PREDICTION OF APICAL THROMBUS FORMATION IN ACUTE ANTERIOR MYOCARDIAL IFARCTION BASED ON LEFT VENTRICULAR SPATIAL FLOW PATTERN

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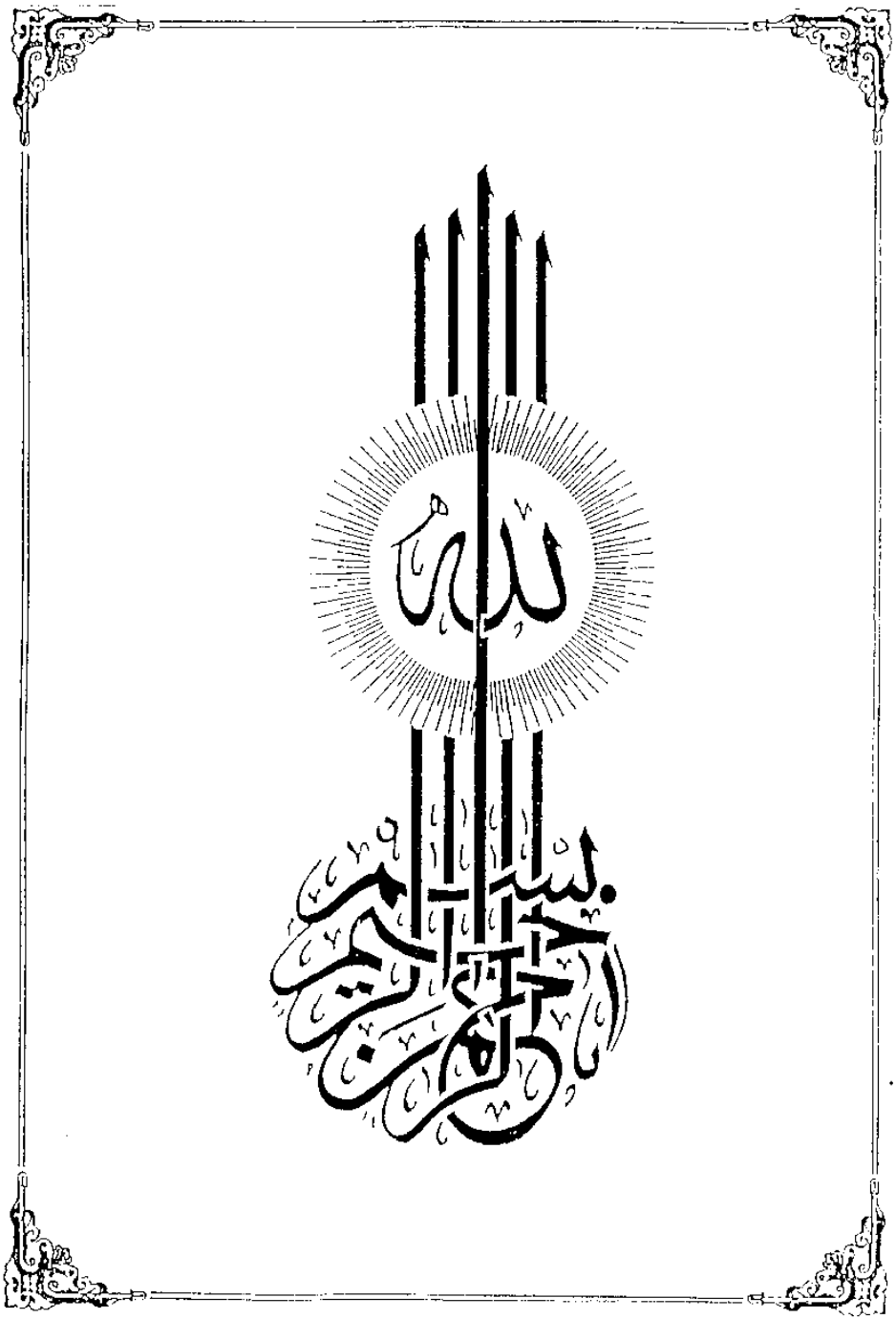

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Left ventricular thrombi represent a well recognized complication of acute myocardial infarction *(Keating et al., 1983)*. The incidence of left ventricular thrombus is greater in patients with anterior compared with inferior wall infarction *(Asinger et al., 1981)* and is almost exclusively limited to those with transmural infarction *(Friedman et al., 1982)*.

The thrombus location is generally apical, with attachment to a dyskinetic or akinetic segment of the ventricular endocardium *(Asinger et al., 1981; Domenicucci et al., 1987; Spirito et al., 1985)*. The majority of left ventricular thrombi develop within the first 10 days after acute myocardial infarction and 50-70% may develop within the first 48 hours *(Asinger et al., 1981)*.

Thrombo embolism is the only and, in most cases, disabling complication of left ventricular thrombosis *(Funke Kupper et al., 1989)*. Sixty percent of emboli of left ventricular origin are a consequence of acute myocardial infarction *(Sherman et al., 1986; Chesebro et al., 1986)*. Several studies suggest that the risk is highest in the first 1 to 3 months after infarction and perhaps even greater in the first 10 days for patients with a large anterior infarct who have a 30 to 40% chance of developing left ventricular thrombus and about a 5% risk of embolism *(Meltzer et al., 1986; Chesebro et al., 1986)*.

In the past, the diagnosis of left ventricular thrombus was based on contrast ventriculographic results or inferred only after clinical evidence for an embolic event *(Haugland et al., 1984)*. New techniques can reliably detect left ventricular thrombus in the absence of clinical evidence for embolization. Of these techniques, two-dimension echocardiography is unique in that, it is not only a sensitive and specific method for detecting left ventricular thrombus *(Stratton et al., 1982)* but also provides information regarding thrombus mobility, shape, and ultrasonic characters *(Ports et al., 1978; ; Meltzer et al., 1978; DeMaria et al., 1979; Reeder et al., 1981; Asinger et al., 1981)*. Some of these characters, such as vigorous intracavitary motion and/or protrusion into left ventricular cavity, appear ominous and have been reported to be associated with embolization *(Visser et al., 1983)*.

Although regional wall motion abnormality as defined by two-dimensional echocardiography has been used to identify patients prone to develop a thrombus it is still not known what initiates thrombus formation *(Delemarre et al., 1990)*.

Recently two abnormal left ventricular flow patterns were described in patients with acute myocardial infarction, a free vortex ring type flow pattern and an apical rotating flow pattern *(Delemarre et al., 1987, 1988)*.

In a recent study in 1989, an association was demonstrated between abnormal left ventricular flow pattern in patients with dilated cardiomyopathy and thrombus formation within the left ventricle *(Maze et al., 1989)*. However,

from that study, it could not be determined whether the abnormal flow pattern was the primary event in the genesis of the thrombus or occurred secondary to thrombus development *(Maze et al., 1989)*.

"The aim of this work" is to prospectively investigate by the pulsed Doppler echocardiography left ventricular flow pattern in patients with recent anterior wall myocardial infarction and to know whether or not this abnormal flow pattern can be used to predict thrombus formation.

REVIEW OF LITERATURE

CHAPTER I

PATHOGENESIS OF LEFT VENTRICULAR THROMBUS

Left ventricular thrombosis represents a common complication of acute myocardial infarction *(Jordan et al., 1952)*. It occurs almost exclusively in patients with anterior rather than inferior myocardial infarction *(Asinger et al., 1981)*. To understand the process of evolution of left ventricular thrombus a brief review about the mechanism of thrombosis will be discussed first.

Thrombi are formed of fibrin and blood cells, and according to the relative proportion of one type of cell to another and to fibrin, two types of thrombi are recognized:

1. **The red thrombus "venous thrombus"**

   It is found almost exclusively in the venous circulation. It is primarily composed of red blood cells and fibrin meshwork in which platelets are trapped in a random fashion. It forms in areas of sluggish blood flow, (blood stasis) and does not require the concomitant presence of an abnormal blood vessel wall *(Deykin et al., 1967)*.

2. **The white thrombus "arterial thrombus"**

   It is found in areas of rapid blood flow e.g. arterial circulation. It consists primarily of platelet fibrin mass and is relatively poor in red blood cells. It forms almost exclusively in areas adjacent to an injured or abnormal blood vessel wall *(Deykin et al., 1967)*.

Thrombogenesis

Thrombosis usually occurs when there is breakdown in the balance between thrombogenic factors and protective mechanisms.

Thrombogenic factors:

1. **Damage of the endothelium (Fig. 1):**

   The normal intact endothelium is non thrombogenic and reacts with neither platelets nor blood components *(Vasiliev et al., 1978)*, when the endothelial cell layer is damaged, there is endothelial loss and exposure of the sub-endothelium to both platelets and blood coagulation factors. A thrombotic reaction starts on the cells, sub-endothelium and on the connective tissue deposited by smooth muscle cells in the deeper layers *(Zwaginga et al., 1990)*.

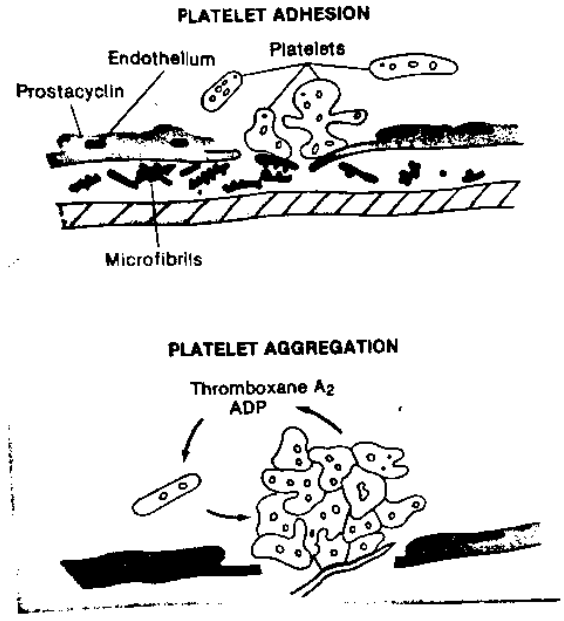

Fig. (1): Overview of primary hemostasis. The initial event is adhesion of platelets to areas of the vessel wall in which the subendothelium has been exposed by endothelial injury. After adhesion, platelets become activated and, under the influence of mediators like ADP and thromboxane A2, recruit addition circulating platelets to bind to the adherent monolayer and form a platelet aggregate (Handin and LoScalzo, 1992).

2. **Stimulation of platelet aggregation:**

When platelets interact with the exposed sub-endothelium they adhere to many surfaces, **the process of platelet adhesion**, they undergo shape change and release their granular contents, the **platelet release reaction** and they alter the nature of their surface in a fashion that facilitates blood coagulation, the **platelet pro-coagulant activity.** *(Sakariassen et al., 1979).*

"**Platelet adhesion**" to the sub-endothelial collagen requires von willebrand factor, which promotes platelet adhesion by binding to a glycoprotein receptor on the platelet surface *(Sakariassen et al., 1979).*

"**Platelet release reaction**": follows platelet adhesion and in which a number of aggregating agents including collagen, thrombin, epinephrine, and thromboxane A_2 cause platelets to release their granular contents *(Kaplan et al., 1979).*

Platelets contain two types of secretory granules, the **dense granules** and the **alpha-granules.** The dense granules contain serotonin and ADP (adenosine disphosphate), while the alpha-granules contain the platelet specific proteins, platelet factor 4, B-thromboglobulin, a platelet derived growth-promoting factor and a variety of other proteins including fibrinogen, factor V, von willebrand factor and alpha$_1$ antitrypsin *(Kaplan et al., 1979).*

"**Platelet aggregation**" can be induced by several stimuli including ADP, collagen, thrombin, thromboxane A_2 and epinephrine (Fig. 1) *(Mustard et al., 1975; Kinglough-Rathbone et al., 1976).*

At least four pathways of platelet aggregation have been defined. These are mediated by ADP, thromboxane A_2, thrombin, and the fatty acid known as platelet activating factor (PAF) *(Kinglough-Rathbone et al., 1976).*

Platelet aggregation requires a platelet membrane glycoprotein receptor for fibrinogen. The binding of fibrinogen is a pre-requisite for platelet aggregation *(Coller et al., 1980).*

"Thromboxane A2" (TXA_2) which is a potent platelet aggregator and vasoconstrictor is one of the final products of platelet prostaglandin synthesis. It is produced in the course of platelet activation by a number of stimuli including thrombin, collagen and epinephrine *(Smith et al., 1980).*

"Collagen" induces platelet aggregation both by stimulating the synthesis of TXA_2 and by releasing ADP through a mechanism independent of platelet prostaglandin synthesis *(Mustard et al., 1975).*

"Thrombin" induces platelet aggregation by stimulating the release of ADP, by activating the platelet prostaglandin pathway to form TXA_2 and by a third poorly understood mechanism *(Mustard et al., 1975).*

"Platelet activating factor" (PAF) is released from leukocytes and macrophages. It is chemotactic and induces platelet aggregation.

All agonists that induce platelet aggregation probably act through a common pathway, the mobilization of calcium from the dense tubular system in the cytoplasm *(Kinglough-Rathbone et al., 1976).*

"Platelet coagulant activity"

Thrombin generation in the plasma is greatly accelerated by the presence of platelets.

Stimulated platelets have enhanced capacity to catalyze interactions between activated coagulation factors e.g. the interaction of activated factor IX with factor VIII and the interaction of activated factor X with factor V and prothrombin occur on the platelet surface and the rates of these reactions are greatly enhanced by the presence of platelets *(Majerus et al., 1978)*.

3. **Activation of blood coagulation**

The process of blood coagulation involves a series of complex steps that terminate in the formation of a fibrin clot. Blood coagulation occurs either by activation of the intrinsic pathway or by activation of the extrinsic pathway *(Davie et al., 1975)*.

Protective Mechanisms

Normally thrombogenesis is modulated by a number of efficient protective mechanisms:

1. **Non thrombogenic properties of the endothelial cells**

Endothelial cells play an important role in the regulation of thrombosis. Normal resting endothelium exhibits antithrombotic activity (Fig. 2). This property is due to an active participation of endothelial cells in the inhibition of platelet adhesion and aggregation, in the inhibition of