THROMBOLYTIC THERAPY IN PATIENTS WITH ACUTE MYOCARDIAL INFRACTION

ESSAY
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M B B CH

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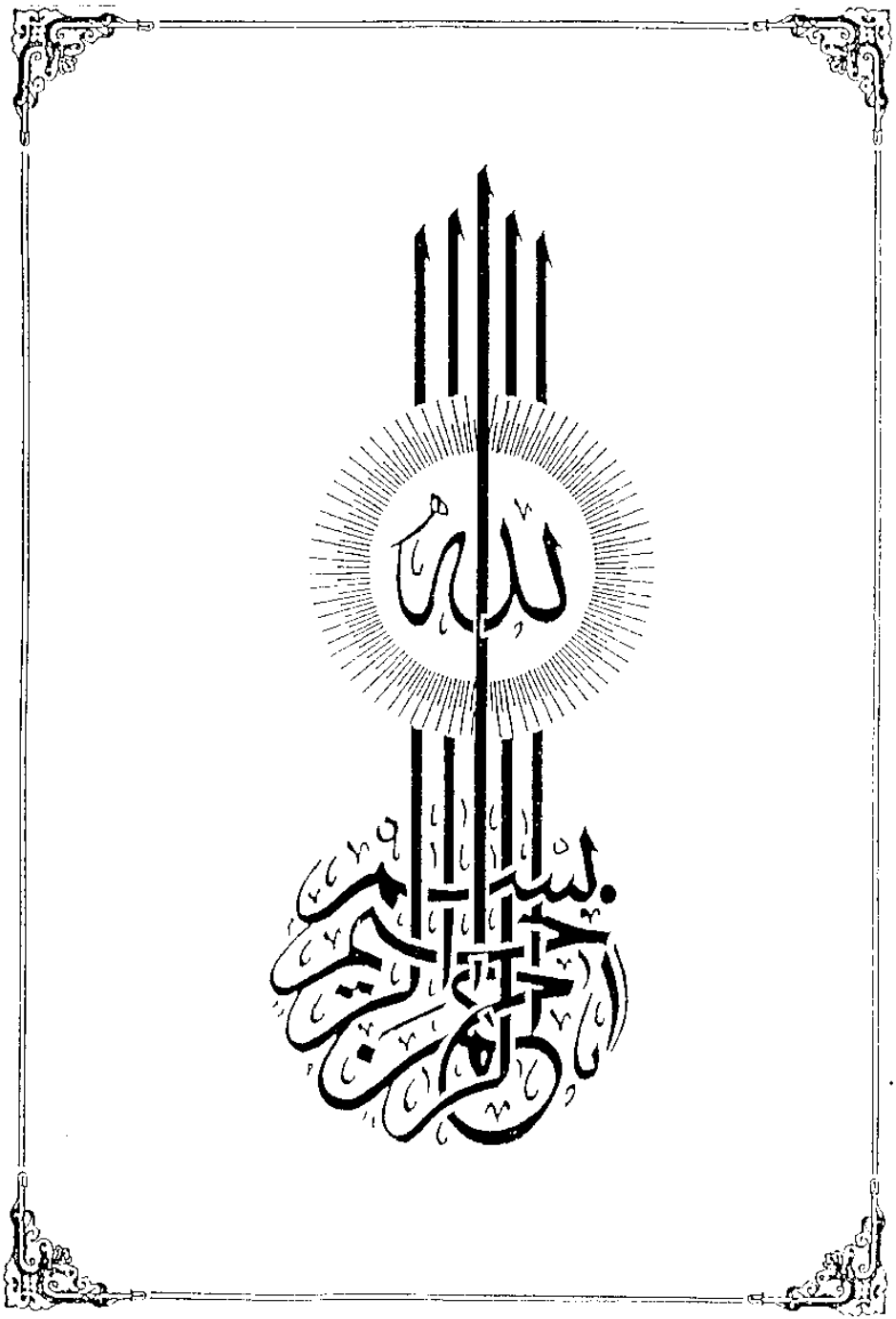
"وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا"

صدق الله العظيم



Dedication

To My Father

ACKNOWLEDGMENT

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Mostafa El Maleh

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CHAPTER I

Etiology of Myocardial Infarction

Acute Myocardial infarction results from an acute imbalance between oxygen supply and demand. The cause and severity of reduction of blood flow during the early phase of acute transmural infarction has become an area of substantial interest (De Wood et al., 1983).

The important cause of regional Myocardial infarction is occlusion of the lumen of a major coronary artery, and in most cases this is caused by thrombosis superimposed on atheroma (Anderson; 1984).

Coronary Thrombosis and Acute Myocardial Infarction:

The role of Coronary thrombosis in the development of myocardial infarction has been the subject of vigerous debate for more than 70 years. Although early investigators postulated that coronary thrombus was the cause of infarct, autopsy studies in the following decades revealed many instances in which severe coronary atherosclerosis was evident but coronary thrombosis was not. These observations led to the alternative hypothesis that coronary thrombosis was the result rather than the cause of acute Myocardial infarction (Laffel and Braunwald; 1984a).

Two lines of evidence have allowed cardiologists to accept the thrombus as an important aetiologic factor (Marder and Francis; 1984).

First: Chandler et al (1974) reported that there are anatomic and pathologic studies that document, the presence of thrombus in very high proportion of patients with Myocardial infarction, although post mortem correlations still may not satisfy critics who suggest that thrombus may be only a secondary development following an obstruction due to vasospasm or other mechanism (Conti C.R.; 1983).

The most important anatomic information has been derived from angiographic demonstration by De Wood et al (1980). That 87% of patients with transmural infarction have occlusion of appropriate coronary vessel within the first four hours of illness; this proportion decreased significantly to 65% when patients where studied 12 to 24 hours after the onset of symptoms (Fig. 1), among 59 patients with angiographic features of coronary thrombosis, the thrombus was retrieved by Fogarty Catheter in 52 (88%) but was absent in 7 (12% false positive), among an additional 20 patients without angiographic features of thrombosis, a thrombus was discovered in five (25% false negative), thus the authors concluded that total coronary occlusion is frequent during the early hours of transmural infarction and decreases in frequency during the initial 24 h., suggesting that coronary spasm or thrombus formation with subsequent recanalization or both may be important in the evolution of infarction.

De Wood et al (1983) demonstrated that thrombus is encountered by arteriography and confirmed by surgical

exploration within the first 6 hours from onset of symptoms of transmural infarction in approximately 80% of patients.

Also Davies and Thamas (1984) demonstrated that among 100 subjects who died from ischaemic heart disease in less than 6 hours coronary thrombi were found in 74. Among 26 patients without an intraluminal thrombus, plaque fissuring was found in 21, also it is present in 103 of 115 cases. The authors concluded that the pathologic process in sudden ishaemic death involves a rapidly evolving coronary artery lesion in which plaque fissuring and resultant thrombus formation are present. They explained that the presence of a plaque fissure leads to two processes: The formation of intra-luminal thrombus over the exposed lipid and the formation of an intraintimal thrombus. The former is known to be influenced by intra coronary thrombolytic therapy, whether the latter is influenced for better or worse in unknown.

The second line of evidence that thrombosis is important in myocardial infarction comes from the successful case studies of intra coronary streptokinase treatment in achieving reperfusion, as well as the unimpressive results of spasmolysis using nitro glycerin (Marder and Francis; 1984). The success of thrombolytic therapy in acute myocardial infarction is linked to pathology; if thrombosis is a late event, dissolution of clot may have little effect on pump salvage, whereas if thrombosis is the proximate cause, rapid dissolution of the clot can be expected to have a dramatic effect.

Also coronary arteriographic findings in acute transmural Myocardial infarction by De Wood et al (1983) demonstrated that: 86% of patients evaluated within 6 hours from symptoms onset demonstrated total coronary occlusion, this fell to 68% in the 6 12 hours and to 64% in the 12-24 hours study group (De Wood et al., 1983). 80% of patients studied in the first 6 hours demonstrated angiographic features of coronary thrombosis, this ratio fell to 59% in 6-12 hours, and to 54% in the 12-24 hours. So that systematic difference between complete coronary occlusion and thrombosis of 6-8% in these patient groups suggests that the two phenomena are not necessarily the same. Therefore, many other factors may affect the coronary tree at the point of occlusive change which include repture of softened plaque, subintimal haemorrhage into fibrous or softened plaque, ulceration of atheromatous plaque and coronary spasm or other poorly defined mechanism.

It appears that a dynamic interaction between coronary artery intimal defects, coronary spasm and platelets aggregation lead to coronary thrombosis which appears to be the final common pathway in the development of acute transmural Myocardial infarction (Laffel and Braunwold; 1984a).

It is obvious that coronary thrombosis is a fundamental mechanism by which chronic ischaemic heart disease is converted to acute transmural myocardial infarction in man (De Wood et al., 1983).

History of Thrombolytic Therapy

In the continuing search for new and improved methods of treating thrombo-embolic diseases, the concept of an agent to dissolve clots has always been attractive. Since Tillett and Garner first demonstrated the fibrinolytic activity of Haemolytic Streptococci in 1933, there has been a great deal of work in thrombolytic treatment. Tillett and Sherry first used streptokinase in humans to aid in resolution of Haemothorax and empyema (Marder; 1983).

Fletcher et al., 1958 were the first to demonstrate the feasibility of using intravenous thrombolytic therapy in patients with acute myocardial infarction. The concept of regional instead of systemic treatment for acute Myocardial infarction (AMI) was considered and applied only 2 years later in 1960 (Marder and Francis, 1984). In 1977, the Food and Drug Administration (FDA) approved streptokinase (SK) for treatment of deep vein thrombosis and pulmonary embolism and urokinase (UK) for treatment of pulmonary Embolism. Three years later (FDA) in conjugation with National Institute of Health (NIH) sponsered consensus development conference on these thrombolytic agents (Sherry et al., 1980). After reviewing the data, the panel issued a strong positive statement encourging physians to employ these plasminogen activators in the management of many thrombo embolic disorders. (Sherry and Gustafsou; 1985).

Primary Mechanism for Thrombolysis

Physiologic plasmiogen activator, such as that released by endo-thelial cells or exogenous activator such as streptokinase activate fibrin bound plasminogen to fibrin bound plasmin. The latter acting on its substrate in a relatively free environment. Thus activating the body's natural fibrinolytic system. Figure (2)

Function of the Fibrinolytic System:

When the insoluble protein fibrin, which provides the matrix of a clot, is formed, it binds a small amounts of native plasma protein pro enzyme, Plasminogen. In the presence of plasminogen activator, a specific protein released from endothelial cells, this pro enzyme bound to fibrin is enzymatically converted to the active fibrin dissolving enzyme, plasmin; dissolution of fibrin follows. (Spann and Sherry; 1984).

Plasmin, the active enzyme is a non specific proteolytic agent that can digest fibrin, fibrinogen, prothrombin and factors V & VIII, it is "specific" for dissolving fibrin clots within the thrombus, in which plasmin inhibitor concerntration is very low; however, in the circulation the large excess of plasmin inhibitor (antiplasmin) neutralizes its action on other circulating protein. (Sharma et al., 1982).

The specifity of plasmin for fibrinolysis in vivo is due to following mechanisms:

1- The binding of plasminogen to fibrin.

2- The requirment of fibrin as a cofactor for the activation of plasminogen by the endothelial cell activator.

3- The inbility of alpha$_2$-antiplasmin (the major antiplasmin of plasma) to inactivate plasmin formed on the fibrin surface, because the fibrin binding site for plasmin is similar to the anti plasmin binding site and the affinity of plasmin for fibrin site is greater than that of anti plasmin, (Spann and Sherry; 1984).

In vivo: plasminogen exist in two phases, plasma or soluble phase plasminogen and fibrin bound or gel phase plasminogen, with the plasminogen plasmin system operating differently in each phase.

Plasminogen; The inactive precursor of the proteolytic enzyme plasmin is a normal circulating constitnent in plasma, its concentration in plasma is analogous to that of prothrombin. Its concentration tends to be low in infants and patients with advanced cirrhosis of liver and disseminated intravascular coagulation, and to be high in conditions associated with increased amount of acute phase reactants e.g. surgery, trauma, infections and AMI. It posses several binding sites for fibrin. The primary one having a very high affinety constant (Collen D., 1981); during clotting, approximately 5% of the surrounding plasma

plasminogen becomes bound to fibrin and at a site that serves as the major binding site for $alpha_2$-antiplasmin, also fibrin enhance rate of activation of plasminogen by plasminogen activators (Wimen and Wallen; 1977). Thus when a plasminogen activator is in circulation and comes in contact with fibrin, activation of fibrin bound er gel phase plasminogen occurs; this produces selective fibrinolysis.

During streptokinase or urokinase therarpy: There is also activation of plasma or soluble phase plasminogen in the circulating blood and this lead to the appearance of free plasmin, which degrades fibrinogen and clotting factors V & VIII and some componant of complement. This action is controlled and dampened by various cheeks and balances, primarly through the action of $alpha_2$-antiplasmin and $alpha_2$-macroglobulin (slow and non stoichiometric) there is also evidence of considerable fibrinogen proteolysis with the appearance of significant amounts of break down products. The resluting hypo-fibrinogenaemia, impairment of platelet function (fibrinogen is necessary for normal platelet function) and the anti coagulant properties of fibringen breakdown products FDPs leads to an impaired hemostatic mechanism; this increases the risk of a bleeding episode, the major complication of thrombolytic therapy. (Sherry and Gustafson; 1985).

Plasminogen Activators in Clinical Practice

(1) STREPTOKINASE: "SK"

It is the first of plasminogen activators introduced into clinical medicine. It was discovered in 1933 by Tillet and Garner when they observed that a filterate of group "C" beta themolytic streptococci lysed a human plasma clot. Subsequently studies, helped to characterize the interaction of this extract with fibrinolytic system and showed the activators substance acted on plasminogen to produce an active enzyme "plasmin". The activator was named streptokinase. In 1959, a thrombi that had been experimentally induced in forearm veins of volunteers was successfully lysed (Sharma et al., 1982).

Chemistry:

SK is produced from cultures of Lancefeild group C beta Haemolytic Streptococci, and has a molecular weight of 47,000 daltons (Sherry and Gustafson; 1985).

Mechanism of Action:

It is an indirect activator converting plasminogen to plasmin by way of a pro-activator activator complex. When SK is administered,it combines with plasminogen on an Equimolar basis (1:1 ratio) to form the activator complex. This SK plasminogen complex activates the fibrinolytic mechanism by