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PLASMINOGEN ACTIVATOR INHIBITOR-1 AND FIBRINOGEN IN ISCHAEMIC HEART DISEASE

Thesis

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INTRODUCTION

INTRODUCTION

Fibrinolytic activity is impaired in many patients with coronary artery disease. It has been suggested that impaired fibrinolysis has a pathogenic role in coronary artery disease. Impaired fibrinolysis could be caused by an increase in the activity of plasminogen activator inhibitor. However, some groups have reported only a very occasional and transient increase in plasminogen activator inhibitor in patients with coronary artery disease (Justo et al., 1988). Furthermore, PAI-1 plasma activity had not been compared to those of age matched non CAD patients but to those of normal young volunteers. Therefore, some authors have suggested that such a plasma PAI-1 elevation might mainly be due to the advanced age of patients with CAD (Huber et al., 1990).

Recent prospective investigations have reported that higher plasma fibrinogen concentration is associated with greater risk of cardiovascular disease (Aaron et al., 1991).

The aim of this work is to determine whether PAI-1 activity and plasma level of fibrinogen are implicated in the pathogenesis of chronic coronary heart disease, stressing on comparing the I.H.D. patients with a well defined age and sex matched control group.

REVIEW
OF
LITERATURE

ISCHEMIC HEART DISEASE

IHD is the generic designation for a group of closely related syndromes resulting from an imbalance between the supply and demand of the heart for oxygenated blood. Although ischemia also invokes reduced nutrient substrates and inadequate removal of metabolites, the critical factor is the insufficiency of oxygen (Robbins, 1989).

The heart may suffer a deficiency of oxygen when 1- An increase in demand outpaces the supply of oxygen, 2- Oxygen transport in the blood is diminished but 3- In over 90% of cases the root cause is reduction in coronary blood flow, owing largely to some complex dynamic interaction among fixed atherosclerotic narrowing of the subepicardial coronary arteries, intraluminal thrombosis overlying a ruptured or fissured plaque, vasospasm, and platelet aggregation (Reimer et al., 1986).

IHD in its various forms, is the leading cause of death in the united states and other industrilized nations and accounts for about 80% of all cardiac mortality. Annually, about 5 million individuals are diagnosed as having IHD, resulting in approximately 550,000 deaths, many more than all forms of cancer collectively (American Heart Association 1988).

The clinical expression of the various phases of coronary heart disease is not self limited or specific. In coronary heart disease,

therefore; the patient may present with or may develop any of the following :

1- Asymptomatic coronary disease, manifested by induced myocardial ischemia.
2- Sudden death.
3- Angina pectoris of effort, variant "prinzmetals" angina, coronary spasm.
4- Unstable angina pectoris "acute coronary insufficiency".
5- Acute myocardial infarction (Sokolow, 1990).

Risk factors for coronary artery disease :

1- Hyperlipidemia :

There is a well-established association between atherosclerosis and plasma cholesterol, but even stronger associations appear when the cholesterol carrying LDL and HDL lipoprotein fractions are considered. LDL-cholesterol levels are predictive of coronary heart disease, but an inverse relationship is seen with HDL-cholesterol, so that high levels appear to be protective.

Cholesterol deposited in atheromatous lesions is derived from LDL and enters the lesion at a rate dependent upon the plasma concentrations. The protective role of HDL may be in mediating hepatic cholesterol excretion by reverse transport of cholesterol from the periphery (Kumar, 1990). serum apolipoprotein A "HDL apoprotein" and apolipoprotein B" LDL apoprotein" were also

evaluated as potential indicators of risk of ischemic heart diseases (Drrington, 1986).

Lipoprotein (a) [LP (a)] is known to be an independent risk factor for coronary artery disease. Several studies suggest that high levels of LP (a) may suppress the profibrinolytic activity at the cell surface and increase the risks of arterio-sclerosis and thrombosis. It was recently reported that LP (a) like plasminogen can bind to fibrin and that it competes with plasminogen and tissue type plasminogen activator for fibrin binding. In addition, LP (a) attenuates the fibrin-dependent enhancement of tissue-type plasminogen activator activity against a native substrate, and in plasma milieu LP (a) inhibits clot lysis induced by tissue-type plasminogen activator (Eberhard et al., 1991).

2- Hypertension :

Hypertension increase the filtration of lipid from plasma to the intimal cell by virtue of increased arterial pressure, especially in the presence of elevated plasma lipids. Hypertension as well as hyperlipidemia may injure the intima, leading to platelet aggregation and proliferation of smooth muscle cells in the media.

Increased susceptibility to injury from shear forces, torsion, and lateral wall pressure changes may also be important.

Hypertension is now the most common and most important risk factor in the pathogenesis of atherosclerosis, atherosclerotic

complications constitute the most common cause of death in hypertensive patients (Sokolow, 1990).

3- Diabetes :

The asymptomatic hyperglycemia of adults with diabetes mellitus may be a risk factor independent of and additive to the effect of blood pressure and serum lipids.

Diabetes affects the capillary basement membrane "microangiopathy" of all tissues. It produces abnormalities in the myocardium, in small coronary vessels, and in the major arteries pathologically, atherosclerosis occurs were frequently and at an earlier age in diabetic patients (Waller, 1980). In subjects with impaired glucose tolerance, the mortality rate from coronary heart disease was approximately doubled as compared to that in patients with normal glucose tolerance after a 7.5 year period of observation (Fuller, 1986).

4- Family history :

A positive family history may reflect.

1- Genetic predisposition to the development of hypertension, hyperlipidemia, or diabetes or.

2- Enviromental influences such as diet, stress and life-style.