HAEMOSTATIC CHANGES IN ISCHAEMIC HEART DISEASES

Essay

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"I am always so grateful to God who helps me"

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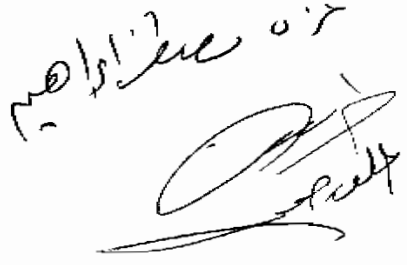

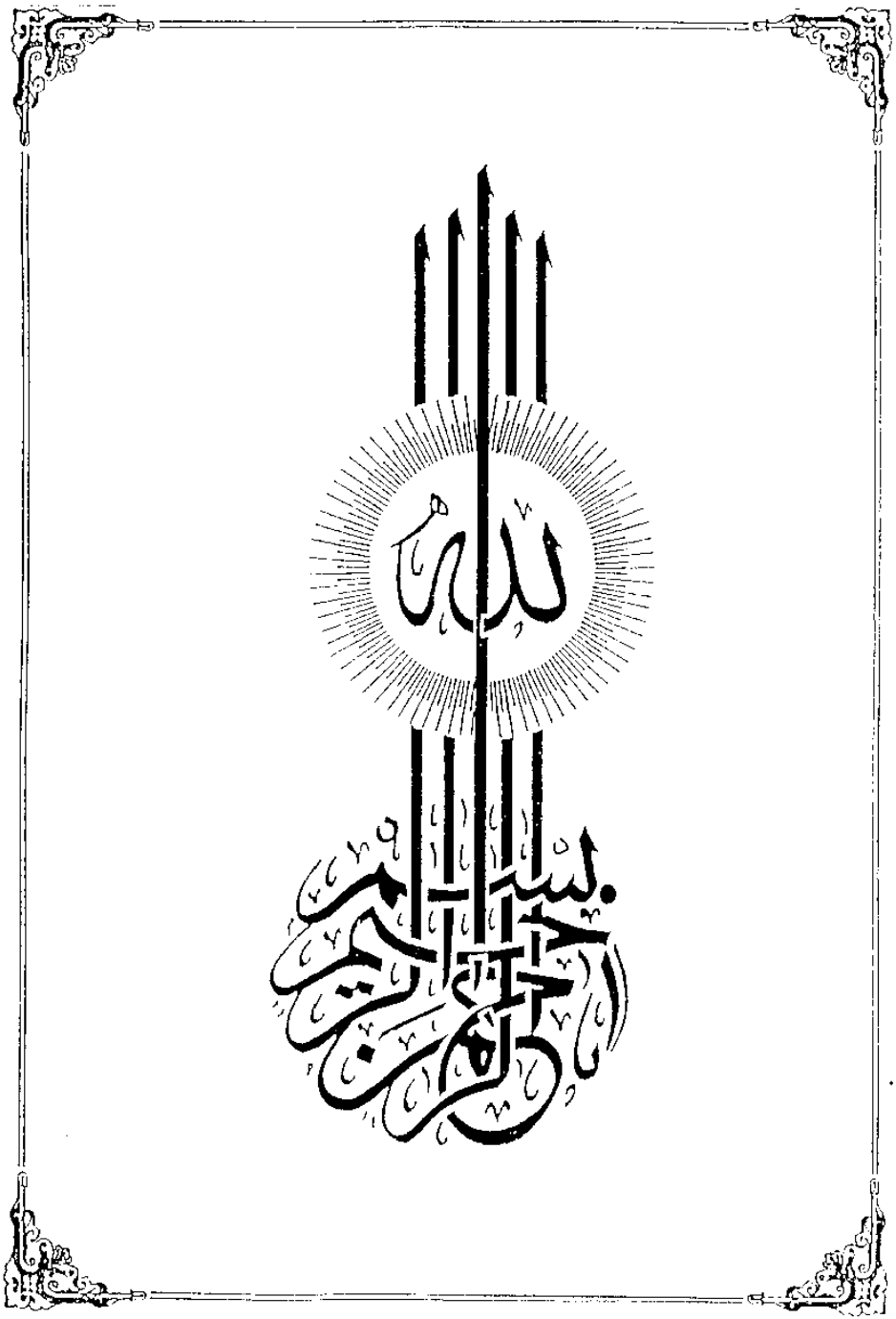

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Most workers who are interested in thrombotic lesions of the heart accept that, in the aetiology of coronary heart disease, there are two elements of great importance, atherogenesis and thrombogenesis.

So far, most of epidemiological and aetiological researches on ischaemic heart diseases has mainly dealt with conventional risk factors such as atherogenesis, but studies on haemostatic system have been insuficient to clarify the problem. In most cases of myocardial infarction, rapidly progressing coronary atherosclerosis is the underlying disease. Haemostatic function has been implicated in atherogenesis as well as in thromboembolic disorders.

Stepwise discriminant analysis indicated that concentration of fibrinogen, Von Willebrand factor and inhibitor of plasminogen activator were high in those patients [Wilhemsen et al, 1984 and Hamsten et al, 1986]. Also increased level of factor VII was found to be associated with increased risk for ischaemic heart diseases [Meade et al, 1986]. At the same time, low level of antithrombin III have been reported in the acute as well as in the recovery phase after myocardial infarction and in patients with angina pectoris [Sixma, 1980].

/Therefore, it was found useful to review function of blood coagulation and fibrinolysis in patients with ischaemic heart diseases/

MECHANISM
OF
NORMAL HAEMOSTASIS

MECHANISM OF NORMAL HAEMOSTASIS

Haemostasis is the combined effect of various mechanism involved in the prevention of spontaneous haemorrhage and in the arrest of escape of blood from injured vessels.

The mechanism of haemostasis comprises the function of four components: vessels, platelets, coagulation system and fibrinolytic system. All four components must be functioning correctly if haemostasis is to be normal.

ROLE OF BLOOD VESSELS IN HAEMOSTASIS

Traumatic vascular injury causes bleeding with subsequent contraction of the vessels involved. This contraction is probably a reflex action and due to serotonin release. It is of great importance for immediate haemostasis. The contraction is only temporary, but normally lasts long enough for a plug to form and seal the defect in the vessel.

The escaping blood comes in contact with the damaged vessel wall and the subendothelial collagen which initiates the processes of platelet adhesion, platelet aggregation and blood coagulation.

The subendothelial collagen also activate factor XII

which starts both coagulation and fibrinolysis.

Moreover, the vascular endothelial cell secretes Von Willebrand's factor [F VIII - VW] which mediates platelet adhesion and helps in clot formation.

Recently, the vascular endothelium has been shown to participate actively in inhibiting clot formation so that clot is limited to the injured site and not propagated to occlude the vessel and block the blood flow. Both enodthelial cell surface and intracellular factors contribute to this regulation [Esmon et al, 1982].

Two distinct anticoagulant mechanism are triggered by contact with the cell surface. One involves cell surface heparin like molecules that can function to accelerate the inactivation of coagulation proteases by antithrombin III [Busch et al, 1982]. The other involves thrombomodulin, a thrombin binding protein that changes the specific procoagulant effect of thrombin to an anticoagulant effect, by decreasing the ability of thrombin to catalyse clot formation [Esmon et al, 1982], and at the same time converting thrombin into a potent protein C activator [Esmon and Owen, 1981]. Protein C then functions as an anticoagulant by inactivating factor Va and VIIIa [Walker et al, 1979; Fulcher et al, 1983].

Intracellular components also contribute to the vascular regulation of the clotting process. Prostacyclin [Moncada et al, 1976], an inhibitor of platelet activation, and plasminogen activator [Sakata et al, 1985] are both synthesized and released from endothelium.

Thus the endothelial cell contributes to the control of clotting mechanism, platelet activation and clot dissolution.

ROLE OF PLATELETS IN HAEMOSTASIS

In mammals the major function of platelets is haemostasis [Mac Farlane, 1970]. This is achieved by forming a platelet plug and promoting thrombin production.

The balance between the vascular, coagulation factor, platelet and fibrinolytic system is shown in fig. [1].

The interaction between platelets, plasma factor and vessel wall in order to keep normal haemostasis is demonstrated in fig. [2].

This includes: vascular injury results first in adhesion of platelets to the vessel wall. This is followed by the transformation of normal discoid platelets into spheres with small cytoplasmic protrusions and the formation of platelet aggregates. Adherent and aggregated platelets release stored ADP. Simultaneously, activated

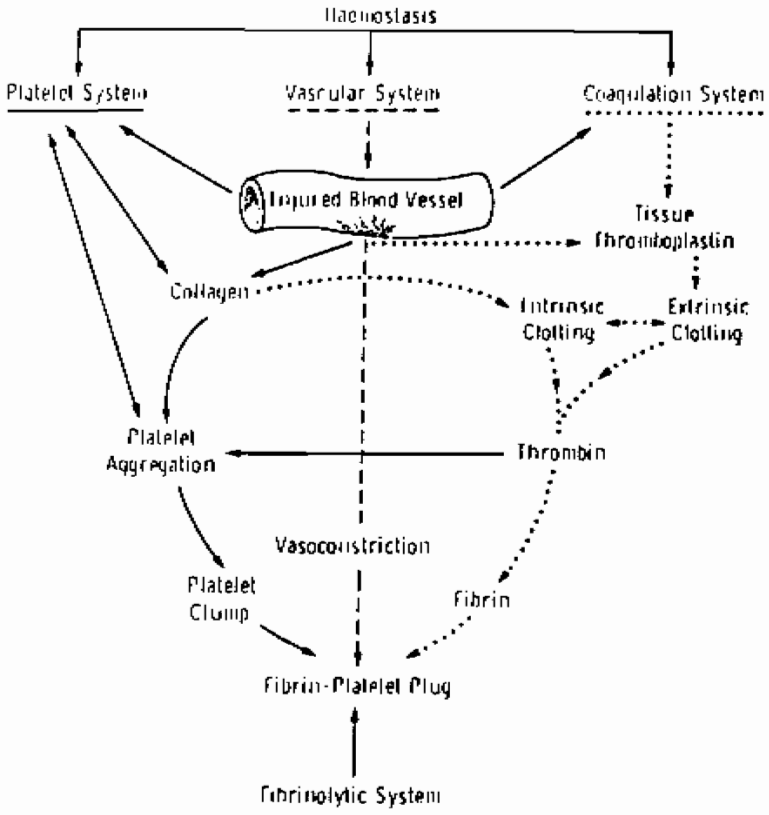

Fig. (1) : Haemostasis and the balance between the vascular, coagulation factor, platelet and fibrinolytic systems. (Roger & Robert 1984).

platelets synthetize prostaglandin and thromboxanes which mediate the release reaction and may induce aggregation directly. Activation of platelet factor III and initiation of blood coagulation then follow, leading to consolidation of platelet plug by fibrin. Subsequently, the phenomenon of clot retraction is seen [Wintrob, 1981].

PLATELET ADHESION:

The initial event in formation of a platelet plug is the transformation of platelets from a non adhesive to an adhesive state. Plasma contains several proteins that adhere to platelets, including fibrinogen, fibronectin and Von Willebrand factor [VWF]; platelets contain these 3 adhesive proteins plus thrombospondin packaged in their ∝ granules [Jandl, 1987]. The storage site for platelet fibrinogen, fibronectin, VWF and thrombospondin is the ∝ granule.

All 4 ∝ granule adhesives are discharged simultaneously in response to thrombin.

Thrombospondin is released from ∝ granule and expressed on platelet surfaces upon thrombin stimulation [Phillips et al. 1980; Margossian et al, 1981]; the membrane site to which thrombin binds in the glycocalicin portion of platelet GPIb at a site remote from the point of ristocetin dependent VWF binding [Takamatsu et al, 1986]. Thrombospondin is the endogenous lectin of stimulated platelets; it locks onto fibrinogen, collagen, and

fibronectin; in the presence of heparin it forms trimolecular complexes with histidine-rich glycoprotein and plasminogen [Jaffe et al, 1982; Leung, 1984; Leung et al, 1984; Silverstein et al, 1985]. When stimulated by thrombin, platelet release thrombospondin and fibrinogen, which then colocalize into a macromolecular complex with GPIIb - IIIa on tha activated membrane surface [Asch et al, 1985; Lawler, 1986]. Thrombospondin promotes bonding of unlike molecules and adhesion of unlike cells and facilitates the deposition of fibrin [Silverstein er al, 1984]. Platelet adherence to subendothelial matrix at physiologic shear rates requires VWF, platelet receptors for VWF, thrombospondin and calcium. Adherence to insoluble collagen fibrils requires no cofactors but may be expedited by platelet membrane receptors for specific collagen types [Chiang and Kang, 1982; Fauvel et al, 1983; Stemerman et al, 1984].

PLATELET AGGREGATION:

After adhesion of the bottom layers of platelets to the injured vessel wall, the hemostatic plug enlarges by aggregation of platelets to each other.

There are many agents that induce platelets to aggregate together. These include adenosine diphosphate [ADP], adrenaline, noradrenaline, serotonin, thromboxane A2, thrombin and a platelet activating factor. All these agents aggregate platelets directly. Fibrillar collagen

also induce platelets to aggregate, this aggregation is indirect and mediated by thromboxane A2 that is synthesized and the ADP that is released from platelets [Lewis and Watts, 1982].

Primary platelet aggregation is an immediate consequence of platelet stimulation and can be induced by ADP, thrombin, or epinephrine. Following exposure to low concentration [1 μm] of ADP the response is reversible, self-limited, and unassociated with platelet secretion or generation of prostaglandins [Shattil and Bennett, 1981].

The secondary aggregation that may follow primary aggregation is caused by the platelet granular "release reaction" in which platelets are stimulated to secrete ADP and arachidonic acid, metabolites of the latter are potent aggregators [Jandl, 1987]. Free ADP released in micromolar concentrations from damaged endothelium or other tissues, or secreted by previously stimulated platelets, induces aggregation by reacting with ADP receptors on the externally oriented membrane [Colman, 1986; Figures et al, 1986]. ADP may bind to at least 2 and possibly 3 different functional sites: 1 involved in inhibition of adenyl cyclase; another involved in shape change [Adler and Handin, 1979], and a third responsible for exposing the fibrinogen receptor.