Mechanism Underlying the Formation of Thrombus in the Coronary Artery and Drugs Affecting this Process

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There is now sufficient evidence to indicate that thrombus superimposed on a ruptured atherosclerotic plaque is the cause of the vast majority of ischaemic syndromes such as unstable angina, myocardial infarction, and sudden death. Discussed in this article is the mechanism by which a thrombus in the coronary artery is formed. Also outlined briefly are the mechanisms by which different drugs act as antithrombotic / thrombolytic agents.

INTRODUCTION

In 1887, Welch defined **thrombus** as a solid mass or plug formed within the heart, arteries, veins, or capillaries from the components of the streaming blood.¹ Three main factors (**Virchow's triad**) may be responsible in the pathogenesis of thrombus - stasis, hypercoagulability, and change of the vessel wall.² In arteries, thrombus predominantly consists of platelets and is called **white thrombus** but thrombus in veins mainly consists of red blood cells and is generally called **red thrombus**.³

VASCULAR ENDOTHELIUM

The **vascular endothelium** is not a passive structure. It plays important role in maintaining blood flow and also in keeping platelets in inactive and non-aggregating state. Firstly, the negative charge of the endothelial wall repels platelets, which are also negatively charged. Secondly, the intact endothelial lining covers and hides from platelets different subendothelial substances like collagen fibrils, proteoglycan, glycosaminoglycans, fibronectin,

and elastin. Thirdly, endothelium elaborates different active substances.⁴

One of the important substances elaborated by the endothelium is **prostacyclin** (PGI₂). PGI₂ increases cyclic AMP (cAMP) concentration by activating adenylate cyclase. Cyclic AMP is a vasodilator and inhibitor of platelet aggregation.⁵

In response to various substances such as thrombin, 5-hydroxytryptamine (serotonin), neurotransmitters, adenosine triphosphate and adenosine diphosphate, the endothelium releases a substance known as **endothelium-derived relaxing factor** (EDRF). EDRF is now known to be nitric oxide (NO). Once released, NO quickly leads to the formation of cyclic GMP (cGMP) by activating guanylate cyclase. Cyclic GMP then causes relaxation of the vascular smooth muscle.⁶ It seems that PGI₂ and EDRF are synergistic in inhibiting platelet aggregation and dilating blood vessels.⁵ In addition to EDRF, the endothelium may secrete another vasodilating factor, which has been named as **endothelium-derived hyperpolarizing factor** (EDHF).

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The endothelium also releases two contracting factors. They have been called **Endothelium-derived contracting factors** (EDCF). One is insensitive to indomethacin (EDCF₁) while the other is sensitive to indomethacin (EDCF₂). EDCF₁ may be **endothelin** and EDCF₂ may be **superoxide anion**.⁵

Less EDRF is produced locally when the endothelium is damaged by an atherosclerotic process. Because of the decrease in EDRF production, there is increase in vasoconstriction and platelet aggregability in the neighbourhood of the atherosclerotic plaque; this further enhances the atherosclerotic process. EDRF production may be impaired in hypertension, too.⁵

It is interesting to note that **eicosapentanoic acid** (present in fish oil) stimulates EDRF production, which may be the reason why it has antiatherogenic property.⁵ Eicosapentanoic acid also leads to the synthesis of prostaglandin I₃, which is anti-aggregatory.¹

PLATELETS

Platelets (thrombocytes) are intimately related in the causation of coronary artery diseases (CAD). They participate in this process by (i) contributing to atheroma formation, (ii) contributing to superimposition of thrombus on the atheromatous plaque, and (iii) releasing substances capable of causing coronary vasoconstriction.⁵

Platelets contain different pro-aggregatory substances like **adenosine diphosphate** (ADP), **5-hydroxytryptamine**, and **thromboxane A₂**. Thromboxane A₂ is produced from arachidonic acid by the action of cyclo-oxygenase and thromboxane synthase.

THROMBOGENESIS IN THE CORONARY ARTERIES

An artery may be occluded by (i) spasm, (ii) haemorrhage into an atheromatous plaque, (iii) thrombosis of an atheromatous plaque, or (iv) embolization of a thrombus. Of all these

causes, thrombosis is the commonest.⁴ One of the commonest sites of occlusive thrombi formation is the coronary artery. In the vast majority of cases a thrombus is superimposed on an atherosclerotic lesion.⁷ **Soft atherosclerotic plaques** are more dangerous than hard plaques because the former are more liable to rupture with consequent exposure of their subendothelial surface.⁸

Platelets quickly adhere to the exposed subendothelial sites by a process called **platelet adhesion**. This happens because platelets have on their surface different **receptors** which have high affinity for adhesive glycoproteins present in subendothelium. Some of these receptors belong to integrin superfamily of adhesion receptors.⁹

Following adhesion to the subendothelial surface, platelets release different pro-aggregatory substances, which cause more and more platelets to aggregate with each other. This process is called **platelet aggregation**.

Thromboxane A₂, generated as a result of platelet release reaction, combines with its receptor and causes release of platelet agonists such as ADP and serotonin from storage granules. These platelet agonists further enhance the process of aggregation.

The final common pathway in platelet aggregation is the exposure of **GP IIb/IIIa receptors** present in platelets. The activated GP IIb/IIIa receptors bind with different adhesive glycoproteins, leading to aggregation and thrombus formation.⁹ The newly formed thrombus is stabilized by fibrin network.⁸

Thrombogenesis and thrombolysis are dynamic processes.¹⁰ These events are normally balanced. But if the process of thrombogenesis becomes unchecked, **occlusion** can occur due to the evolution of thrombus. The thrombus may extend into the post-stenotic area because at this site there is flow separation, recirculation, and turbulence in blood flow. Furthermore, because of stagnation and coagulation of blood both proximal and distal to the site of occlusion, red thrombi composed mainly of RBCs and fibrin

may be secondarily formed.⁸

ANTITHROMBOTIC/ THROMBOLYTIC DRUGS

Till now there is no treatment available that can effectively prevent the disruption of the surface of atheromatous plaques in the coronary arteries.¹¹ It is, however, possible to hinder the process of thrombus formation and also decrease chances of platelet embolization by the use of **antiplatelet (antithrombotic)** therapy. **Thrombolytic** therapy, on the other hand, can be used to lyse thrombi that have already formed.

The use of **aspirin** as an antiplatelet agent has been widely studied. Aspirin irreversibly acetylates platelet cyclo-oxygenase,¹² thus inhibiting the production of cyclic endoperoxide precursor of thromboxane A₂. This inhibition lasts throughout the lifespan (7-10 days) of platelets because they are anucleate and cannot synthesize new enzyme.² Although aspirin may also inhibit endothelial cyclo-oxygenase, regeneration of new enzymes at this site may occur within 36 hours.³ The dose of aspirin to act as an antithrombotic agent is much less than the doses required for its other actions. Repeated administration of aspirin has been found to have cumulative effect on platelet function.²

Sulfinpyrazone, a uricosuric drug, inhibits certain platelet functions like release reaction and adherence to subendothelium; it also suppresses prostaglandin synthesis. But its real usefulness is not as yet known clearly.²

Dipyridamole, a vasodilator drug, inhibits platelet phosphodiesterase and consequently increase the concentration of cAMP, which inhibits aggregation. This drug may also block adenosine uptake; adenosine stimulates platelet adenylyl cyclase. But this drug has not been found to be really useful. When given alone, dipyridamole offers little or no benefit.² It is also not clear if there is any benefit of adding this drug to aspirin.¹²

An investigational drug **ticlopidine** has

been found to inhibit platelet aggregation by interacting with and inhibiting exposure of platelet GP IIb/IIIa receptors by an unknown mechanism.^{2, 9} The drug is currently being tested.

Although thrombus in coronary artery contains mainly platelets, it is fibrin which enmeshes and stabilizes them. It has been seen that dissolution of fibrin network can help in recanalization of the artery and establishment of reflow of blood. This objective has been achieved to some extent by the intravenous use of fibrinolytic (thrombolytic) drugs - **streptokinase, anisoylated plasminogen streptokinase activator complex, and recombinant tissue-type plasminogen activator**. Properly used, they can reduce the size of myocardial infarction and also mortality. However, there are some problems in the use of these agents, which are (i) need to give them quickly after infarction, (ii) development of reocclusion upon cessation of therapy, and (iii) increased chances of spontaneous bleeding.¹³

It seems that in myocardial infarction a combination of streptokinase and aspirin is much more effective in reducing mortality (from vascular causes) than either drug given alone; this has been shown by a large study known as the Second International Study of Infarct Survival (ISIS-2).¹⁴ **Heparin**, an anticoagulant drug, also seems to be useful as a conjunctive therapy for persistent coronary arterial patency in patients who have evolving acute myocardial infarction.¹³

NEW DRUGS

New approaches are being explored for possible usefulness in the treatment of coronary thrombosis. They are:

- (i) Thromboxane synthase inhibitors.
- (ii) Serotonin receptor antagonists.
- (iii) Endoperoxide receptor antagonists.
- (iv) Platelet glycoprotein IIb/IIIa receptor blockers. (Different possible blockers are monoclonal antibodies directed against this receptor, peptides derived from the venom of vipers, and small synthetic

- peptides containing arginine-glycine-aspartic acid.)
- (v) Inhibition of thrombin. (Possible candidates are hirudin and its derivatives, selective tripeptide chloromethyl ketones, and synthetic thrombin inhibitors).¹³

CONCLUSION

Most of the cases of ischaemic

syndromes of the heart seem to be due to fissuring of atherosclerotic plaque in the coronary artery with subsequent development of thrombus over it. Several studies have shown the usefulness of low-dose aspirin as an antithrombotic agent. In recent years there has also been an advance in thrombolytic therapy. Search for newer and better antithrombotic/thrombolytic drugs is continuing.

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