
بسم الله الرحمن الرحيم

Blood & Immunity Module

Small Group Discussion (SGD)

FIRST YEAR MBBS BATCH 50

Topic

Platelets Formation & Function
Hemostasis
Blood Coagulation Test
(BT, CT. PT, APTT, INR)

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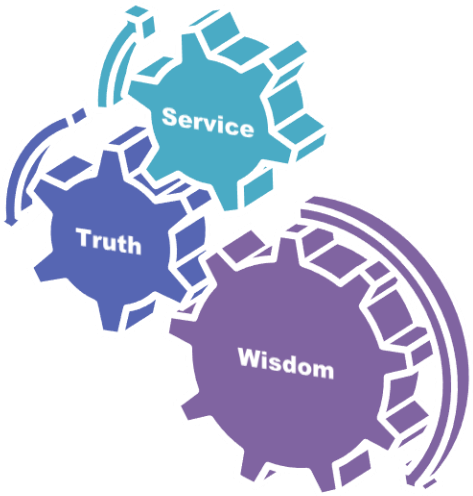
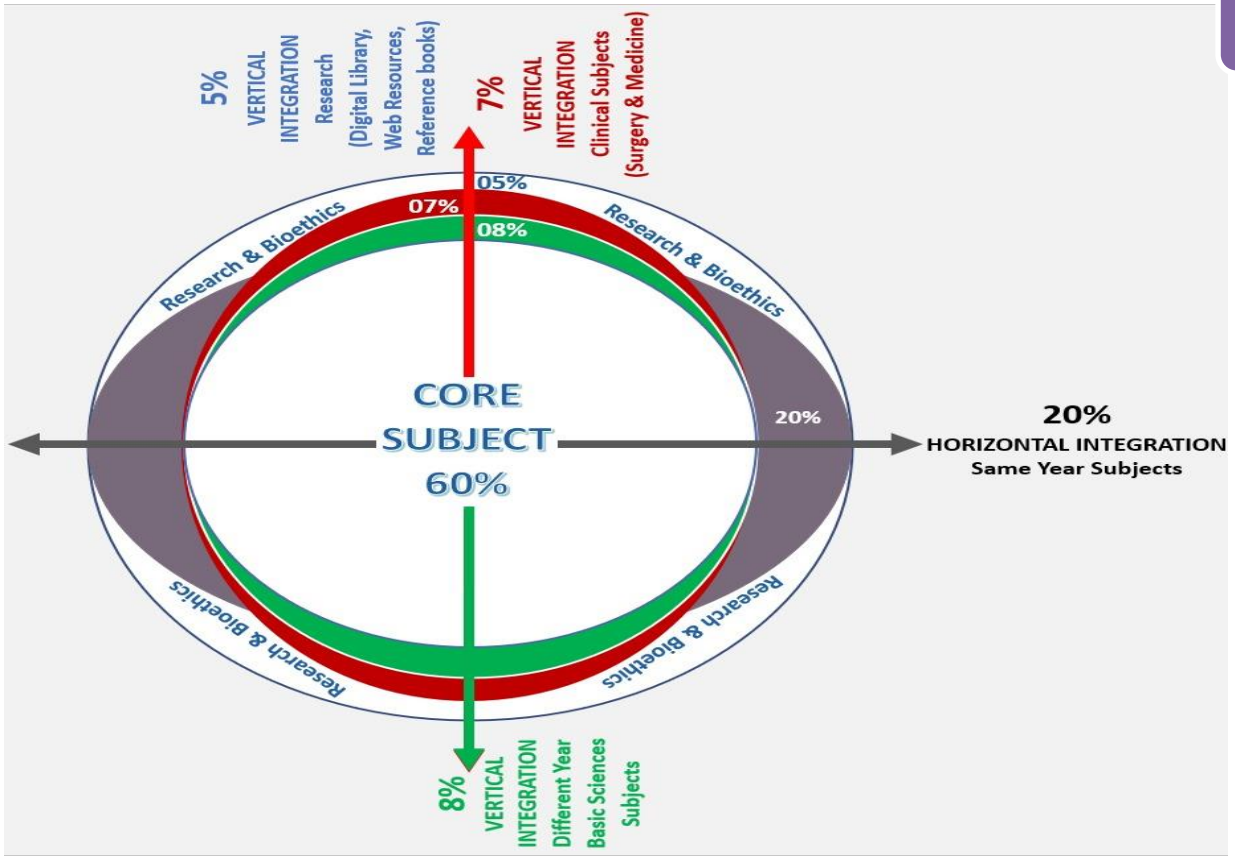
Motto



Vision; The Dream/Tomorrow

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Professor Umar Model of Integrated Lecture



60% CORE SUBJECT

20% HORIZONTAL INTEGRATION Physiology biochemistry

8% VERTICAL INTEGRATION Pathology pharmacology

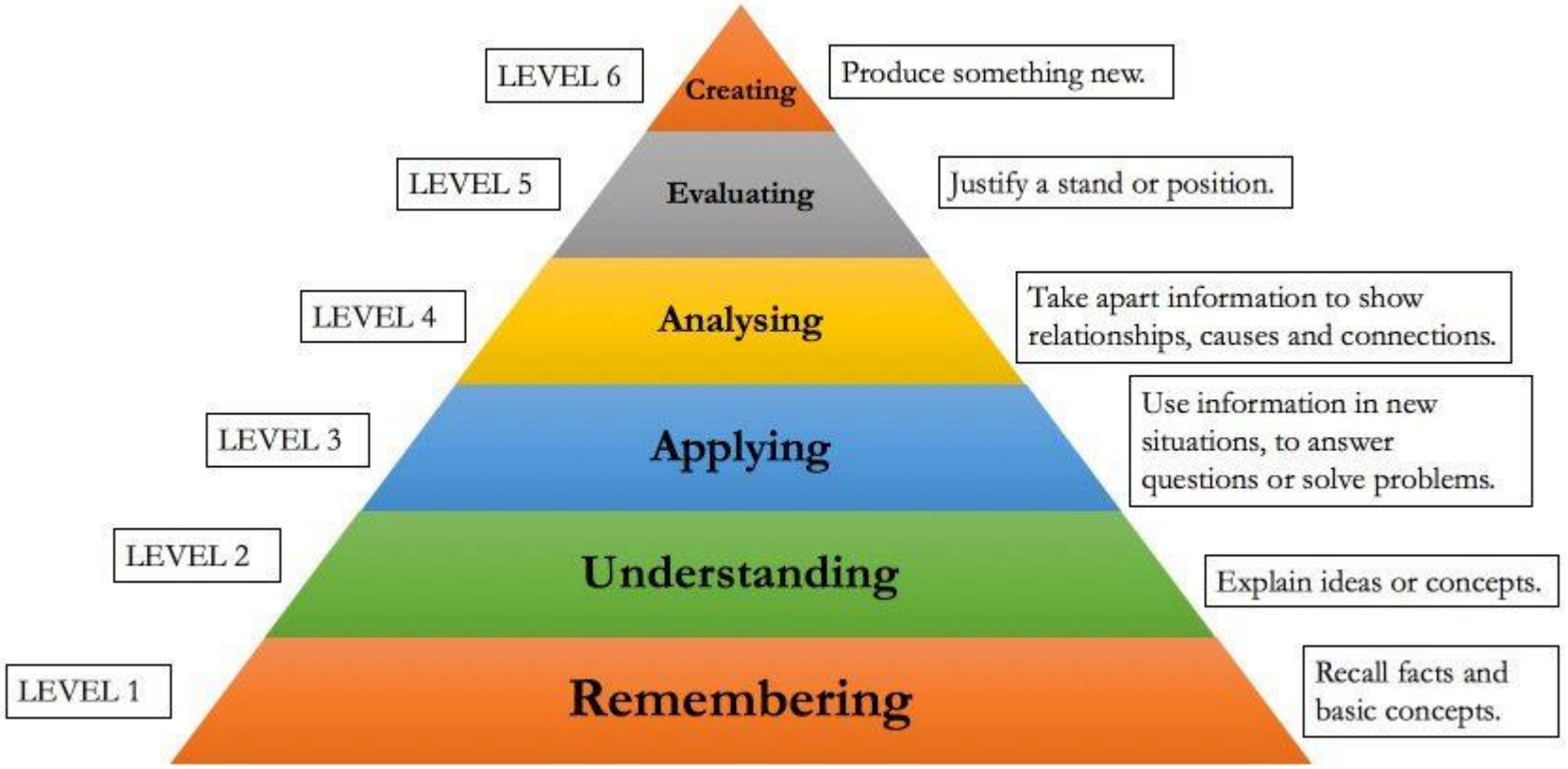
7% VERTICAL INTEGRATION Clinical integration

5% VERTICAL INTEGRATION Research, professionalism Ethics Digital library

BLOOM'S TAXONOMY : DOMAINS OF LEARNING

Sr. #	Domain of learning	Abbreviation	Levels of the domain	Meaning
1	cognition	C	C1	Recall / Remembering
2			C2	Understanding
3			C3	Applying / Problem solving
4	Psychomotor	P	P1	Imitation / copying
5			P2	Manipulation / Follows instructions
6			P3	Precision / Can perform accurately
7	Attitude	A	A1	Receiving / Learning
8			A2	Respond / Starts responding to the learned attitude
9			A3	Valuing / starts behaving according to the learned attitude

BLOOM'S TAXONOMY OF THE COGNITIVE DOMAIN



LEARNING OBJECTIVES

Sr. #	Learning Objective	Domain of Learning
1	To study different stages of hemostasis.	C1
2	To Describe formation and development of platelets.	C2
3	To Recognize different clotting factors & cascade of clotting.	C2
4	To Recognize the role of thrombin in coagulation.	C2
5	To correlate Clinically with different clotting and bleeding disorders.	C3
6	To diagnose and investigate patients with Von Willibrand disease	C3
7	Explain the process of fibrinolysis and function of plasmin.	C2

Horizontal integration

Biochemistry:-

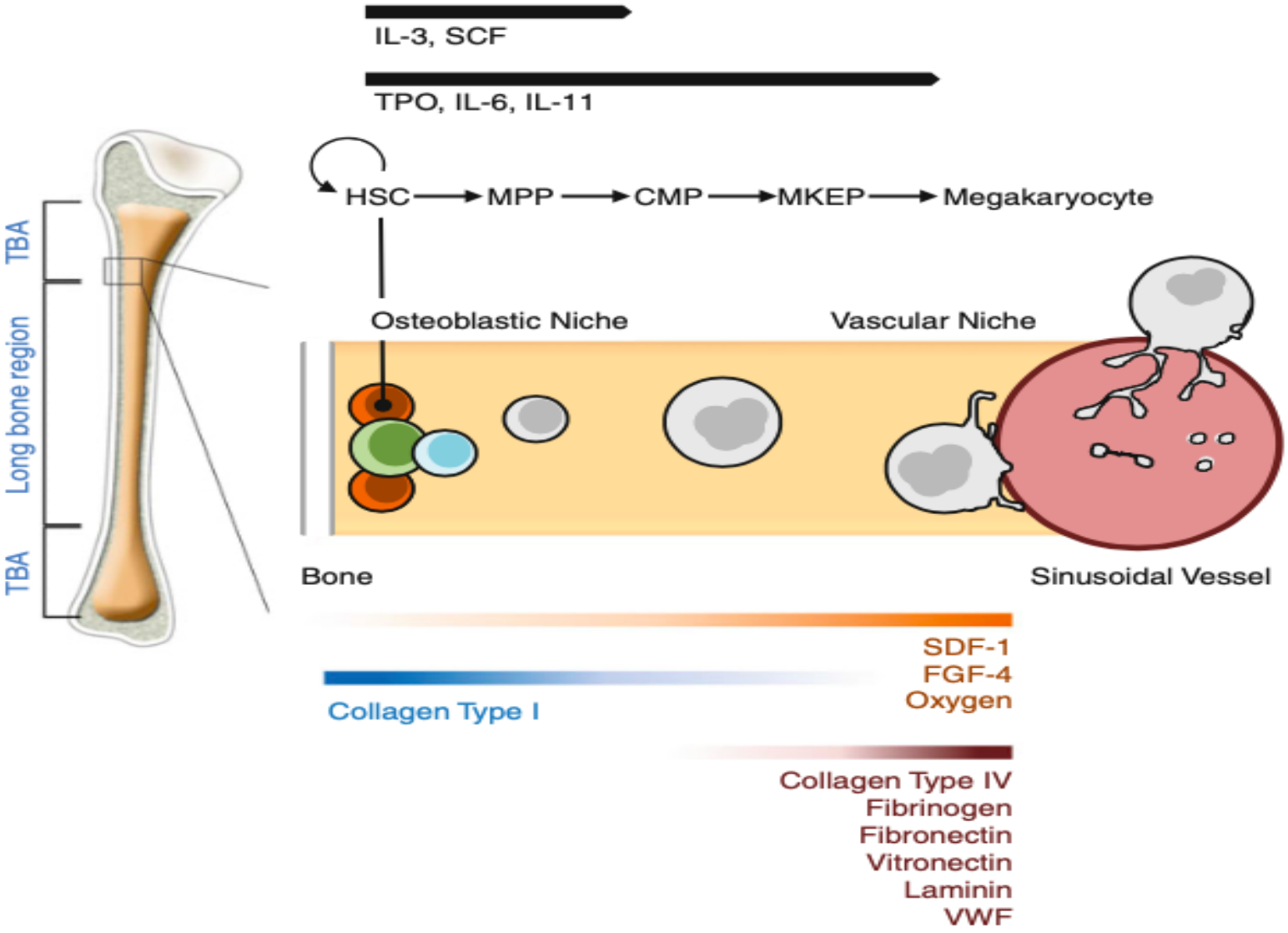
- Hematopoietic stem cells residing next to the endosteal bone surface produce progenitors that migrate to blood vessels at the center of the bone marrow cavity.

- Upon each division, a single daughter cell leaves the bone to proliferate and differentiate into various possible lineages.

- Differentiation down the megakaryocytic lineage is driven predominantly by TPO.
- TPO is supported by additional growth factors such as IL-3, SCF, IL-6, and IL-11.
- This process is assisted by the extracellular matrix proteins type I and type IV collagen, fibrinogen, fibronectin, vitronectin, laminin, and VWF.

- Soluble factors such as SDF-1 and FGF-4, as well as the presence of intact sinusoids in the bone marrow help target megakaryocytes to the vascular niche during maturation.

Biochemistry



Reference:- Wikipedia image of hemostasis biochemistry

- An elaborate intracellular program of nuclear amplification and protein production in maturing megakaryocytes precedes the mechanical extension of proplatelet elongations into the sinusoidal blood vessels of the bone marrow.

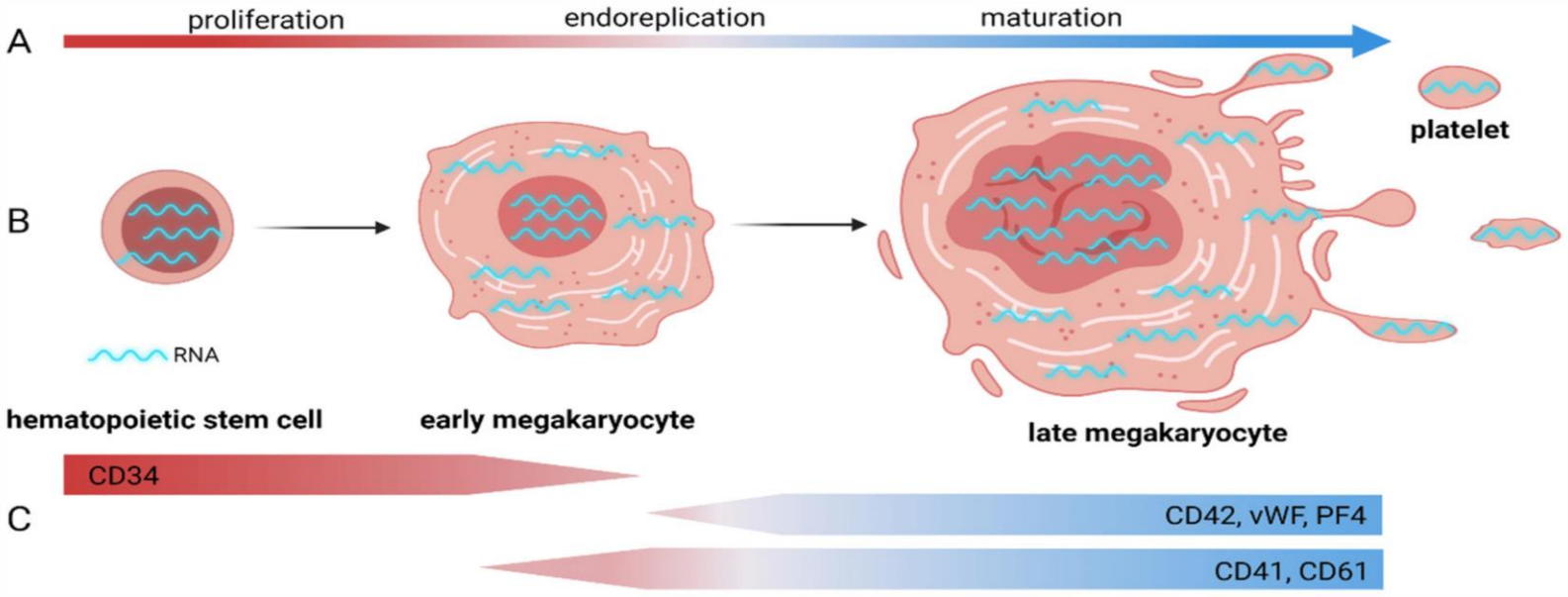
- Released proplatelets continue to mature in the vasculature and ultimately release individual platelets from their tips.

CMP common myeloid progenitor, HSC hematopoietic stem cell, IL interleukin, MKEP megakaryocyte erythroid progenitor, MPP multipotent progenitor stem cell, SCF stem cell factor, TBA trabecular bone area, TPO thrombopoietin.

Core Concept

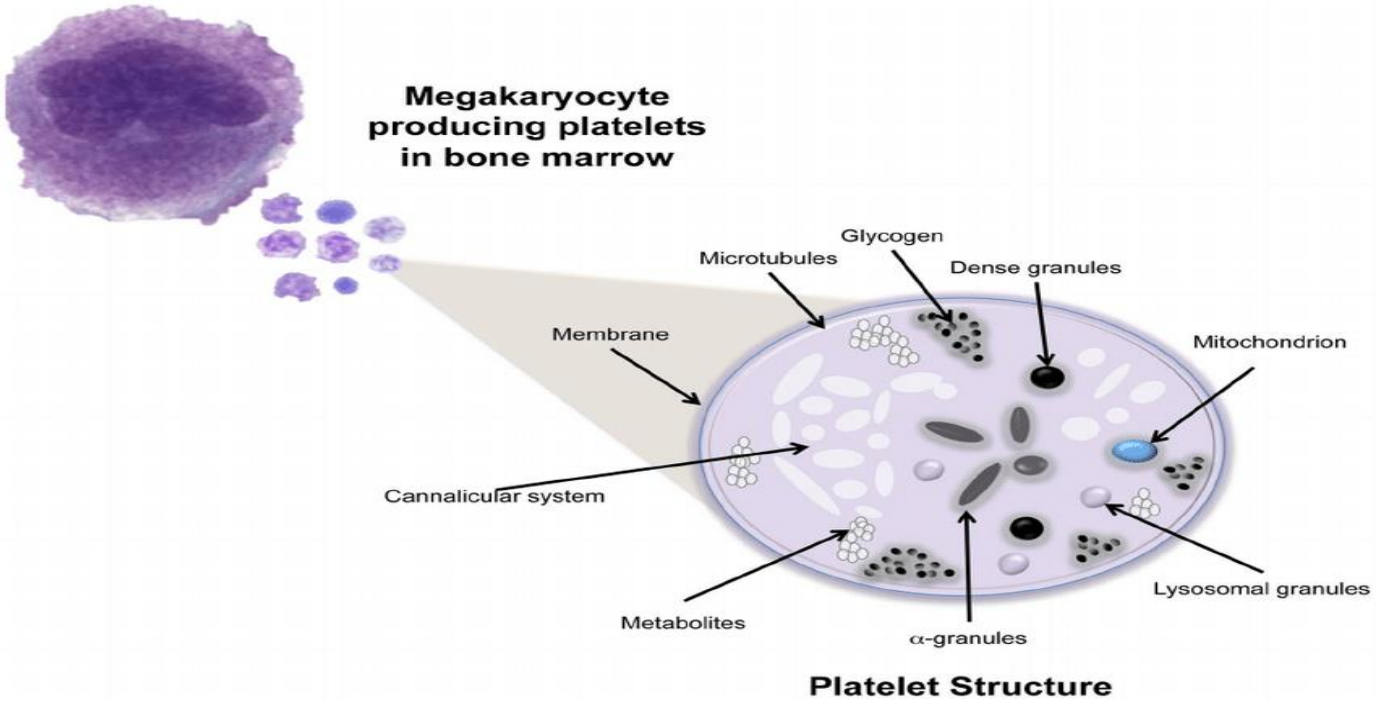
Introduction:-

- Megakaryocytes arise from pluripotent hematopoietic stem cells that are mostly restricted to the bone-proximal osteoblastic niche.
- These develop into burst- and colony-forming precursors, both of which express the CD34 antigen, and which continue to mature along an increasingly restricted lineage that culminates in the formation of precursors that develop into megakaryocytes.
- Differentiation is predominantly driven by TPO signaling.



Structure & Function:-

- 150-350,000 /µl,
- life span 8-12 days, no nucleus
- They are not true cells rather circulating fragments of cells
- Cytoplasm
- Actin and Myosin molecules
- Thrombosthenin For platelet contraction



Introduction:-

Alpha Granules:

- Von Willibrand Fctor (vWF)
- Fibrinogen
- PF4
- Beta Thromboglobulin
- PDGF
- Thrombospondin

Dense granules (Delta)

- ADP, ATP
- Serotonin
- Calcium

Hemostasis:-

Primary vs. Secondary vs. Tertiary

- Primary Hemostasis
  - Platelet Plug Formation
  - Dependent on normal platelet number & function
  - Initial Manifestation of Clot Formation
- Secondary Hemostasis
  - Activation of Clotting Cascade ➔ Deposition & Stabilization of Fibrin
- Tertiary Hemostasis
  - Dissolution of Fibrin Clot
  - Dependent on Plasminogen Activation

Hemostasis:-

It is the arrest of bleeding to avoid blood loss from the vessel. It usually, but not always, involves formation of a blood clot.

1. Vascular constriction

2. Formation of platelet plug

3. coagulation

4. Clot retraction and repair

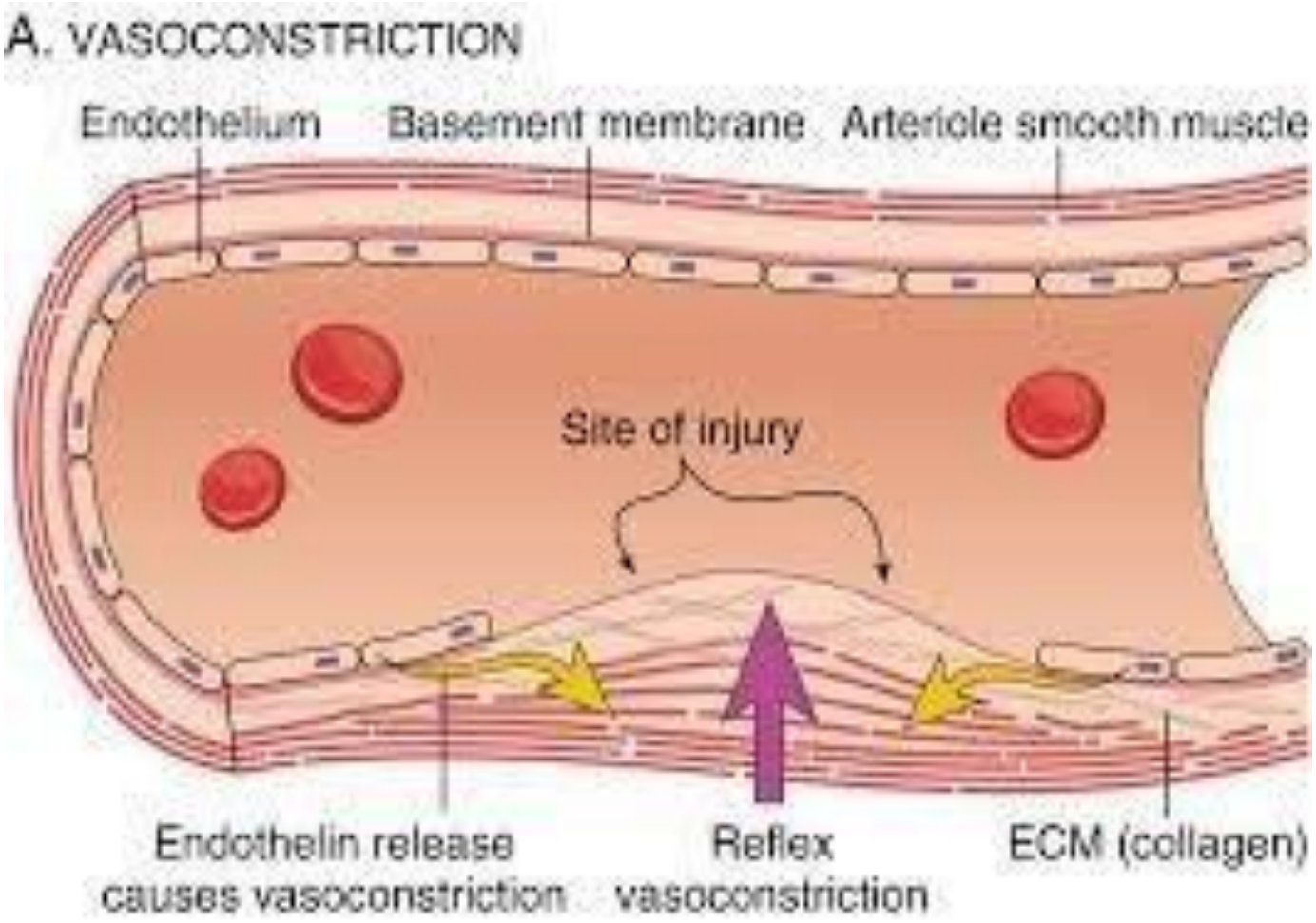
5. Fibrinolysis

1. Vascular constriction

- Immediately after injury, the blood vessel constricts and decreases the loss of blood from damaged portion, as a result from contraction of the smooth muscle of the vessel wall.
- Constriction blocks small blood vessels (arterioles and small arteries), thus preventing blood flow.
- When the blood vessels are cut, the endothelium is damaged and the collagen is exposed. Platelets adhere (von Willebrand factor) to this collagen and get activated.
- The activated platelets secrete serotonin and other vasoconstrictor substances which cause constriction of the blood vessels.
- Platelets release thromboxanes, which consider as vasoconstrictors and
- potent hypertensive agents; they facilitate platelet aggregation.

Vascular constriction

1. ENDOTHELIN
2. MYOGENIC MECHANISM
3. NOCICEPTOR ACTIVATION



2. Formation of platelet plug

- Platelets adhere to the exposed collagen fibers of the connective tissue of the damaged blood vessels.
- Platelets release adenosine diphosphate, thromboxanes which consider as **vasoconstrictors, and other chemicals that make other platelets to stick in the area, and to clump together to form a platelet plug.**
- Platelet plugs are very effective in **preventing blood loss in small blood vessels, and with fibrin threads form tight plugs.**

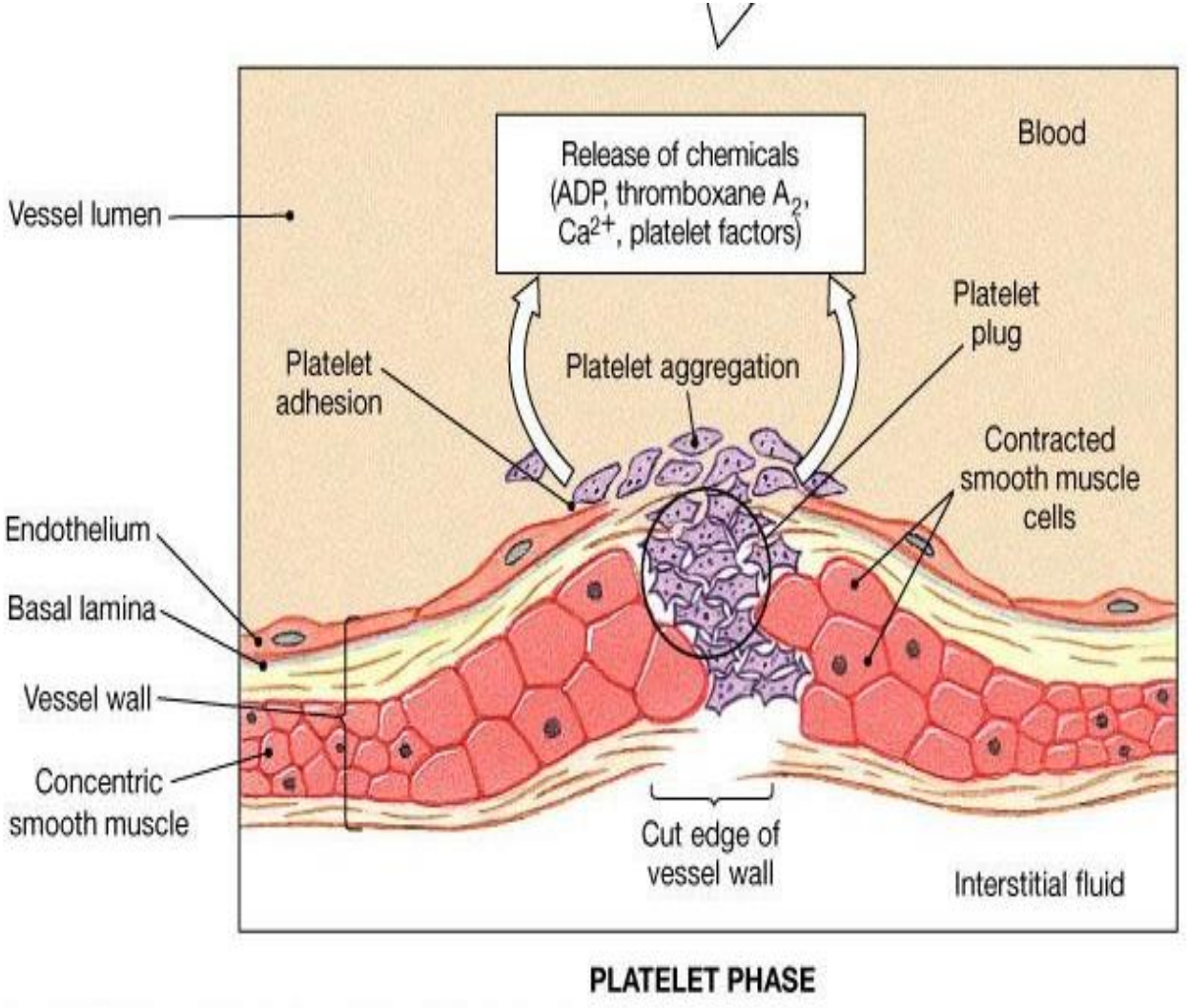
Formation of platelet plug

- Von willi brand factor Attachment with GP1b receptor

- Release of ADP, THROMBOXANE A2

chemtaxis

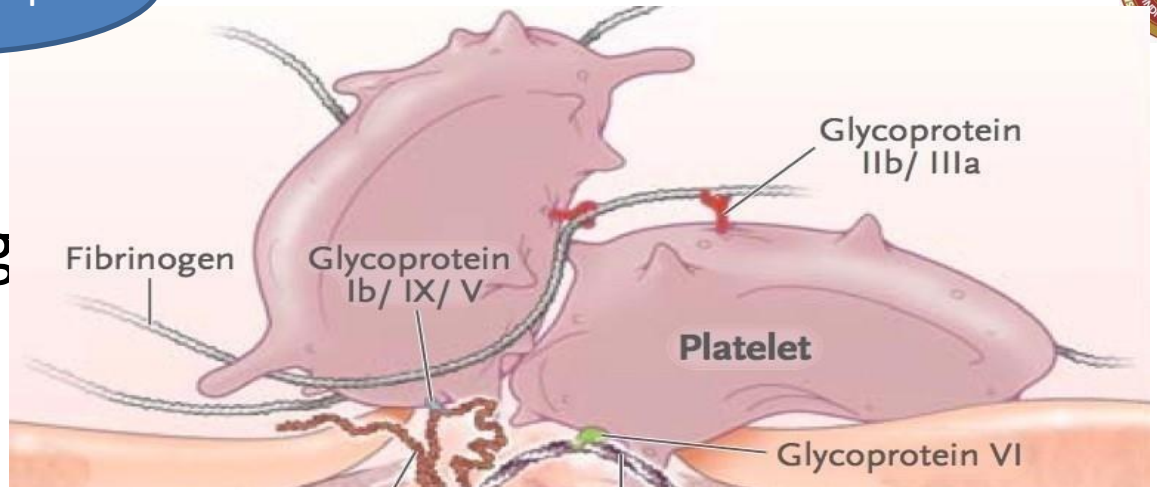
Platelets aggregation



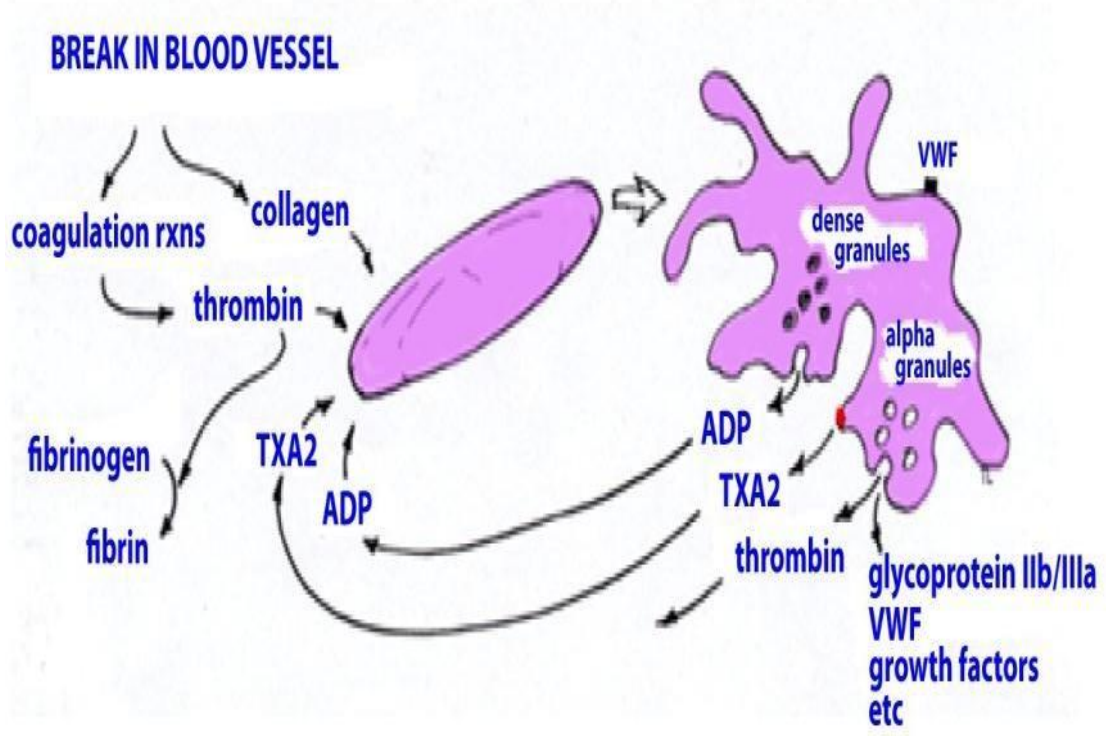
PLATELET PHASE

Core Concept

Platelet to platelet Adhesion forming plug



Role of Serotonin, TXA2 (Contraction Of smooth muscles)



3. COAGULATION OF BLOOD

- Through out life blood – in fluid state but when removed or shed or collected in container become jelly like – clot
- **Fluidity** – necessary for circulation.
- **Coagulation** – protect

CLOTTING FACTORS

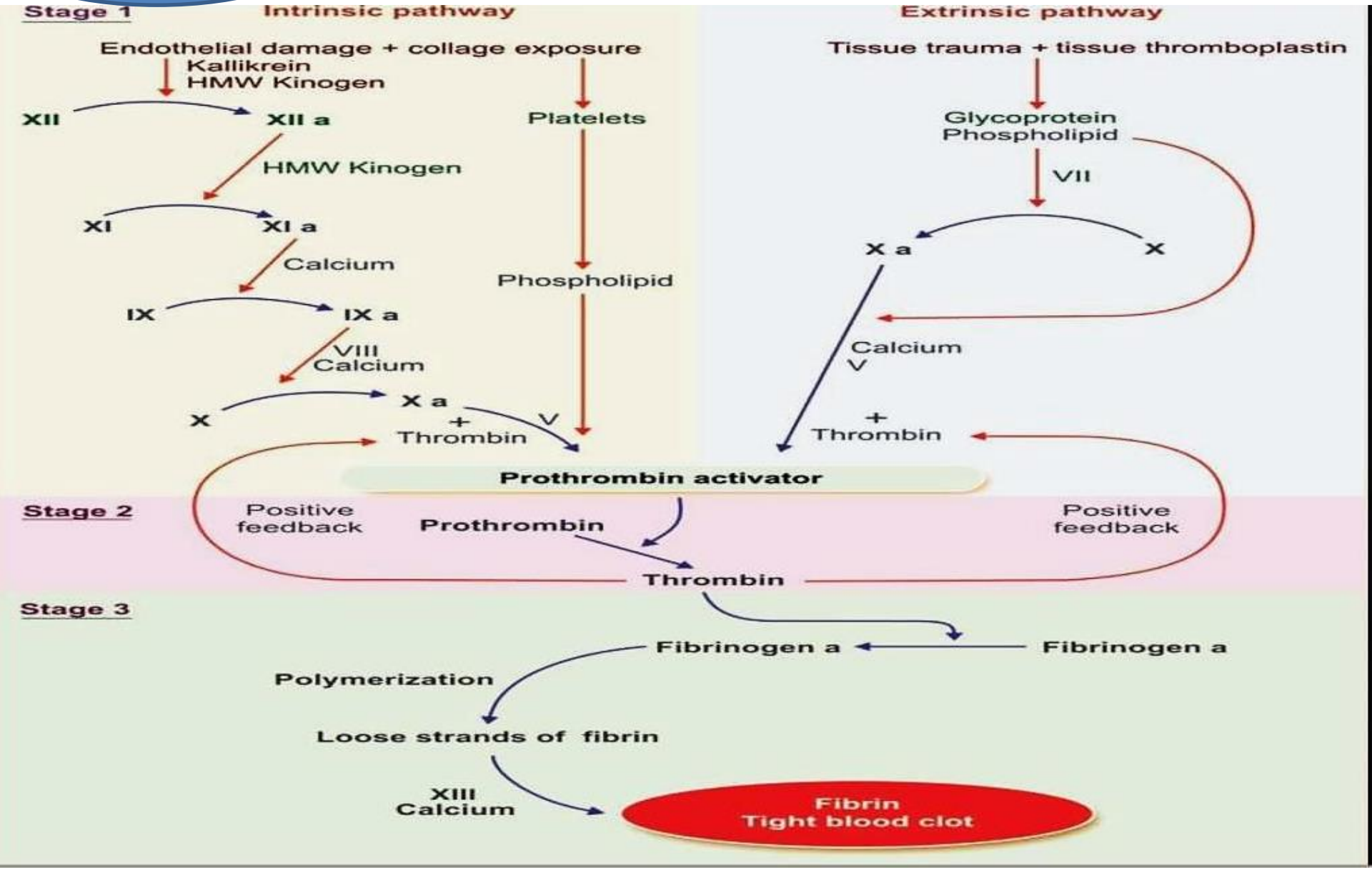
Clotting Factor	Synonyms
Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III; tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin; labile factor; Ac-globulin (Ac-G)
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B
Factor X	Stuart factor; Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
High-molecular-weight kininogen	Fitzgerald factor; HMWK (high-molecular-weight kininogen)
Platelets	

Enzyme Cascade Theory

Stages of Blood Clotting:-In general, blood clotting occurs in three stages:

- Formation of prothrombin activator
- Conversion of prothrombin into thrombin
- Conversion of fibrinogen into fibrin.

Core Concept



Reference:- Ganong physiology edition 23rd chapter 32 figure 13

STAGE 1: FORMATION OF PROTHROMBIN ACTIVATOR:

- Blood clotting commences with the formation of a substance called prothrombin activator, which converts prothrombin into thrombin.

Thus, formation of prothrombin activator occurs through two pathways:

i. Intrinsic pathway

ii. Extrinsic pathway.

STAGE 2: CONVERSION OF PROTHROMBIN INTO THROMBIN

Blood clotting is all about thrombin formation.

Once thrombin is formed, it definitely leads to clot formation.

STAGE 3: CONVERSION OF FIBRINOGEN INTO FIBRIN

The final stage of blood clotting involves the conversion of fibrinogen into fibrin by thrombin

4. Clot Retraction & Repair:-

- After the formation, the blood clot starts contracting.
- Release of platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF) for repair.
- The process involving the contraction of blood clot and oozing of serum is called clot retraction.
- Contractile proteins, namely Actin, Myosin and Thrombosthenin in the cytoplasm of platelets are responsible for clot retraction.

5. Fibrinolysis:-

- Lysis of blood clot inside the blood vessel is called fibrinolysis.
- It helps to remove the clot from lumen of the blood vessel.
- This process requires a substance called plasmin or fibrinolysin.

Why no clot formation in my blood in normal state?

1. Thrombomodulin activates protein C

- Protein C
- Inactivates inhibitor of TPA
- Increases Plasmin formation + inhibits factor II

2. Nitric oxide and Prostaglandin i-2 inactivates platelets

Continued:-

3. Heparin sulphate Activates antithrombin-3 which inhibits factor II, IX, X.

4. Continuous circulation of blood.

5. Smooth endothelial lining of the blood vessels.

Clotting Time:-

Test for **intrinsic system**

- Simple test but takes time and rarely done now

Method:

Venous blood is taken and placed on glass test tube at 37°C and it observed at time intervals until clotting occurs

- Normal blood takes 5-10min to clot
- Longer periods leads to Coagulation defects (e.g. Hemophilia)

Bleeding Time:-

Provides assessment of platelet count and function

Method:

It is determined by noting time at which blood coming out a small cut, no longer forms a spot on a piece of filter paper placed in contact with cut surface

The normal range from 1-9 min

Bleeding time is increased in thrombocytopenia, DIC & Aspirin toxicity.

Prothrombin Time (PT):-

Measures effectiveness of the extrinsic pathway.

Method:

An excess of tissue factor and Ca2+ ions are added to diluted plasma containing citrate (anticoagulant) and then the time taken for the mixture to clot is measured.

High PT refers to low levels of thrombin.

Refers to liver disease due to deficiency of FIBRINOGEN, PROTHROMBIN, FACTOR V, VII, X.

NORMAL VALUE = 10-15 seconds

Activated Partial thromboplastin Time (APPT):-

Measures effectiveness of the INTRINSIC pathway.

Method:

Calcium chloride and Ca2+ ions added to diluted plasma containing anticoagulant and then the time taken for the mixture to clot is measured.

High APPT monitors Heparin Therapy.

Refers to liver disease due to deficiency of FACTOR VIII, IX, XI, XII.

The international normalized ratio (INR) is the PT expressed as a ratio of the control used by the specific laboratory (usually for monitoring of warfarin therapy)

Vertical integration

Disseminated Intravascular Coagulation (DIC)

Massive Activation of coagulation that overwhelms control mechanisms → thrombosis acute consumption of coagulation factors & platelets leads to Bleeding.

Trauma, shock, infection, malignancy (especially APML), Obstetric complications. Common as well in the critically ill patients.

INVESTIGATIONS (DIC)

- PT and APTT **are elevated**
- **Decreased** level of fibrinogen (may be normal because of acute phase)
- Positive D-Dimer/FDP7
- **Decreased** level of platelets,
- Positive Schistocytes
- High Lactate Dehydrogenase (LDH)
- Low Haptoglobin

Diagnosis of exclusion, treat the underlying cause! You can't do anything else!

TREATMENT:-
(DIC)

There is No treatment for Disseminated Intravascular Coagulation.

- Treat underlying process
- Fresh Frozen Plasma
- Cryoprecipitate (Goal Fibrinogen > 100 mg/dL)
- Platelets concentrate

List of Clotting Disorders Table

Coagulation disorders	*Congenital*: Haemophilia A, Haemophilia B (Christmas disease) and Von Willebrand's disease. *Acquired*: Anticoagulants, liver disease, DIC, vit K deficiency.
Vascular defects	*Congenital*: Connective tissue disease (Ehlers-Danlos syndrome), Osler-Weber-Rendu syndrome. *Acquired*: Senile purpura, infections, steroids, scurvy.
Platelet defects **1. Platelet number defects**	Decrease marrow production: Aplastic anaemia, marrow infiltration (leukaemia, myeloma), marrow suppression (cytotoxic drugs, radiotherapy). Excessive destruction: immune thrombocytopenic purpura (ITP), SLE, CLL, heparin treatment, viruses. Thrombotic thrombocytopenic purpura (TTP), sequestration (as in hypersplenism).
2. Platelet structural defects	Myeloproliferative disease, increase urea, Von Willebrand's disease, Bernard-Soulier (giant platelet) syndrome, alcoholism, drug-induced (Aspirin, NSAID).
Fibrinolytic defects	DIC and streptokinase treatments.

REFERENCE = **Robins Pathology Basics, 10th Edition**

Biomedical Ethics

BREAKING BAD NEWS:-

The aim for any health-professional is to use their skills to deliver bad news clearly, honestly and sensitively in order that patients can both understand and feel supported.

6 STEPS STRATEGY:-

Setting up and starting. Mentally rehearse and arrange for privacy.

Perception. Elicit the patient's perspective.

Invitation. Ask the patient what they would like to know.

Knowledge. Provide information in small pieces.

Emotions. Recognize and empathize with the patient's emotions.

Strategy and summary. Set out a medical plan of action.

Step 1> Setting Up the Interview:-

The aim of this is to get the physical context right, reserve privacy, avoid interruption, to help patients listen and understand, respect confidentiality and provide support.

WHAT? Make sure you have checked all the available information and have test results (including getting the right patient!) Decide general terminology to be used

WHERE? Arrange for some privacy,

WHO? Should break the news, should other staff be there or significant others?

STARTING OFF? Introductions and appropriate opening

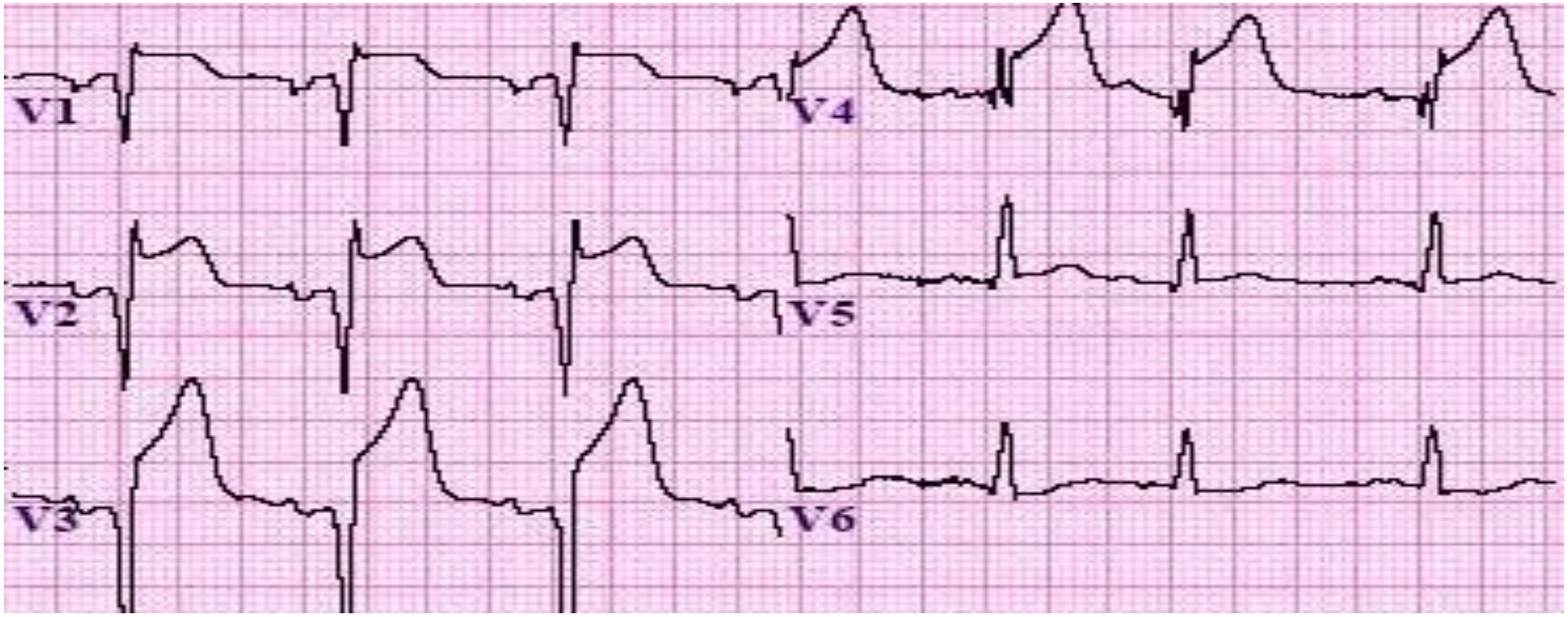
Brain Storming

Question & Answer

Brain Storming

Clinical Scenario

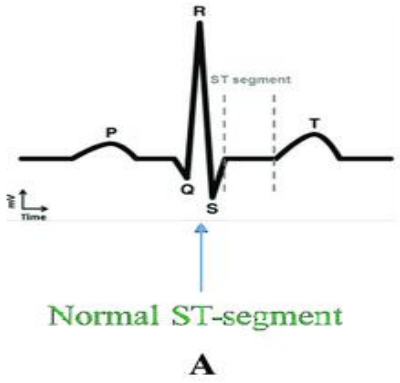
A 60-year-old male with a past medical history of hypertension, hyperlipidemia, and smoking presents to the emergency department with acute onset chest pain that radiates to his left arm and is associated with shortness of breath and diaphoresis. The patient is diagnosed with an ST-segment elevation myocardial infarction (STEMI) based on the electrocardiogram (ECG) findings. The emergency team decides to administer tissue plasminogen activator (TPA) promptly.

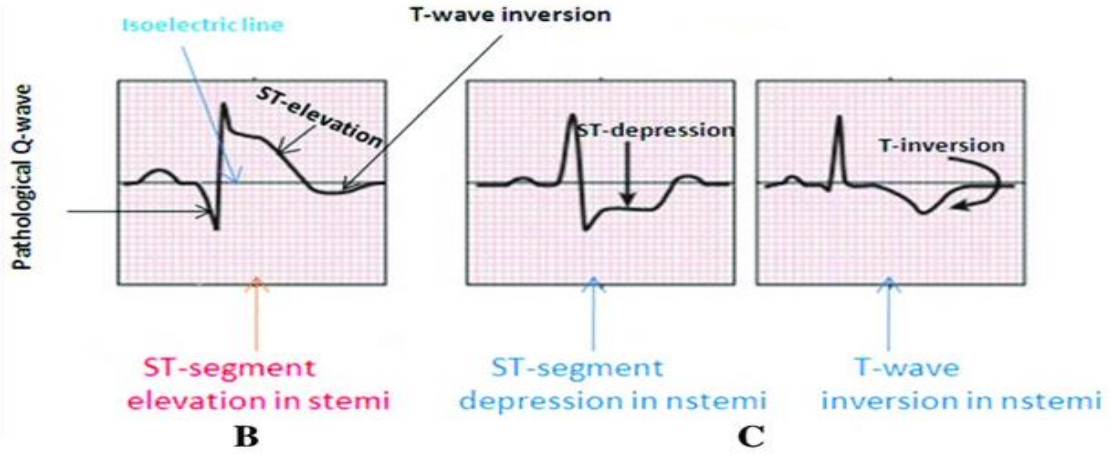


Brain Storming

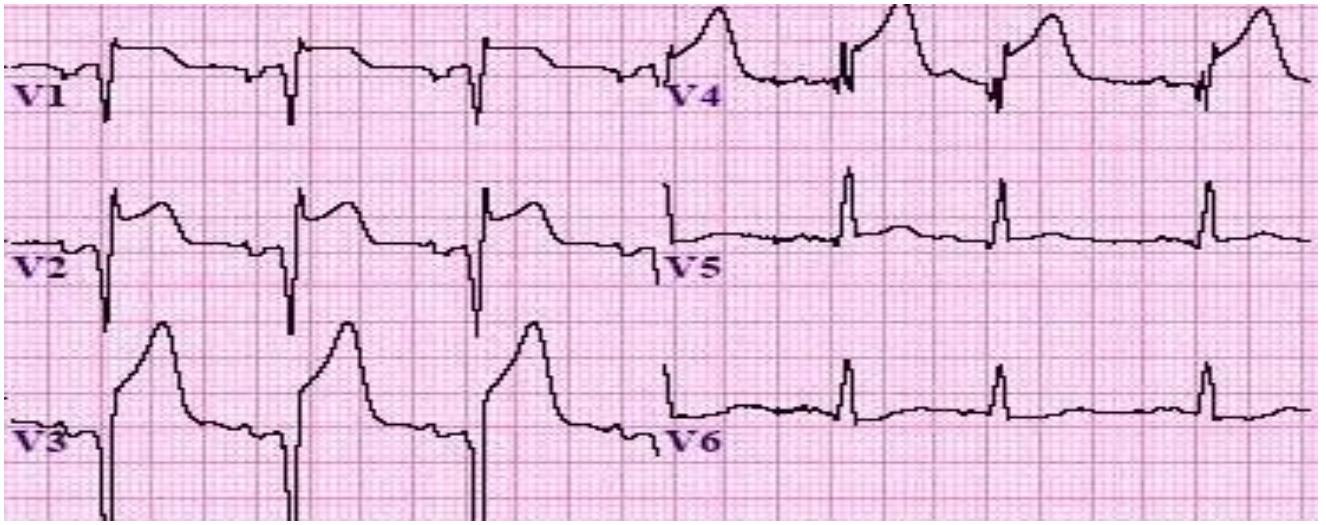
Clinical Scenario

Changes Seen in Myocardial Infarction ECG.





Identify the changes In this ECG of the patient Given in the scenario.



Question Related to Scenario

Question 1 : Why is tissue plasminogen activator (TPA) administered in this patient with a STEMI?

Answer:

Tissue plasminogen activator (TPA) is administered in patients with ST-segment elevation myocardial infarction (STEMI) to help dissolve the blood clot (thrombus) that is causing the occlusion of a coronary artery. By breaking down the clot, TPA helps to restore blood flow to the affected area of the heart muscle, reducing the extent of myocardial damage and improving the patient's prognosis.

Question Related to Scenario

Question 2 : What is the mechanism of action of TPA analogue drugs?

Answer:

1. **Binding to Fibrin:** TPA analog drugs specifically target fibrin, which is the structural component of blood clots. They have a higher affinity for fibrin within the clot than for fibrinogen, which circulates in the blood.
2. **Conversion of Plasminogen to Plasmin:** Once bound to fibrin, TPA analog drugs facilitate the conversion of plasminogen (an inactive precursor) into its active form, plasmin.
3. **Fibrin Clot Dissolution:** Plasmin generated at the site of the clot starts cleaving the fibrin strands, leading to the dissolution of the fibrin clot into smaller fragments.
4. **Inhibition of Clotting Factors:** TPA analog drugs can also activate the intrinsic coagulation pathway, which leads to the inhibition of some clotting factors (e.g., factor VIII and factor V). This further enhances fibrinolysis and prevents new clot formation.

Question Related to Scenario

Question 3 : What are the Contraindications of giving TPA analogue drugs to the patients?

Answer:

Treatment plan for the MI patient includes TPA analogue drugs, it is contraindicated in the patients with:-

- Active Internal Bleeding.
- History of Intracranial Hemorrhage.
- Suspected Aortic Dissection.
- Ischemic Stroke within the Past 3 Months.
- Severe Uncontrolled Hypertension.
- Bleeding Diathesis.
- Recent Trauma or Surgery.

Suggested Research Article

Related Research Article

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6549064/

J Stroke. 2019 May; 21(2): 160–174.
Published online 2019 May 31. doi: 10.5853/jos.2019.00584

PMCID: PMC6549064
PMID: 31161761

tPA Helpers in the Treatment of Acute Ischemic Stroke: Are They Ready for Clinical Use?

Jong S. Kim

Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Abstract

Go to: ▸

Tissue plasminogen activator (tPA) is the only therapeutic agent approved to treat patients with acute ischemic stroke. The clinical benefits of tPA manifest when the agent is administered within 4.5 hours of stroke onset. However, tPA administration, especially delayed administration, is associated with increased intracranial hemorrhage (ICH), hemorrhagic transformation (HT), and mortality. In the ischemic brain, vascular remodeling factors are upregulated and microvascular structures are destabilized. These factors disrupt the blood brain barrier (BBB). Delayed recanalization of the vessels in the presence of relatively matured infarction appears to damage the BBB, resulting in HT or ICH, also known as reperfusion injury. Moreover, tPA itself activates matrix metalloproteases, further aggravating BBB disruption. Therefore, attenuation of edema, HT, or ICH after tPA treatment is an important therapeutic strategy that may enable clinicians to extend therapeutic time and increase the probability of excellent outcomes. Recently,

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Link:https://www.topstudyworld.com/2020/05/access-hec-digital-library.html?m=1

REFERENCES

Books:-

1. Guyton and Hall text book of medical physiology, 14th edition
2. Human Physiology by Lauralee Sherwood, 9th edition
3. Ganong's Review of Medical Physiology, 26th Edition
4. Robins Pathology Basics, 10th Edition
5. Davidson Principles and Practice of Medicine.

Research:-

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6549064/

Images and Links:-

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Thank You!