coexisting conditions (e.g., hypertension and dyslipidemia) are also risk factors ***(American Diabetes Association, 2007).***

DM is associated with diverse derangements in platelet function, the coagulation factors, and the fibrinolytic system, all of which contribute to prothrombotic state. Some are clearly related to metabolic derangements, particularly hyperglycemia; others appear to be related to insulin resistance and hormonal derangements ***(Schneider et al, 2009).***

Effect of diabetes mellitus on platelets:

Platelet abnormalities occur in diabetes parallel with endothelial cells, including activation of protein kinase C, decreased production of platelet-derived nitric oxide, and increased oxidative stress. Diabetes impairs platelet calcium homeostasis, which may contribute importantly to abnormal platelet activity, because calcium regulates platelet shape change, secretion, aggregation, and thromboxane formation. Moreover, platelets from patients with diabetes have increased expression of the adhesive glycoprotein (GP) Ib and GP

IIb/IIIa. Patients with type 2 diabetes have attenuated insulin-mediated antagonism of platelet activation and higher levels of pro-thrombotic platelet micro-particles ***(Ferreira et al., 2006 and Brown et al., 2009).***

Table 1: Potential Impact of Insulin Resistance and Diabetes on Thrombosis ***(Schneider et al, 2009).***

Factors predisposing to thrombosis:
Increased platelet mass
Increased platelet activation
• Platelet aggregation
• Platelet degranulation
Decreased platelet cAMP and cGMP
• Thromboxane synthesis
Increased procoagulant capacity of platelets
Elevated concentrations and activity of procoagulants
• Fibrinogen
• Von Willebrand factor and procoagulant activity
• Thrombin activity
• Factor VII coagulant activity
Decreased concentration and activity of anti-thrombotic factors
• Anti-thrombin III activity
• Sulfation of endogenous heparin
• Protein C concentration

cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate.

There is increased production of thromboxane A2 and altered cellular distribution of guanine nucleotide-binding proteins (G proteins) which contributes to the increased platelet reactivity, as well as the increased concentrations of glucose increases platelets reactivity directly ***(Iwase et al., 2009)***.

Insulin alters reactivity of platelets, exposure of platelets to insulin decreases platelet aggregation in part by increasing

synthesis of nitric oxide (NO) that increases intra-platelet concentrations of the cyclic nucleotides, cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP). Both of these cyclic nucleotides are known to inhibit activation of platelets ***(Keating et al., 2003).***

Aspirin has been recommended as a primary and secondary therapy to prevent cardiovascular events in diabetic and non diabetic individuals. One large meta-analysis and several clinical trials demonstrate the efficacy of using aspirin as a preventive measure for cardiovascular events, including stroke and myocardial infarction. Many trials have shown a ~30% decrease in myocardial infarction and a 20% decrease in stroke in a wide range of patients, including young and middle-aged patients, patients with and without a history of CVD, males and females, and patients with hypertension ***(Hayden et al., 2002).***

Effect of Diabetes on Coagulation Factors:

Patients with DM have increased concentrations in blood of the prothrombotic factors fibrinogen, von Willebrand factor, and factor VII coagulant activity. Among the three coagulation factors, fibrinogen has been most strongly associated with the risk of development of CVD ***(Knobl et al., 2004).*** Thus, the generation of coagulation factor Xa and of thrombin is increased by three- to sevenfold in samples of blood containing

platelets from diabetic patients compared with those who are not diabetic subjects ***(Lupu et al., 2009).***

Type2 diabetes and its associated metabolic abnormalities in the coagulation and fibrinolytic systems that support clot formation and stability. Type 2 diabetes increases plasminogen activator inhibitor type 1 (PAI-1) levels, impairing fibrinolytic capacity in atherosclerotic lesions. Moreover, diabetes increases the expression of tissue factor and levels of plasma coagulation factors, and decreases levels of endogenous anticoagulants ***(Eckel et al., 2002).***

The balances between the activity of prothrombotic factors and anti-thrombotic factors in blood and between thrombogenicity and fibrinolytic system capacity are important determinants of the nature and extent of a thrombotic response to plaque rupture. Both the severity of vascular injury and the extent of plaque rupture, influence the extent to which blood is exposed to subendothelium and consequently to thrombogenicity. In subjects with type 2 diabetes, the balances between determinants are shifted toward potentiation and persistence of thrombosis and hence toward acceleration of atherosclerosis ***(Fernandez-Ortiz et al., 2004).***

Activation of the coagulation system leads to the generation of thrombin and thrombin-mediated formation of fibrin from fibrinogen. The generation of thrombin depends on activation of pro-coagulant factors. It is limited by

antithrombotic factors and inhibitors. Fibrinopeptide A (FPA) is released when fibrinogen is cleaved by thrombin. FPA has a very short half-life in the circulation and is cleared promptly by the kidneys. Elevated concentrations in blood are indicative of thrombin activity in vivo ***(Scharfstein et al., 2006).***

The increased generation of thrombin in people with diabetes, is likely to be dependent on increased activity of factor Xa. This has been observed in patients with type 1 diabetes. Factor Xa, a major component of the prothrombinase complex, is formed from components including circulating coagulation factor X assembled on phospholipid membranes in association with the tissue factor VIIa complex ***(Ceriello et al., 2010).***

Table 2: Potential Impact of Insulin Resistance and Diabetes on Fibrinolysis

Factors attenuating fibrinolysis:
Decreased t-PA activity
Increased PAI-1 synthesis and activity
• Directly increased by insulin
• Increased by hyperglycemia
• Increased by hypertriglyceridemia and increased FFA
• Synergistically increased by hyperinsulinemia combined with elevated triglycerides and FFA
Increased concentrations of α 2-antiplasmin

t-PA, tissue-type plasminogen activator; PAI-1, plasminogen activator inhibitor type-1; FFA, free fatty acid. ***(Schneider et al, 2009).***

Decreased fibrinolytic system capacity is observed consistently in blood from patients with DM, particularly those

with type 2 diabetes. It has been known for many years that obesity is associated with impaired fibrinolysis and that elevated blood triglycerides and other hallmarks of hyperinsulinemia are associated with increased activity of PAI-1 and that elevated PAI-1 is a marker of increased risk of acute MI ***(Calles-Escandon et al., 2010).***

Metabolic Abnormalities in Diabetes:

Diabetes causes metabolic abnormalities, including hyperglycemia, dyslipidemia, and insulin resistance, that disrupt normal arterial function and render arteries susceptible to atherosclerosis. It specifically alters the function of vascular endothelium and smooth muscle cells, as well as platelets, in ways that promote atherogenesis ***(Goldfine et al., 2008).***

Hyperglycemia decreases NO production from endothelial nitric oxide synthase (eNOS) and increases its degradation via generation of reactive oxygen species (ROS). Hyperglycemia triggers the production of ROS in vascular cells through enzymatic (protein kinase C and the reduced form of nicotinamide adenine dinucleotide phosphate [NADPH] oxidases) and non enzymatic sources of oxidant stress (e.g., the formation of advanced glycation end products, AGEs). Similar to the effects of hyperglycemia, free fatty acids activate intracellular enzymatic oxidant sources, including protein kinase C, NADPH oxidases, and eNOS, yielding analogous increases in superoxide anion ***(Rask-Madsen and King, 2005).***

In diabetes, hyperglycemia and increased free fatty acids increase the concentration in the cell of the metabolite diacylglycerol. Diacylglycerol activates a family of enzymes known as protein kinase C (PKC) that perform key regulatory functions by phosphorylating proteins important in metabolic control. PKC enzymes are implicated in cardiovascular complications of diabetes. Activation of PKC can inhibit the expression of eNOS, augment cytokine-induced tissue factor gene expression and procoagulant activity in human endothelial cells, and increase the production of proinfla-mmatory cytokines, proliferation of vascular wall cells, and production of extracellular matrix macromolecules that accumulate during atherosclerotic lesion formation ***(Rask-Madsen and King, 2005).***

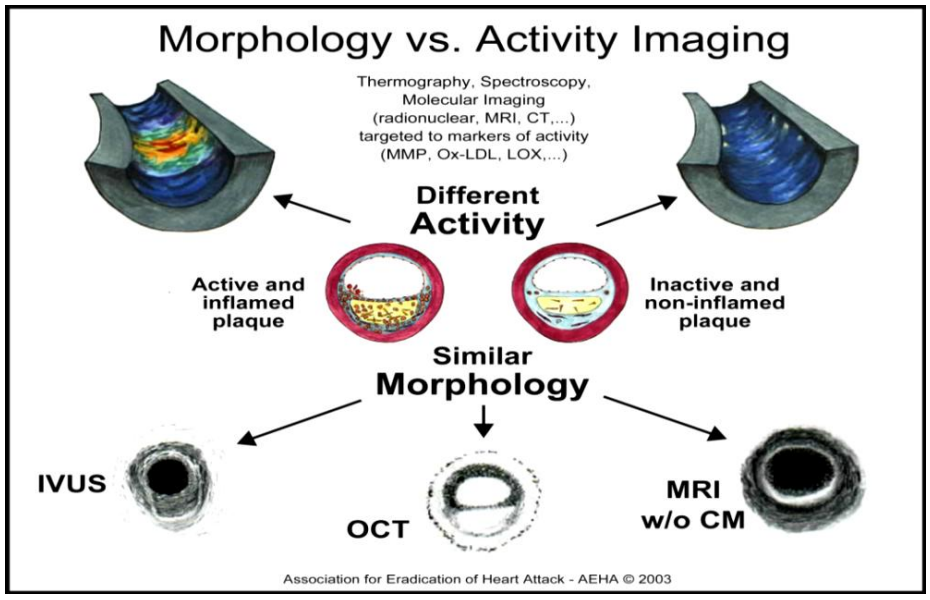

Figure 1: Abbreviations: OCT: Optical Coherence Tomography, IVUS: Intravascular ultrasonography, MRI: Magnatic resonance imaging. Plaque morphology and activity ***(Naghavi et al., 2003).***

Endothelial insulin resistance alters the pattern of activation of intracellular signaling pathways which decreases nitric oxide production, increases endothelin production, stimulates the transcription of inflammatory genes, and increases the tendency to coagulation. Drug-induced improvement in insulin sensitivity reduces cytokine production and inflammatory transcription factor activation and increases nitric oxide bioavailability ***(Montagnani et al., 2002).***

Diabetes impairs vascular smooth muscle function and augments the production of vasoconstrictor mediators, including endothelin-1, which causes vascular smooth muscle growth and inflammation. Levels of other atherogenic mediators, including angiotensin II and vasoconstrictor prostanoids are increased in diabetes as well. Patients with type 2 diabetes have impaired vasodilatation, possibly reflecting an abnormality in NO signal transduction ***(Beckman et al., 2003).***

CORONARY ARTERY BYPASS GRAFTING

Coronary artery bypass grafting is one of the most common procedures for the treatment of symptomatic CAD. Coronary bypass surgery approach for the treatment of patients with angiographically documented coronary atherosclerosis was begun by Garrett, Dennis, and DeBakey who first used CABG as a "bailout" procedure. Early coronary bypass operations were based almost entirely on aorta-to-coronary reversed saphenous vein grafts (SVG) ***(Sabik et al., 2005).***

Many patients who present with acute coronary syndrome (ACS) are candidates for coronary artery bypass grafting (CABG). Approximately 500,000 CABG operations are performed each year in the United States, and many of these patients present with acute coronary syndrome. According to 2011 ACC/AHA guidelines ***(Anderson, Adams et al. 2011)***, left main stenosis greater than 50% and three-vessel coronary artery disease represent a class I indication for coronary artery bypass grafting in patients with unstable angina or non-ST elevation myocardial infarction. In addition, patients with 2-vessel coronary artery disease and either diabetes or left ventricular dysfunction may benefit from coronary artery bypass grafting (Class II recommendation).

Types of Arterial or Vein Grafts:

1. Saphenous Vein Graft (SVG):

The SVG was first successfully used in a CABG operation by Sabiston in 1962. Saphenous veins are simple to access from the lower extremities, and they are more versatile and widely available than arterial grafts. In addition, during the intra- and peri-operative period, saphenous veins are resistant to spasm versus their arterial counterparts. However, the use of SVG is limited by distortion from varicose and sclerotic disease as well as a higher occurrence of intimal hyperplasia and atherosclerotic changes after exposure to systemic blood pressure, resulting in lower patency rates. Graft occlusion can also occur due to vascular damage during harvesting of the saphenous vein. In a large study, the SVG patency was 88% perioperatively, 81% at 1year, 75% at 5 years, and 50% at greater than or equal to 15 years ***(Fitzgibbon et al., 2010).***

Much of the late attrition of SVGs appears to be related to intrinsic pathologic changes in those grafts; intimal fibroplasia and vein graft atherosclerosis. Almost all SVGs examined within a few months after operation exhibit intimal fibroplasia, a hypercellular proliferative hyperplasia that involves the intima which distributed throughout the length of the graft. With time they become less cellular and more fibrotic. Intimal fibroplasia may cause stenosis and occlusions ***(Bourassa et al., 2001).***

Vein graft atherosclerosis (VGA) is characterized by lipid infiltration of areas of intimal fibroplasia and is different in distribution and character than native coronary atherosclerosis. VGA is distributed throughout the length of vein grafts; it is circumferential, not encapsulated, and extremely friable. With time the early circumferential lesion will often progress to eccentric lesions causing severe stenosis. VGA is a dangerous lesion, because of the friability and non-encapsulated nature of this lesion, embolization of atherosclerotic debris is a major risk during percutaneous interventions on vein grafts and during re-operations, and it is probable that spontaneous embolization may occur ***(Pfister et al., 2005).***

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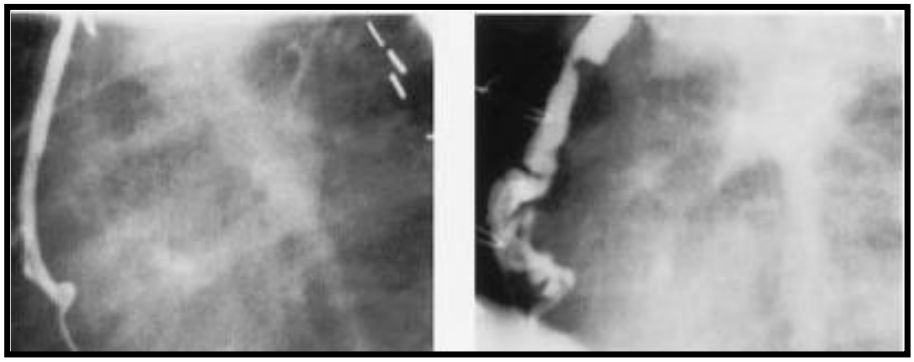

Figure 2: Angiography of SVG to the RCA. Angiographic anatomy 1 year after operation (left) showing patent vein grafts to the RCA. Seven years later (right) the RCA graft exhibits diffuse irregular stenosis characteristic of vein graft atherosclerosis ***(Lytle et al., 2004).***

Statin therapy to achieve LDL levels less than 100 mg/dL in addition to clopidogrel was independently associated with improved graft patency in the Clopidogrel after