EFFECT OF INTRAVENOUS STREPTOKINASE FIBRINOLYSIS ON REGIONAL LEFT VENTRICULAR WALL MOTION ABNORMALITIES IN ACUTE MYOCARDIAL INFARCTION ASSESSED BY SERIAL TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Thesis

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By

Ezz El Arab Saad Fam
(MB. B.Ch., Cairo University)

Supervised By

Prof. Dr. Mahmoud El-Sherbeny
Professor of Cardiology, Ain Shams University

Dr. Nagwa Mahmoud Nagy
Assistant Professor of Cardiology, Ain Shams University

Dr. Maiy Hamdy El-Sayed
Lecturer of Cardiology, Ain Shams University

Dr. Baher Mohamed El-Zein, M.D.
Fellow of Cardiology, National Heart Institute.

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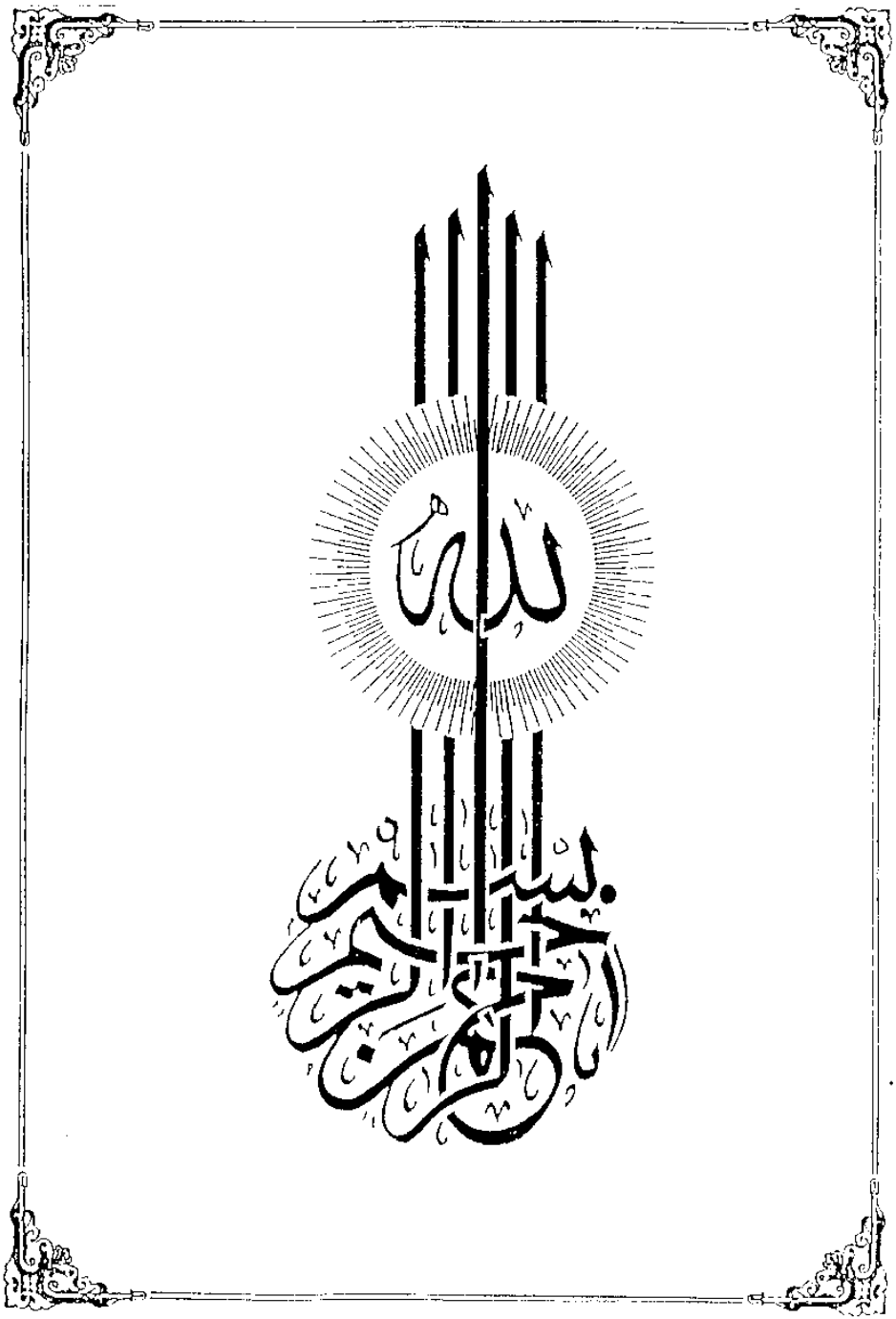

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INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

Atherosclerotic heart disease is one of the major medical problems that burdens the economey of the world.

Myocardial infarction was first described in 1912 by James B. Herrick but it is most certainly not a new affliction to man kind.

In 1974, the perfectly preserved body of a lady of the court of Chinese Emperor Hui, who died in 143BC., was exhumed. This 50 years old women underwent modern postmortem examination and was found to have died from myocardial infarction (William, 1986).

The major problems originating from this catastrophic disease, arise from the facts that:

. It is the major cause of death in many countries.

. A significant proportion of death, 40% of mortality of all patients within 1 month of acute myocardial infarction, occurs in relatively young patients.

. Male patients are not only prone to ischemic heart disease, but had also subsequent higher morbidity and mortality than female patients (Abdou, 1989).

. MI leaves behind several millions of survivors all over

the world, half of them are physically limited by their disease.

. It is associated with several billions (100 billion in USA) annually in direct health costs and in economic cost (Gotto and Farmer, 1988).

Treatment of AMI was first directed towards allowing healing and preventing camplications. The concept nowadays is directed towards early salvage of Jeoperdized myocardium by attempts of early reperfusion (Gotto and Farmer, 1988).

REVIEW OF LITERATURE

PATHOPHYSIOLOGY OF CORONARY OCCLUSION IN ACUTE MYOCARDIAL INFARCTION

The notion of coronary occlusion is traditionally associated with that of myocardial infarction. However, total occlusions in absence of infarction are frequently observed both during angiographic and postmortem examinations in patients without symptoms or signs of ischemic events (Elliot et al., 1971).

Coronary occlusions are most likely to cause myocadial necrosis when occurring suddenly in vesseles that are not already critically obstructed and have no adequate or no functional distal collaterals. Conversely, when occlusions are not associated with detectable ischemic events, they probably have developed gradually in a vessel with distal functioning collaterals (Elliot et al., 1971). It seems reasonable to assume that the development of infarction is usually determined by the balance between four factors:

1) The rate of progression of the occlusion.
2) Its duration.
3) The extent of collaterals.
4) The coronary and myocardial response to ischemia (Maseri et al., 1986).

Nature of Acute coronary occlusion:

From the theoretical point of view, acute occlusion may be caused by thrombus, intraplaque or subintimal haemorrhage, embolization, some form of vasospasm or possibly more often by variable combination of these factors.

Undoubtedly thrombosis plays a major role in the first 6 hour from onset of symptoms going with the high incidence of recanalization with thrombolytic therapy. Conversely within the same period, spasm seems to play a minor role because all reports show a low incidence of recanalization after intracoronary nitroglycerin (Rentrop et al., 1981).

No definite explanation is yet available for 20-30% of cases in which both nitrates and thrombolysis are ineffective in reopening the artery. In some cases no thrombus was found at postmortem. Thrombus not reached or resistant to thrombolytic agents or spasm refractory to nitrates are possible alternatives (Mathey et al., 1981). An alternative explanation could be provided by subinitmal hemorrhage into a plaque. However postmorterm studies suggest that this event is a rare cause of occlusion. This lesion is uaully confused with plaque fissuring which have a large opening towards the lumen but cannot cause obstruction

by itself unless associated with thrombus (Fulton, 1965).

Coronary thrombosis:

Postmortem studies provide information on at least one type of patients with acute myocardial infarction, those who die. Thrombus was found in 30-55% of patients in one series (Roberts and Buja, 1972) and in about 70-93% in another series (Champen, 1978). Patients selection and methods of examination account for these wide discrepancies.

Thrombi are found less frequently in subendocardial infarction and small infarcts than in large ones complicated by pump failure. Early spontaneaus recanalization may explain their absence (Dewood et al., 1980).

Postmortem study of the thrombi provides a clue to their origin. If platelets and fibrin are the main components, a white thombus must have develped in flowing blood. However if red cells are present in all segments of the thrombus without trace of white thrombus, the red thrombus or clot must be secondary to total occlusion by another mechanism. When platelets rich white thrombus do not occlude the lumen completely, either partial lysis or postmortem release of spasm is considered (Spain and Bradess, 1970).

A potential vicious cycle: local vasoconstriction caused by substances released by thrombi such as thrombaxane A_2, serotonin, and thrombin is a possible mechanism of persistent or recurring occlusion. If the local spasm is sufficiently great it could be the element of a potential viscious circle determining total occlusion in the presence of thrombus and favouring reocclusion when ever its release bring blood flow and hence more plateletes. Conversely with thrombolytic therapy release of spasm allows more delivery of the agent over whole length of the thrombus (Maseri et al., 1985).

Initial causes of occlusions:

Although the role of the thrombus is unquestionable the mechanisms responsible for its initiation and progression are still sepeculative (Maseri et al., 1985).

A) Plaque Fissuring:

Fissuring of plaques seems to be the most likely triggering event for thrombosis. Microanatomic studies showed the presence of a fissured plaque with intraintimal thrombus extending into the lumen (Falk, 1985). It is possible that the arterial segment corresponding to the fissured plaque devolps occlusive spasm in response to vasoactive substance (Davis and Thomes, 1984).

Plaque fissure with variable degree of intraintimal hemarrhage extending towards the media was also frequently observed by Falk (1985) in patients with unstable angina. This author suggested that plaque rupture with variable degree of intimal haemarrhage and luminal thrombosis could represents the missing link between morphology (atherosclerosis) and function (Spasm) (Falk, 1985).

B) Critical stenosis:

Turbulence at the site of a critical stenosis creating high shear stress was proposed to cause platelets damge and aggregation either directly or because of Adenosine diphosphate release (Born, 1980).

In animals transient platelets plugs form only at the site of an acute stenosis narrowing the lumen more than 95%. Lumen reductions of lesser severity up to 70% still allow 300-400% increase of flow during reactive hyperemia (Gould et al., 1974).

Therefore, it appears that only a very severe stenosis coupled with high flow rates can produce a sufficiently high shear stress to damge platlets and red cells. In patients who died with acute infarction, the preexisting obstruction

at the site of thrombus is found to reduce lumen by 70% or more in 80-90% of cases. Collaterals are often present in patients with the most severe stenoses reducing forward flow (Baroldi, 1978). However less severe or minimal lesions are found in 10-20% of cases (Roberts and Buja, 1972).

C) Thrombus formation:

The initial stage of thrombus formation is the deposition of platelets on a vascular surface which occurs under three circumstances: (1) when the endothelial lining is damged.

(2) When there is stasis allowing the platelets to fall out of the axial stream and impinge on the wall.

(3) When the stream line of the blood is disrupted and eddy currents are produced which deflect the platelets onto the wall.

The damged platelets release Adenosine diphosphate and a pale thrombus is steadily build up. With fibrin deposition more red blood cells and platelets are trapped and a mixed thrombus is formed.

A dynamic equilibrium between thrombosis and thrombalysis will determined its fate. (Mustard et al., 1981). The high flow rate tend to limit thrombus in three

way; first by the dilution effect on local Coagulant factors. Second, plasmin which has very short half life can be reformed by newly delivered plasminogen and lastley, the superficial layers of thrombus tend to be dislodged because of the shear effect of flow. Indeed platelets emboli were found distally (Maseri et al., 1986).

Although it is understandable that large thrombus may form at the site major obstructive plaques with large tears, the mechanism of occlusion in arteries with only minor or no detectable fissures and without critically obstructive plaques are less clear. Local factors such as spasm and/or marked displacement of the thrombotic thrombolytic equilibrium towards thrombosis may play an important role (Maseri et al., 1986).

D- Coronary spasm:

The reduction of caliber of epicardial coronary arteries in response to constrictor stimuli is rather small both in dogs (Vatner et al., 1980) and man (Brown et al., 1980) and it can impair flow only in pliable segments of arteries with a critical subintimal plaques. Conversely, spasm seen in variant angina can cause total occlusion, even in vessels without critical lesion, in response to stimuli that cause only mild or no detectable constriction in