SUCCESS OF INTRAVENOUS STREPTOKINASE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION& ITS RELATION TO ANTI - STREPTOLYSIN O. TITRE

Thesis
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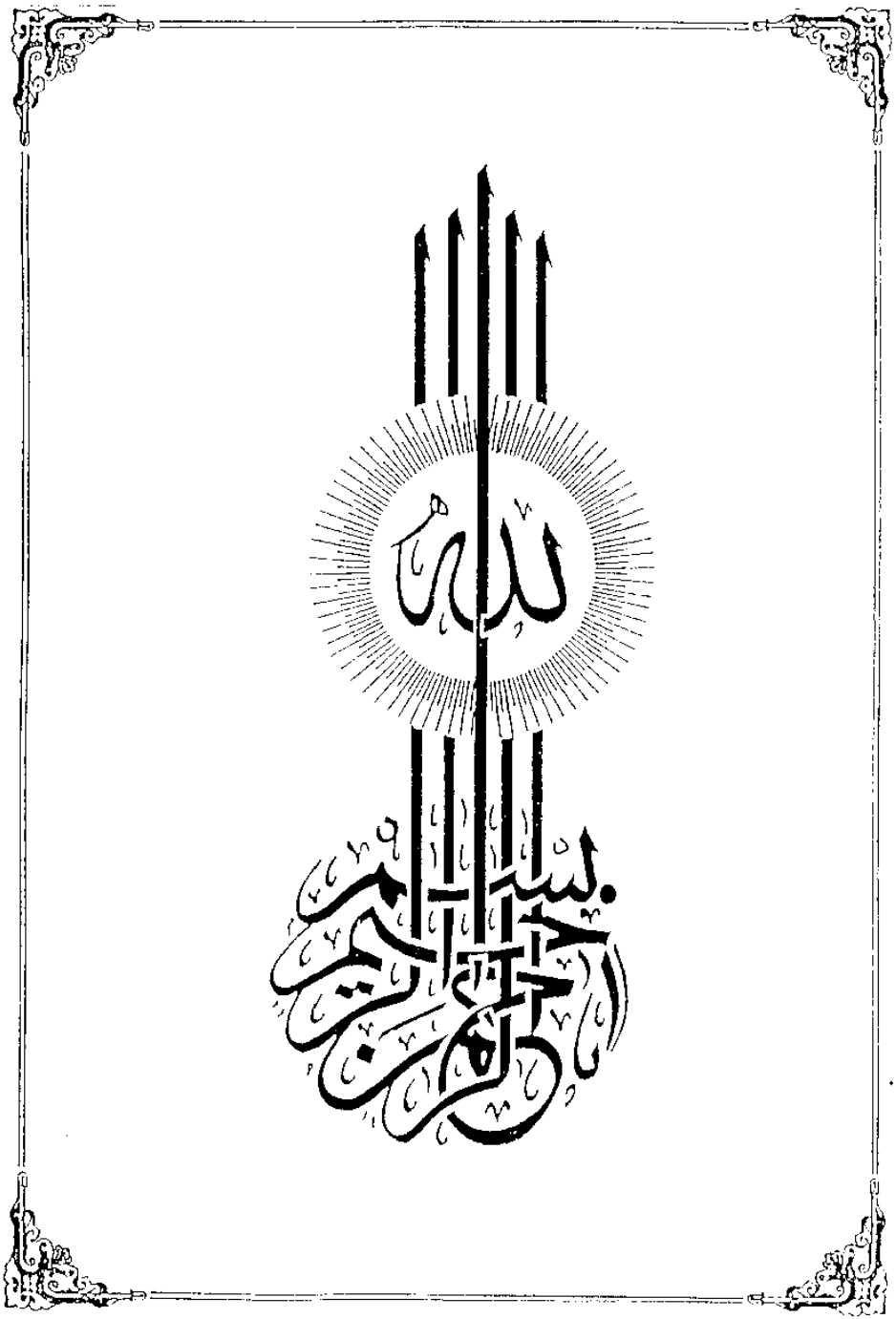

CONTENTS

AIM OF THE WORK

The aim of this work is to evaluate the efficacy of rapid high dose IV SK in patients with evolving myocardial infarction and its relation to the level of ASOT.

PATHOGENESIS OF ACUTE ISCHEMIC SYNDROMES

Over the last few years clinical / pathologic observations & experimental investigation have led to a better understanding of the pathogenetic factors leading to the acute coronary syndromes : unstable angina, myocardial infarction, and ischemic cardiac death.

The elegant pathologic studies of ***Falk, 1983 & Davies and Thomas, 1985*** have emphasized that thrombus formation secondary to plaque rupture and fissuring in the atherosclerotic coronary artery play a major & frequent role in the acute coronary syndromes.

Gorlin, et al., 1986 have established that this pathologic phenomenon is a common link between the three acute coronary syndromes in man.

Angiography in patients with unstable angina or myocardial infaction with subtotal coronary occlusion often reveals eccentric stenosis with irregular borders suggesting ruptured atherosclerotic plaques, as has been documented by angioscopy and at autopsy.

In addition, rapid changes in the angiographic patterns preceeding & following the acute coronary syndromes suggest rapid dynamic biological processes.

Thus, ***Fuster V, et al., 1988*** have investigated the relationship among plaque disruption, platelet activation, rheology - dependant localization of thrombi, and the time period of thrombotic occlusion or reocclusion; as a result, a hypothesis is proposed accounting for the dynamic biological processes leading to the acute coronary syndromes.

The results of ***Fuster, V, et al., 1988*** combined with those of others, show the following :

Plaque Disruption :

It is now recognized that plaque disruption is the underlying event that frequently precedes all the acute coronary syndromes. The reason for such disruption may be four fold :

A) Plaques that undergo disruption tend to be small and soft with a high concentration of cholesterol at the base of the plaque; thinning of the fibrous cap overlying the lipid core precedes it rupture. ***(Davies & Thamas, 1985).***

B) Pathologic analysis at the site of disruption shows a large number of macrophages (probablyt monocytes with high content of fat uptake from the interstitium) infiltrating the fibrous cap and the lipid core at the site of the fissure; it has been

suggested that enzymes in these cells, which digest collagen and elastin, may weaken the cap & precipitate plaque disruption *(Davies MJ, 1988)*.

C) The shear forces at the level of the stenosis, acute changes in coronary pressure related changes in coronary tone, and bending / twisting of an artery with each heart beat may also predispose a plaque to disrupt *(Gorlin, et al., 1986)*.

D) Atherosclerotic coronary arteries are highly vascular; thus, in a few cases it is possible that hemorrhage within a plaque may contribute to plaque disruption *(Barger, et al., 1984)*.

Platelet Activation and Thrombin Generation :

In acute deep arterial injury or plaque disruption four aspects of platelet activation are important.

A) Platelets adhere via platelet membrane glycoproteins (GP) Ia & Ib to the vessel wall to form a monolayer; thus, exposed collagen (type I is more prevalent than type III in diseased vessel) binds to GIPa while von Willebr and Factor (VWF), a high molecular weight glycoprotein found in plasma, in platelets and in endothelial cells, binds GPIb also supporting platelet adhesion *(Fuster, V, et al., 1988)*.

B) Further more, vascular damage of this magnitude stimulates thrombin formation through the intrinsic (surface activated) and extrinsic (tissue factor dependant) coagulation pathways (*Fuster, V, et al., 1988*).

C) Platelets then aggregate as they are stimulated by three pathways : a pathway, which is collagen and thrombin dependant, and the two intraplatelet arachidonate and ADP pathways; thus, the three pathways lead to exposure of platelet receptors (GPIIb/IIIa), and subsequent aggregation; fibrinogen and VWF participate in aggregation by binding to GPIIb/IIIa; simultaneously, thrombin stimulates the formation of fibrin that stabilizes platelet aggregates (*Hawiger, J, 1987*), (*Vermylen J, et al., 1986*) & (*Badimon L, et al., 1987*).

D) Both a platelet adhesive monolayer and aggregation wih thrombosis, produce vasoconstriction due to release of platelet products (serotonin, thromboxane A_2 & PDGF); further more, hormonal related vasoconstriction as a result of endothelial damage and lack of endothelial derived relaxing factor (EDRF) can also contribute (*Corl J. Pepine, 1989*).

Rheology Dependant Localization of Thrombi :

A) Stenotic lesions produce a high local shear rate, which enhances platelet - vessel wall interaction and, in the presence of acute plaque disruption, this interaction results in platelet deposition and thrombosis *(Badimon L, et al., 1986)*.

B) Platelet deposition & thrombosis are particularly favored if the site of rupture includes the apex of the stenotic plaque with its high shear rate, while the stasis in the post - stenotic region favors propagation of thrombus with a major fibrin component *(Badiman L, et al., 1986)*.

Time - Period of Thrombotic Occlusion or Reocclusion :

A) Plaque rupture produces a rough surface and exposes collagen type I; this stimulates occlusive thrombosis; such thrombus is either fixed or labile depending on the degree of plaque rupture of damage and, therefore, on the amount of collagen type I exposed. After thrombolysis significant residual thrombus contributes to the residual stenosis visualized at angiography *(Brown BG, et al., 1986)*.

B) After spontaneous or pharmacological reperfusion, high shear rate at the residual stenosis and the surface of the residual thrombus are very thrombogenic and therefore may contribue to a

recclusion phenomenon within the following hours or days; preliminary information indicates that the surface of the residual thrombus is very thrombogenic (platelet activation & fibrin formation) because thrombin generrated during the original clotting and which remained bound to fibrinogen - fibrin, after reperfusion is again exposed to the circulatory blood (***Badimon L, et al., 1987***) & (***Fitzgerald DJ, et al., 1988***).

Pathogenesis of Unstable Angina :

Ambrose JA, et al., 1985 have proved that mild rupture (Fissure) of a generally small plaque leads to a change in the geometry of the plaque as seen by arteriography in the form of eccentric stenosis with scalloped or overhanging edges.

Sherman CT, et al., 1986 & Forrester JS, et al., 1987 have used angioscopy to examine the coronary arteries of patients undergowing surgery for unstable angina. Patients with progressive symptoms, but without pain at rest, had disrupted plaques without mural thrombosis. This finding might suggest that rupture per se, with a change in the geometrical configuration of the plaque but without overlying thrombus, can increase the degree of stenosis, thus producing exertional angina.

Fuster V, et al., 1988 have contributed chest pain at rest in unstable angina due to subsequent labile thrombi attached to collagen type I within the fissured plaque. Indeed, frequent angiographic detection of thrombus occurs only if the angiogram is obtained soon after an episode of pain at rest. In addition, the body of the thrombus is usually distal to the most severe stenosis.

Vasoconstriction may also contribute to attacks of transient pain at rest. Abnormalities in coronary tone have been demonstrated in patients and experimental animals by coronary arteriography after the intracoronary injection of acetylcholine, suggesting a defect in endothelial vasodilator function presumably a decrease in endothelial relaxing factor ***(Ludmer PL, et al., 1986) & (Penny WJ, et al., 1986).***

Lam JYT, et al., 1987, have reveald that during arterial thrombosis, aggregated platelets may ontribute to vasoconstriction by releasing prostanoids, serotonin, & platlet - derived growth factor.

The above mentioned dynamic intracoronary processes may account for about 75% of patients presenting with unstable angina; the remaining 25% appear to relate to an increase in oxygen demand (heart

rate - blood pressure product), related or not with periods of stress (*Fuster V, et al., 1988*).

Non - Q-wave Infarction :

The precise pathophysiology of non - Q-wave infarction is not clear. About 25% of patients with non - Q-wave infarction have a completely occluded infarct related - vessel at angiography soon after infarction, with the distal territory usually being supplied by collaterals (*DeWood M, et al., 1986*).

In 75% of patients, the infarct - related artery is patent. The angiographic morphology of the responsible stenosis is the same as that seen in unstable angina, confirming the role of plaque fissuring in non - Q-wave infarction as well (*Ambrose JA, et al., 1988*).

According to experimental data previously discussed, we speculate that in non - Q-wave infarction there is a greater degree of atherosclerotic plaque damage than in unstable angina, with a longer persistence of thrombus with or without vasoconstriction. However, the thrombotic occlusion is of insufficient duration to provide Q-wave infarction. Indeed, the earlier rise in peak creatine kinase, and the spontaneous resolution of ischemic dysfunction seen