Impaired Brachial Artery Flow-Mediated Dilation and Risk of Restenosis in non Diabetic Patients with Single Vessel Disease Undergoing Elective Coronary Stent Implantation

Thesis
Submitted in Partial Fulfillment of the M.D Degree in Cardiology

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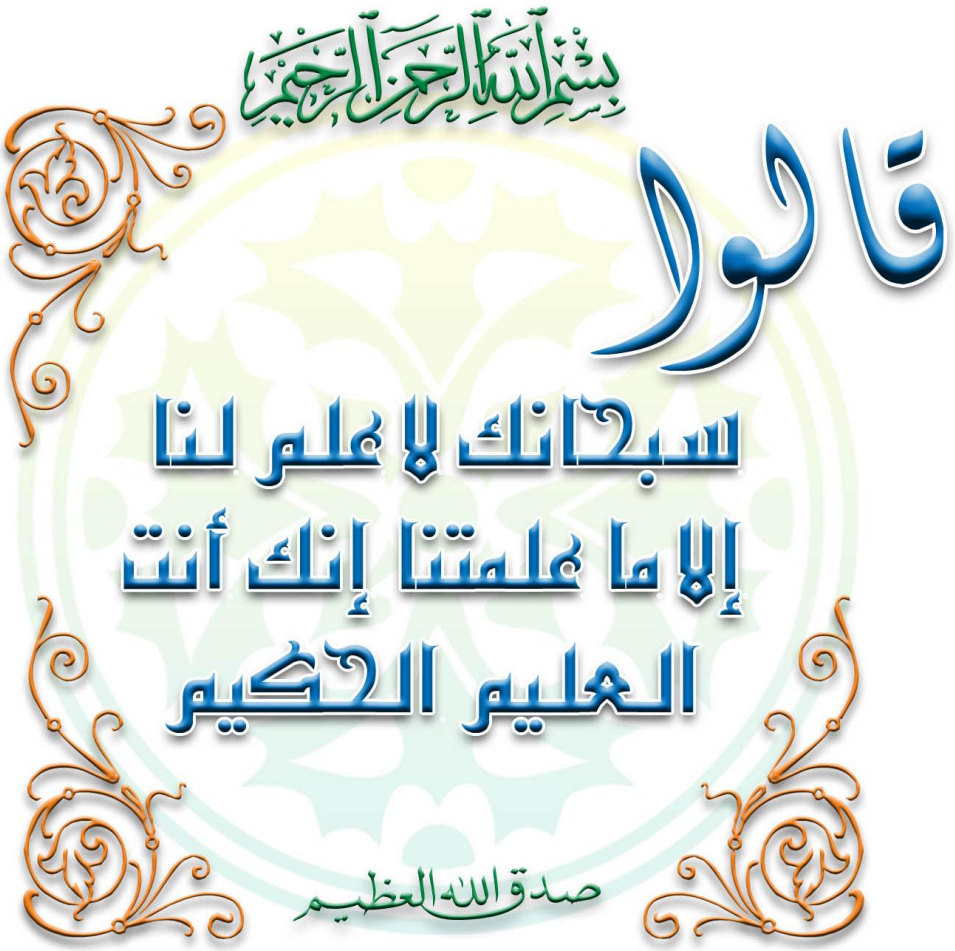

سورة البقرة الآية: ٣٢

Dedication

To my family for their help, support, patience and encouragement

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List of Abbreviations

Abb.	Meaning
2D	2 Dimensional Echocardiography
AAVs	Adeno-associated viruses
ACEI	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
AVs	Adenoviruses
BA	Balloon angioplasty
BB	Beta blocker
B-mode	B-mode Echocardiography
BMS	Bare- metal stent
Bp	Blood pressure
CAD	Coronary artery disease
CB	Cutting balloon
CCB	Calcium channel blocker
CRP	C-reactive protein
DES	Drug-eluting stent
DGC	Dystrophin-glycoprotein complex
DS	Diameter stenosis
ECG	Electrocardiogram/electrocardiographic
ECM	Extracellular matrix
ECs	Endothelial cells
eNOS	Endothelial nitric oxide synthase
FMD	Flow-mediated vasodilation
GM	Geographic miss
GP	Glycoprotein
IL-6	Interleukin-6
ISR	Instent restenosis
IVUS	Intravascular ultrasound
MI	Myocardial infarction
MIH	Myo-Intimal Hyperplasia
MLD	Minimal lumen diameter
MMP	Matrix metalloproteinase
NO	Nitric oxide
NOS	Nitric oxide synthase

Abb.	Meaning
NTG	Nitroglycerin
PCI	Percutaneous coronary intervention
PDGF	Platelet drived growth factor
PES	Paclitaxel-eluting stents
PTCA	Percutaneous trans coronary angioplasty
PWD	Pulsed wave Doppler
QCA	Quantitative coronary arteriography
SES	Sirolimus-eluting stents
TLR	Target lesion revascularization
TNF-alpha	Tumour necrosis factor-alpha
TVR	Target vessel revascularization
VEGF	Vascular endothelial growth factor
VSMCs	Vascular smooth muscle cells

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INTRODUCTION

Impairment of endothelial function is an early event in the atherosclerotic process, and markers of endothelial dysfunction have been used as a surrogate of disease activity **(Verma et al., 2003; Widlansky et al., 2003; Willerson and Kereiakes, 2003)**.

Abnormal endothelial function in the coronary circulation may precede development of angiographically evident coronary plaques **(Ludmer et al., 1986)**, has been associated with a higher prevalence of coronary artery disease (CAD) **(Cox et al., 1989),** and may be predictive of future cardiovascular events **(Schachinger et al., 2000; Suwaidi et al., 2000)**. However, direct assessment of coronary vasomotor response is invasive and cannot be widely applied in clinical practice.

Preserved endothelial function with release of molecules with anti-inflammatory, anti-thrombotic, and anti-proliferative effects (including nitric oxide, prostacyclin, and other hyperpolarizing factors) is crucial for the prevention of luminal narrowing by neointimal thickening **(Ross, 1993; Vita and Keaney, 2002)**.

Dysfunctional endothelium may release several substances, such as endothelin-1, angiotensin II, and growth factors (platelet-derived growth factor, macrophage colony stimulating factor, and transforming growth factor), that may induce or enhance migration of smooth muscle cells and intimal hyperplasia **(Widlansky et al., 2003)** thus contributing to the

in-stent restenosis process. Local production by dysfunctional endothelium of pro-inflammatory cytokines, tumor necrosis factor, adhesion molecules, and chemotactic factors may also play a role via activation of local inflammatory pathways. Indeed, in vivo data demonstrate that impaired endothelial function may enhance intimal hyperplasia after balloon angioplasty **(Schwarzacher et al., 1997; Lafont et al., 1999).**

Endothelial dysfunction is considered a systemic process **(Verma et al., 2003; Widlansky et al., 2003)** therefore; endothelium-dependent vasomotion detected in peripheral arteries with noninvasive tests reflects coronary endothelial function.

Ultrasound assessment of brachial artery flow-mediated dilation (FMD) is a sensitive test for quantifying endothelium-dependent vasomotion **(Corretti et al., 2002)** and a close relationship has been demonstrated between this technique and coronary vasomotor responses to acetylcholine **(Anderson et al., 1995).**

Percutaneous coronary intervention (PCI) with stenting has now become an effective and widespread treatment modality for patients with CAD, but in-stent restenosis remains its main limitation; therefore, early identification of patients with higher risk of restenosis after PCI is the object of active investigation.

In-stent restenosis due to intimal hyperplasia occurs after PCI with stent implantation in 10% to 40% of cases at 6

months, depending on various clinical, angiographic, and procedural features. Therefore, early stratification of patients according to the risk of development of in-stent restenosis appears crucial after percutaneous revascularization and may influence clinical management.

Mechanisms involved in the pathogenesis of in-stent restenosis include platelets and inflammatory cell activation due to procedural vascular injury with subsequent local release of cytokines and growth factors, leukocyte adherence, smooth muscle cell proliferation, and extracellular matrix synthesis **(Ferns and Avades, 2000; Patti et al., 2002)**.

FMD by brachial artery ultrasound imaging has been correlated with the occurrence of adverse events in patients with chest pain **(Neunteufl et al., 2000)** and after vascular surgery **(Gokce et al., 2002).**

Impaired FMD is an independent predictor of in-stent restenosis in patients with single-vessel CAD undergoing PCI. Although there are several evidences of the close relationship between endothelial dysfunction and atherosclerosis **(Ludmer et al., 1986; Cox et al., 1989; Quyyumi, 1998; Okumura et al., 1992)** the role of endothelium in the process of restenosis after stent implantation is still unclear **(Wu et al., 2000)**.

Previous studies have found an independent correlation between coronary endothelial function and risk of cardiovascular events **(Halcox et al., 2002; Schindler et al., 2003)** but there are no data on the possible association between

endothelial dysfunction in the coronary circulation and risk of restenosis. FMD is a noninvasive technique that is easily applied in clinical practice, especially if repeated measurements are required **(Corretti et al., 2002)**. FMD depends largely on nitric oxide synthesis but may also reflect local release of other endothelium-derived factors (ie, prostacyclin and bradykinin) **(Verma et al., 2003; Widlansky et al., 2003)**. Furthermore, brachial artery FMD correlates well with coronary endothelial function, **(Anderson et al., 1995)** particularly that of conduit epicardial vessels **(Widlansky et al., 2003).**

Aim of the Work

The aim of this study is to investigate whether early evaluation after coronary stenting of FMD by brachial artery ultrasound imaging could predict in-stent-restenosis in a consecutive cohort of patients followed up for 9 months after the procedure.

Patients and methods:

Patients:

This study will be conducted in Ain Shams university hospitals, cardiology department on 50 consecutive patients of both sexes with coronary artery disease who will be treated with elective PCI and will be followed up as per study protocol for up to 9 months.