

# **Tissue Factor Pathway Inhibitor and Endothelin-1 as Risk Factors in Coronary Artery Disease**

Thesis

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## **Introduction**

Acute myocardial infarction (AMI) can be fatal. However, survival and cardiovascular morbidity are improved by thrombolytic therapy at onset (Kamikura et al., 1997). Hypercoagulability may be involved in the pathogenesis of AMI and in reocclusion of the coronary artery.

Coronary thrombosis generally occurs at sites of stenosis, often precipitated by fissuring of atherosclerotic plaque (Davies and Woolf, 1998).

Tissue factor (TF) is recognized as the initial trigger for blood coagulation in normal hemostasis and plays a major role in thrombogenesis associated with atherosclerosis (Falciani et al., 1998).

Tissue factor pathway inhibitor (TFPI) is a protease inhibitor that may act as a natural anticoagulant to regulate TF – induced coagulation (Lorena et al., 1997). TFPI is present in the vascular compartment in three different pools: endothelial (50 – 90%), plasma (10 – 50%), in which most of it is bound to lipoproteins with only 5% circulating as

free uncomplexed, and platelet associated (2.5%) (Lorena et al., 1997).

TFPI most probably protects against thrombosis secondary to exposure of blood to low concentrations of TF, however, no thromboembolic disease due to a hereditary deficiency of TFPI has been described (Kamikura et al., 1997).

Patients with homozygous abetalipoproteinemia and hypobeta lipoproteinemia have very low plasma TFPI antigen levels and don't have thrombosis suggests that lipoprotein associated TFPI may not be essential (Novotny et al., 1991). However, since LDLs accumulate in atheromas in which thrombosis is likely to occur, the increase in LDL – associated TFPI may play a role in the prevention of local Thrombosis (Lesnik et al., 1992). Furthermore increased LDL cholesterol may attract TFPI from endothelium, so making the endothelial surface more susceptible to thrombosis (Lorena et al., 1997).

Endothelin (ET)-1, a potent vasoconstrictor peptide first isolated from endothelial cells, is also generated in heart, in cardiac monocytes, and in fibroblasts where it acts

as positive inotrope and stimulates myocardial hypertrophy (Smith et al., 2000).

Endothelins are potent vasoconstrictors and pressor peptides and important mediators of cardiac, renal and endocrine functions. Increased ET-1 levels in disease states such as congestive heart failure, pulmonary hypertension, renal failure and acute myocardial infarction may be suggestive that, endothelin system may be an attractive target for pharmacotherapy (Gueldner and Inomata, 2000). Acutely elevated levels of ET-1 in myocardial infarction, correlate with the severity of infarct and of prognostic value (Smith et al., 2000).

## **Aim of the Work**

1. To investigate the predictive role of TFPI and endothelin-1 in the prothrombotic state in different clinical settings of coronary artery disease.
2. To evaluate the relation between the previous parameters, cholesterol, lipid profile and coagulation profile in coronary artery disease patients.

## **Subjects and Methods**

This study will be conducted on adequate number of adult patients with different clinical settings of coronary artery disease (stable, unstable angina and myocardial infarction) and comparable group of healthy individual as a control group.

All members of this study will be subjected to the following:

1. Thorough clinical examination and history.
2. laboratory investigations including:
  - a) Complete blood picture.
  - b) Coagulation profile (P.T and P.T.T)
  - c) Complete lipid profile (cholesterol, LDL, HDL, triglycerides).
  - d) Cardiac enzymes.
  - e) Total TFPI by ELISA technique.
  - f) Endothelin-1 by ELISA technique.

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# دراسة دور العامل النسيجي المثبط المسار وأحادى الإندوثيلين فى حدوث أمراض الشريان التاجى

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## INTRODUCTION

Coronary thrombosis generally occurs at the site of a preexisting atherosclerotic plaque, usually triggered by fissuring or ulceration of the plaque. It is currently believed that a major initiator of intracoronary thrombus formation is tissue factor (TF), a cell-surface protein abundantly expressed by cells residing within the plaque (*Davies et al., 1993*).

Several studies have identified both TF antigen and activity within human atherosclerotic plaques and suggested that TF might represent an important determinant of thrombogenicity after plaque rupture. Tissue factor pathway inhibitor (TFPI) is a protease inhibitor that may act as a natural anticoagulant to regulate TF-induced coagulation (*Lorena et al., 1997*).

TFPI is present in the vascular compartment in three different pools: endothelial (50-90%), plasma (10-50%), in which most of it is bound to lipoproteins with only 5% circulating as free uncomplexed, and platelet associated (2.5%). TFPI most probably protects against thrombosis secondary to exposure of blood to low concentrations of TF, however, no thromboembolic disease due to a hereditary deficiency of TFPI has been described (*Kamikura et al., 1997*).

Endothelin-1, a potent vasoconstrictor peptide first isolated from endothelial cells, is also generated in heart, in cardiac monocytes, and in fibroblasts where it acts as positive inotrope and stimulates myocardial hypertrophy (*Smith et al., 2000*).

Endothelin-1 is a potent vasoconstrictor and pressor peptide and is an important mediator of cardiac, renal and endocrine functions. It has been documented that an elevated endothelin-1 plasma concentration is associated with an increased risk of serious coronary events and the presence of angiographically documented coronary artery disease (*Popiolek et al., 2003*).

## **AIM OF THE STUDY**

The aim of this study is to investigate the predictive role of TFPI and endothelin-1 in the prothrombotic state in different clinical settings of coronary artery disease and to evaluate the relation between the previous parameters, cholesterol, lipid profile, coagulation profile and cardiac enzymes in coronary artery disease patients.

## **ANATOMY AND MICROSCOPY OF CORONARY ARTERIES**

### **(A) Coronary Anatomy:**

The major coronary vessels, also referred to as the epicardial vessels, travel over the outer surface of the heart in grooved depressions or sulci. Their ostia, or connections to the aorta, are located just beyond the cusps of the aortic valve. The aortic cusps take their names from their association with the coronary arteries. The left coronary artery originates from above the left coronary cusp of the aortic valve.

The right coronary artery originates from above the right coronary cusp. The third cusp referred to as the non-coronary cusp, is located posterior to the other cusps (*Waller and Schlant, 1994*).

### **(B) Microscopic structure of the coronary artery:**

The intima as the innermost lining of the vessel consists of a single layer of endothelial cells that form a smooth, thrombus resistant surface. Being metabolically active, the endothelium produces highly potent substances that either promotes arterial vasodilatation or vasoconstriction. These activities of the endothelium play a major role in maintaining vessel function. The internal

elastic lamina forms the outer limit of the intima. It consists of a matrix of elastic fibers with multiple small openings which permit cell movement between the intima and the media, the adjacent middle layer of the vessel (**Ross, 1997**).

The media is the thickest portion of the normal coronary vessel and consists of multiple layers of smooth muscle cells arranged in a spiral pattern and surrounded by connective tissue. The internal and the external elastic laminae form the boundaries of the media, separating it from the intima and the outermost layer of the vessel, the adventitia. The smooth muscle cell within the media sustain the tone of the arterial wall allowing for a steady flow of blood through the vessel lumen. The size of the lumen of normal coronary arteries is regulated by the extent of contraction of the smooth muscle cells within the media (**Ross, 1997**).

The adventitia is composed of an array of collagen fiber bundles, elastic fibers, numerous fibroblasts, and some smooth muscle cells. The adventitia contains a blood supply in the form of vasa vasorum or capillaries, venules, and arterioles. Nerve fibers and lymphatic channels are also distributed within this layer (**Ross, 1997**).

## **RISK FACTORS FOR CORONARY ARTERY DISEASE**

### **(A) Age and Gender:**

Incidence and mortality of ischemic heart disease increases with age. Males included in the age group 55-64 years have about 15 folds higher risk for ischemic heart disease mortality than those aging 35-40 years. Similarly, women aging from 55-64 years have 30 folds higher risk for coronary artery disease (CAD) than those aging 35-40 years; thus the absolute number of women dying from CAD exceeds the number of men (*American heart association, 1998*). Although women have lower levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) prior to menopause than do men of similar age, this advantage disappears afterwards. Increased prevalences of dyslipidemia, hypertension and diabetes are seen after menopause. Emerging evidence suggests that estrogen produces favorable changes in lipid profile, with reduction in LDL and TC and an increase in HDL (*Williams et al., 1995*). It also improves the vascular reactivity of coronary arteries and prevent the progression of coronary atherosclerosis. It has also been suggested that estrogen also may act as an antioxidant (*Gutta and Cannon, 1996*).

**(B) Obesity:**

Amongst the pathogenic causes of coronary artery disease is the cluster of risk factors named the insulin resistance syndrome or syndrome X. The key features of this syndrome include hypertension, dyslipidemia and abnormal fibrinolysis (**Reavan, 1995**). This syndrome is associated with obesity, which is accompanied by high leptin levels (**considine et al., 1996**).

**(C) Hypertension:**

A strong relation between elevated blood pressure and CAD has been observed and the treatment of hypertension was found to reduce CAD by 9% to 30% (Rich et al., 1995). Hypertension was established as a major modifiable risk factor for the developing of atherosclerosis and is frequently coexisting with other risk factors such as dyslipidemia.

Animal studies showed that hypertension alone never led to atherosclerosis. When animals were fed diets rich in cholesterol and fat, hypertension was found to accelerate and aggravate atherosclerosis. Thus, hypertension has an additive effect in the presence of other risk factors, mainly hyperlipidemia. Hypertension may lead to more infiltration of the atherogenic lipoprotein into the coronary arteries