ANESTHESIA AND PLATELET DISORDERS

An essay submitted for the partial fulfillment of
The Master Degree in Anesthesiology

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Abstract

When bleeding from a wound suddenly occurs, the platelets gather at the wound and attempt to block the blood flow. The mineral calcium, vitamin K, and a protein called fibrinogen help the platelets to form a clot.

A normal platelet count in a healthy person is between 150,000 and 400,000 per mm^3 of blood. Normal platelet counts are not a guarantee of adequate function. In some states the platelets, while being adequate in number, are dysfunctional.

By using a special method called platelet aphaeresis, whole blood is separated into components, and the platelets are removed. The clinical response to platelet transfusion can be assessed by measuring the increment in platelet concentration achieved in the patient's blood.

The complications of platelet transfusion most frequently result from contaminating leukocytes, red cells, plasma proteins and microorganisms.

Keywords:

Platelets, Hemostasis, Coagulation, Platelet disorders, Thrombocytopenia, Platelet transfusion.

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List of Abbreviations

ADP	Adenosine diphosphate.
AML	Acute myelogenous leukemia.
AMP	Adenosine monophosphate.
Anti HPA-1a	Anti human platelet antigen-1a.
APP	Amyloid precursor protein.
aPTT	activated partial thromboplastin time.
Arg-Gly-Asp	Arginine-Glycine-Aspartate.
AS	Aortic stenosis.
ATP	Adenosine triphosphate.
ATPase	Adenosine triphosphatase.
AVWS	Acquired von Willebrand syndrome.
BSA	Body surface area.
BSS	Bernard-Soulier Syndrome.
BT	Bleeding time.
C	Complement system.
CABG	Coronary Artery Bypass Grafting.
CAMP	Cyclic adenosine monophosphate.
CAMT	Congenital Amegakaryocytic thrombocytopenia.
CCI	Corrected count increment.
CD	Cluster of differentiation.
CD40L	CD40 ligand.
CD4+T	CD4+ T-Helper cells.
COX-1	Cyclooxygenase-1.
COX-2	Cyclooxygenase-2.
CR	Clot retraction.
CTAP-III	Connective tissue-activating peptide-III.
CXC	Chemokines.
DDAVP	1-desamino-8-D-arginine vasopressin (Desmopressin).
DIC	Disseminated intravascular coagulopathy.
EACA	Epsilon Amino Caproic Acid.
Ecto-ADPase	ecto-adenosine diphosphatase.
EDTA	Ethylene Diamine Tetra Acetic Acid.
FC	Crystalline fraction.
FcγRIII	Fc gamma receptor III (Leukocytic receptor).
FDPs	Fibrin degradation products.
FPS	Familial platelet syndrome.
FSPs	Fibrin split products.
Gas6	Growth arrest specific gene.
GDP	Guanosine diphosphate.

GMP	Guanosine monophosphate.
GP	Glycoprotein.
GSA	Guanidino succinic acid.
HELLP	Hemolysis (H), elevated liver enzymes (EL), low platelet count (LP).
HIT	Heparin induced thrombocytopenia.
HIV	Human immunodeficiency virus.
HLA	Human leukocyte antigen.
HPA	Human platelet antigen.
HSC	Hematopoietic Stem cells.
HUS	Hemolytic uremic syndrome.
IAP	Integrin associated protein.
IL	Interleukin.
Integrin	Integral membrane protein.
ITP	Immune Thrombocytopenic Purpura.
IVIg.	Intravenous Immunoglobulins.
KMS	Kasabach Merrit Syndrome.
Lys-Gln-Ala-Gly-Asp-Val	Lysine-Glutathione-Alanine-Glycine-Aspartate-Valine.
MDS	Myelodysplastic syndrome.
mRNA	messenger ribonucleic acid.
NADH	Nicotinamide adenine dinucleotide reduced form.
NAP	Neutrophil activating peptide.
NO	Nitric oxide.
NSAIDS	Non Steroidal Anti-inflammatory Drugs.
PAF	Platelet activating factor.
PAIs	Plasminogen activator inhibitors.
PAs	Plasminogen activators.
PARs	Protease activated receptors.
PC	Phosphatidyl-choline.
PCI	Percutaneous coronary intervention.
PDGF	Platelet derived growth factor.
PE	Phosphatidyl-ethanolamine.
PFA	Platelet activating factor.
PF4	Platelet factor 4.
PGI_2	Prostacyclin.
PK	Prekallikrein.
PKC	Protein kinase C.
PNH	Paroxysmal nocturnal hemoglobinuria.
PS	Phosphatidyl-serine.
P-Selectin	Platelet selectin.
PSGL-1	P-Selectin glycoprotein ligand-1.
PT	Prothrombin time.

P2Y12	Purinergic receptors.
RCF	Ristocetin cofactor.
RNA	Ribonucleic acid.
rVIIa	Recombinant activated factor seven (Novoseven).
Selectins	Family of cell adhesion molecules.
SPD	Storage pool disease.
TAR	Thrombocytopenia with absent radii.
TGF-B	Transforming growth factor-B.
t-PA	Tissue plasminogen activator.
TPO	Thrombopoietin.
TSP	Thrombospondin.
TTP	Thrombotic thrombocytopenic purpura.
TXA_2	Thromboxane A_2.
U	Unit.
u-PA	Urokinase-like plasminogen activator.
u-PAR	Urokinase plasminogen activator receptor.
VEGF	Vascular endothelial growth factor.
vWF	von Willebrand factor.
WAS	Wiskott Aldrich syndrome.
WASP	Wiskott Aldrich syndrome protein.

Introduction

When vascular injury first occurs, local factors begin to prepare the site for coagulation. In summary local factors cause vasoconstriction in an attempt to diminish blood flow and allow the clot to form. Exposed collagen attracts platelets which aggregate, become activated and release a multitude of granules including adenosine diphosphate (ADP), serotonin, thromboxane A_2, calcium, clotting and platelet factors and hydrolytic enzymes.
This in turn, attracts more platelets, with the result being a large, contracted platelet plug. This primary hemostatic process is necessary but is not sufficient to produce a permanent and stable clot. That goal depends upon the trombin-mediated deposition of fibrin, which is accompanied by the bifid clotting cascade. [(1)]

Coagulation from platelet abnormalities may result from too few platelets or from derangement of function. Abnormally functioning platelets, regardless of count will prolong the bleeding time. Disorders of platelet function include von Willebrand disease, Bernard-Soulier syndrome and Glanzmann's thrombasthenia which are commonly inherited. While disorders of platelet release are most commonly caused by exogenous administration of the cyclo-oxygenase inhibitors, and may rarely be inherited. Failure to release thromboxane A_2, ADP, or platelet factor III (in storage pool deficiencies) results in abnormal platelet function with lack of the second wave of aggregation. [(2)]

Acquired defects of platelet function as with uremia and alcohol are commonly encountered in surgical patients, drugs such as NSAIDs, penicillin and cephalosporin antibiotics, alpha-agonists, some tricyclic compounds, local anesthetics (including lidocaine) and nitroprusside may also induce platelet dysfunction. [(3)]

Autoantibodies may also have been documented to cause derangement of platelet function and thrombocytopenia. [(4)]

The aim of the study is to review the role of platelets in hemostasis, diseases of the platelets, disorders of platelet function and anesthetic considerations in patients with platelet disorders.

Pathophysiology of Coagulation

Coagulation is the third one of the four components of the haemostatic process. These four components are vasoconstriction of blood vessels, formation of platelet plug, coagulation and clot retraction.

Mechanism of Blood Coagulation:

There are two theories for blood coagulation. There are the classic and the modern theories.

(A) The Classic Theory (Figure 1-1):

When blood vessel is injured and gets in contact with wounded tissues or with foreign surface, clotting reactions start. The damaged tissues and platelets release a substance called thrombokinase which converts the inactive prothrombin into active thrombin in the presence of Ca^{2+}. Thrombin converts soluble fibrinogen into insoluble fibrin. Fibrin forms a network having blood cells in meshes then forms a red jelly like mass called blood clots. The clot then retracts i.e. decreases in volume due to contraction of fibrin filaments and squeezes out clear yellow liquid called serum. [5]

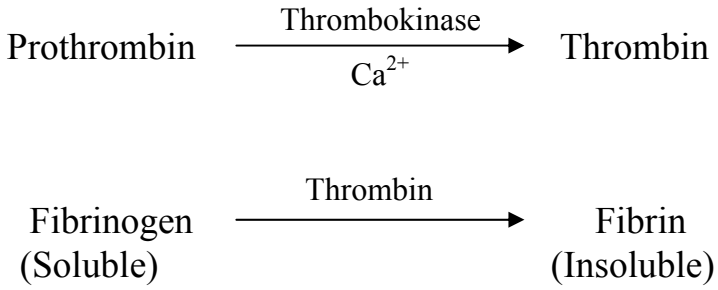


Figure 1-1: Classic Theory [5]

(B) Modern (Enzymatic Cascade) Theory:

It is essentially an extension of the classical theory. More factors are needed in this theory (**table 1-1**). It is the most accepted theory of blood coagulation. [6]

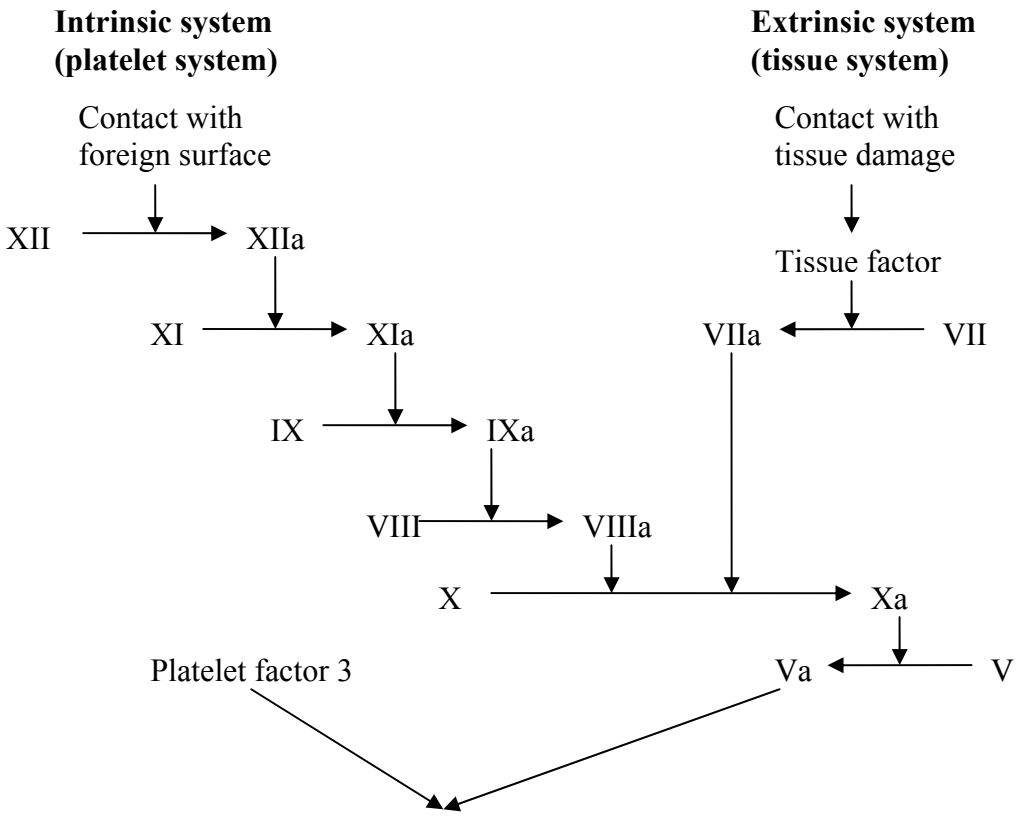
TABLE 1-1: CLOTTING FACTORS: [6]

FACTOR	NAME
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
IV	Ca^{2+}
V	Labile factor
	There is no factor (VI)
VII	Stable factor
VIII	Antihemophilic globulin factor
IX	Christmas factor
X	Stuart-prower factor
XI	Plasma thromboplastin antecedent
XII	Hagemen factor
XIII	Fibrin stabilizing factor

This theory suggests 4 stages for clot formation. These stages are:

I) Stage I:
It is the stage of formation of active thromboplastins which are prothrombin activators. There are two independent systems or pathways for formation of active thromboplastins. These systems are:

1- Intrinsic or Platelet System (Pathway) of Thromboplastin Formation (4-8 Minutes):
In contact with a foreign surface or injured blood vessels, platelets stick together and disintegrate to release certain phospholipids collectively known as platelet factor 3. This factor and factor XII, XI, IX, VIII, X and V interact to activate each other in certain order as shown in figure (1-2) till activated factor V is obtained. Platelet factor 3 reacts with activated factor V to produce active platelet thromboplastins (prothrombin activators). Ca^{2+} is needed for these reactions except during activation of factor XII (the first step) which is activated by contact with the foreign surface. [1]



Stage I: Formation of platelet and tissue thromboplastins in the presence of Ca^{2+}.
Stage II: Activation of prothrombin into thrombin by thromboplastins in the presence of Ca^{2+}.
Stage III: Conversion of fibrinogen into soluble fibrin by thrombin.
Stage IV: Stabilization of soluble fibrin by fibrinogen stabilizing factor (factor XIII) in the presence of Ca^{2+} to insoluble fibrin.

Figure 1-2: **Mechanism of blood coagulation (enzymatic cascade theory)** [6]

2- Extrinsic or Tissue System (Pathway) of Thromboplastin Formation (12-20 Seconds):

Tissue damage releases tissue juice containing a tissue factor which activates factor VII. Activated factor VII activates factor X, then the remaining reactions are the same as for intrinsic pathway (figure 1-2).
So, both systems (intrinsic and extrinsic) activate factor X and when the activated factor X is formed, the coagulation mechanism proceeds rapidly and in a common pathway to get the two different types of active thromboplastin (platelet and tissue thromboplastin).[1]

II) Stage II:

It is the stage of activation of prothrombin to thrombin by thromboplastins in the presence of Ca^{2+}. [7]

III) Stage III:
It is the stage of conversion of fibrinogen into soluble fibrin clot (soft clot) by thrombin. [7]

IV) Stage IV:
It is the stage of stabilization of soluble fibrin to insoluble fibrin by fibrinogen stabilizing factor (factor XIII) in the presence of Ca^{2+}. [7]

Factors that Limit Clot Formation to the Injured Site:

In addition to catalyzing the final steps in the coagulation cascade, thrombin also exerts a wide variety of effects on the local vasculature and inflammation; it even actively participates in limiting the extent of the hemostatic process **(figure 1-3).** Most of these effects are induced via binding a family of Protease-Activated Receptors (PARs). The mechanism of receptor activation involves clipping the extracellular end of the thrombin receptor via the proteolytic activity of thrombin. This generates a tethered peptide, which then binds to the rest of the receptor and causes the conformational changes necessary to activate the associated G-protein. Thus, the interaction of thrombin and its receptor is essentially a catalytic process, which explains the impressive potency of even relatively small numbers of activated thrombin molecules in eliciting downstream effects. [8]

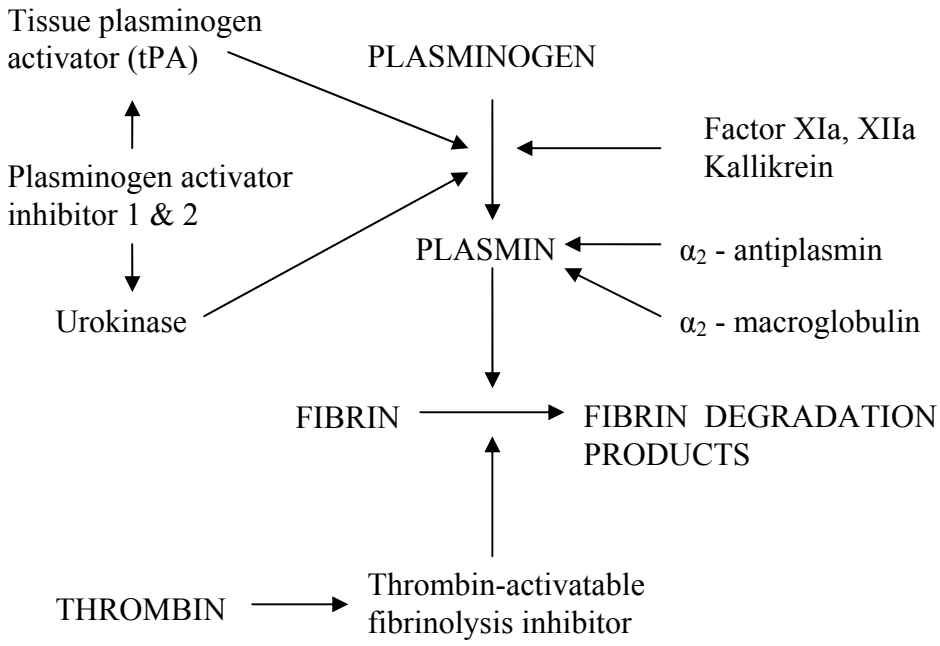


Figure 1-3: Plasminogen effect on hemostatic process [8]