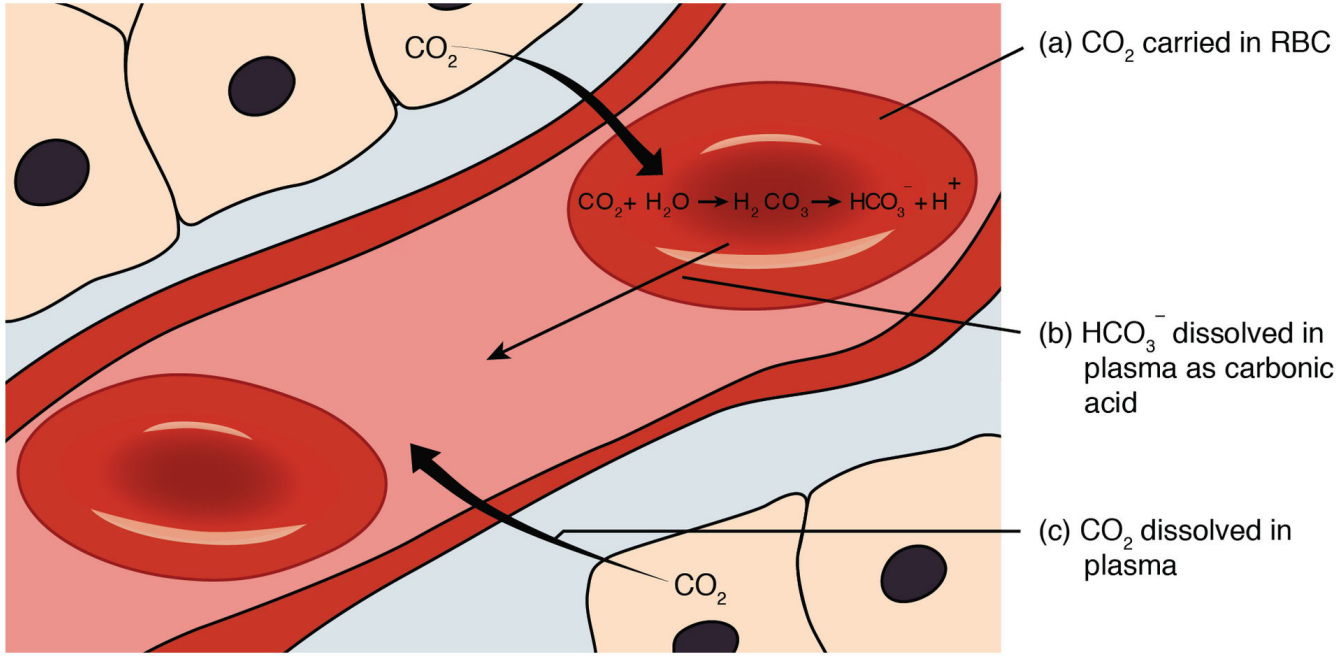
pH in the blood

The Bicarbonate buffer system is an acid-base homeostatic mechanism involving the balance of carbonic acid (H2CO3), bicarbonate ion (HCO−3), and carbon dioxide (CO2) in order to maintain pH in the blood and duodenum, among other tissues, to support proper metabolic function.Catalyzed by carbonic anhydrase, carbon dioxide (CO2) reacts with water (H2O) to form carbonic acid (H2CO3), which in turn rapidly dissociates to form a bicarbonate ion (HCO−3) and a hydrogen ion (H+) as shown in the following reaction:

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows HCO_3^- + H^+$$

As with any buffer system, the pH is balanced by the presence of both a weak acid (for example, H2CO3) and its conjugate base (for example, HCO−3) so that any excess acid or base introduced to the system is neutralized.
Failure of this system to function properly results in acid-base imbalance, such as acidemia (pH<7.35) and alkalemia (pH>7.45) in the blood



Regulation of pH

As calculated by the Henderson–Hasselbalch equation, in order to maintain a normal pH of 7.4 in the blood (whereby the pKa of carbonic acid is 6.1 at physiological temperature), a 20:1 bicarbonate to carbonic acid must constantly be maintained; this homeostasis is mainly mediated by pH sensors in the medulla oblongata of the brain and probably in the kidneys, linked via negative feedback loops to effectors in the respiratory and renal systems. In the blood of most animals, the bicarbonate buffer system is coupled to the lungs via respiratory compensation, the process by which the rate of breathing changes to compensate for changes in the blood concentration of CO_2. By Le Chatelier's principle, the release of CO_2 from the lungs pushes the reaction above to the left, causing carbonic anhydrase to form CO_2 until all excess acid is removed. Bicarbonate concentration is also further regulated by renal compensation, the process by which the kidneys regulate the concentration of bicarbonate ions by secreting H^+ ions into the urine while, at the same time, reabsorbing HCO_3^- ions into the blood plasma, or *vice versa*, depending on whether the plasma pH is falling or rising, respectively.

Blood Coagulation

Introduction: The coagulation pathway is a cascade of events that leads to hemostasis. The intricate pathway allows for rapid healing and prevention of spontaneous bleeding. Two paths, intrinsic and extrinsic, originate separately but converge at a specific point, leading to fibrin activation. The purpose is to ultimately stabilize the platelet plug with a fibrin mesh.

Function:

The function of the coagulation pathway is to keep hemostasis, which is the blockage of a bleeding or hemorrhage. Primary hemostasis is an aggregation of platelets forming a plug at the damaged site of exposed endothelial cells. Secondary hemostasis includes the two main coagulation pathways, ***intrinsic and extrinsic**, that meet up at a point to form the common pathway. The common pathway ultimately activates fibrinogen into fibrin. These fibrin subunits have an affinity for each other and combine into fibrin strands that bind the platelets together, stabilizing the platelet plug

* The **extrinsic pathway** is activated by external trauma that causes blood to escape from the vascular system. ... The **intrinsic pathway** is activated by trauma inside the vascular system, and is activated by platelets, exposed endothelium, chemicals, or collagen.

Mechanism

The mechanism by which coagulation allows for hemostasis is an intricate process that is done through a series of clotting factors. **The intrinsic pathway consists of factors I, II, IX, X, XI, and XII. The extrinsic pathway consists of factors I, II, VII, and X.** Factor **VII is called *stable factor*.**

The common pathway consists of factors I, II, V, VIII, X. The factors circulate through the bloodstream as zymogens and are activated into serine proteases.

These serine proteases act as a catalyst to cleave the next zymogen into more serine proteases and ultimately activate fibrinogen. **The following are serine proteases: factors II, VII, IX, X, XI and XII. These are not serine proteases: factors V, VIII, XIII. The intrinsic pathway is activated through exposed endothelial collagen,** and **the extrinsic pathway is activated through tissue factor released by endothelial cells after external damage**.

CLOTING FACTORS	
Factors I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue Thromboplastin
Factor IV	Calcium lons
Factor V	Labile Factor
Factor VII	Stable Factor
Factor VIII	Antihemophilic Factor
Factor IX	Christimas Factor
	Plasma Thromboplastin
	Component (PTC)
Factor X	Sturt-Prower Factor
Fa ctor XI	Plasma Thromboplastin
	Antecedent (PTA)
Factor XII	Hageman Factor
Factor XIII	Fibrin Stabilizing Factor

Process Of Blood Coagulation

Blood clotting mechanism → Three stages →
- Vascular spasm
- Platelets plug formation
- Coagulation

Stages of blood clotting →
- Formation of prothrombinase:
  1. Intrinsic pathway
  2. Extrinsic pathway
- Prothrombine → Thrombine (enzyme)
- Fibrinogen (soluble) → Fibrin (insoluble)

Intrinsic Pathway

This pathway is the longer pathway of secondary hemostasis. It begins with the activation of Factor XII (a zymogen, inactivated serine protease) which becomes Factor XIIa (activated serine protease) after exposure to endothelial collagen. Endothelial collagen is only exposed when endothelial damage occurs.

Factor XIIa acts as a catalyst to activate factor XI to Factor XIa. Factor XIa then goes on to activate factor IX to factor IXA. Factor IXa goes on to serve as a catalyst for turning factor X into factor Xa.

This is known as a cascade. When each factor is activated, it goes on to activate many more factors in the next steps. As you move further down the cascade, the concentration of that factor increases in the blood. For example, the concentration of factor IX is more than that of factor XI.

When factor II is activated by either intrinsic or extrinsic pathway, it can reinforce the intrinsic pathway by giving positive feedback to factors V, VII, VIII, XI, XIII. This makes factor XII less critical; patients can actually clot well without factor XII. **The intrinsic pathway is clinically measured as the partial thromboplastin time (PTT).**

Summaries

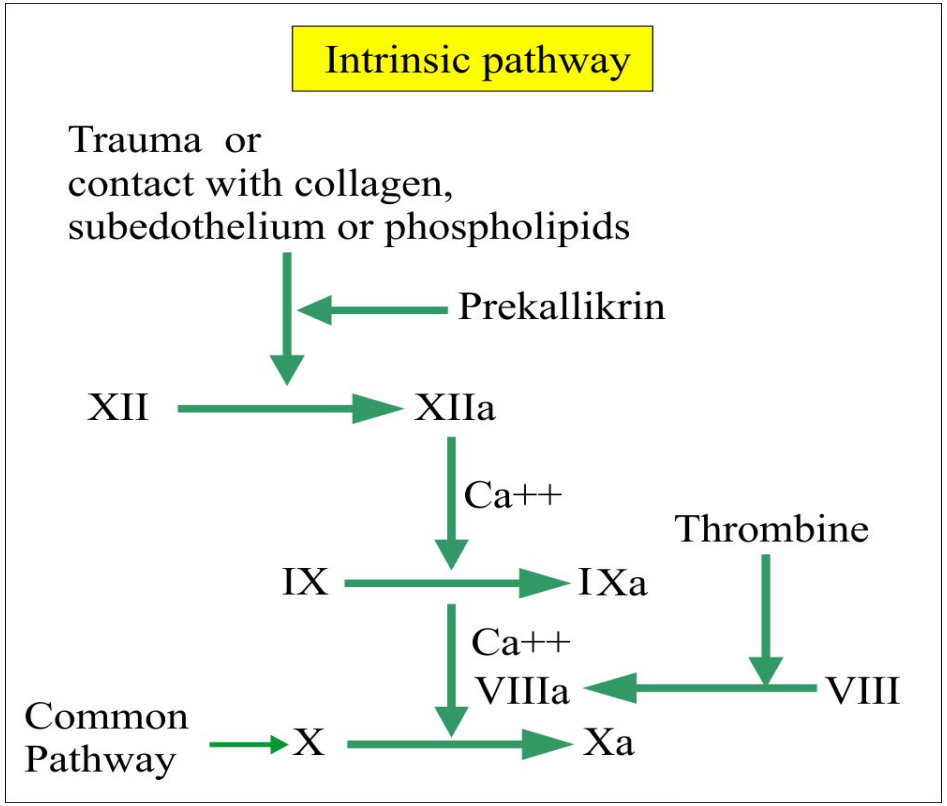
The Blood Clotting Pathways Are:

The intrinsic pathway where the factor XII and other proteins form a comp the injured endothelium.

1. XII→ XIIa → XI to XIa complex form of VIII + XI + X
2. Activated X is formed.
3. Then the common pathway starts.

Intrinsic pathway depends upon:

1. Vessel injury
2. Collagen contact
3. Factor XII, XI, IX, VIII, Ca



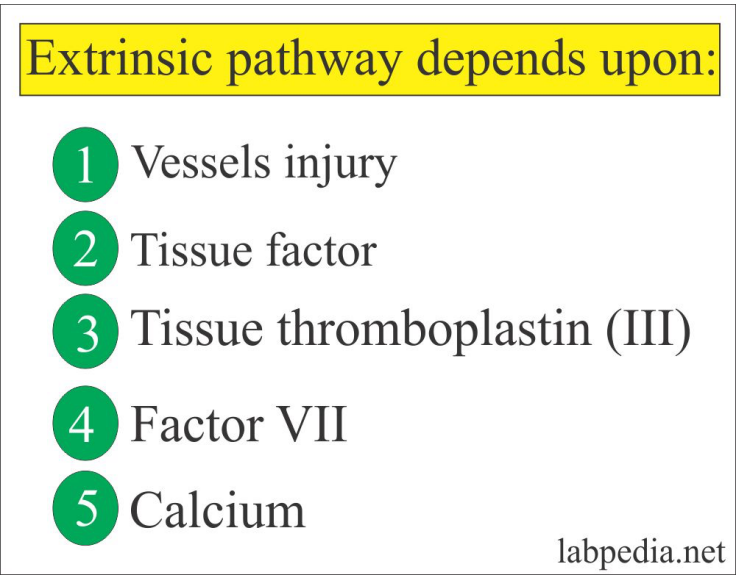
Extrinsic Pathway

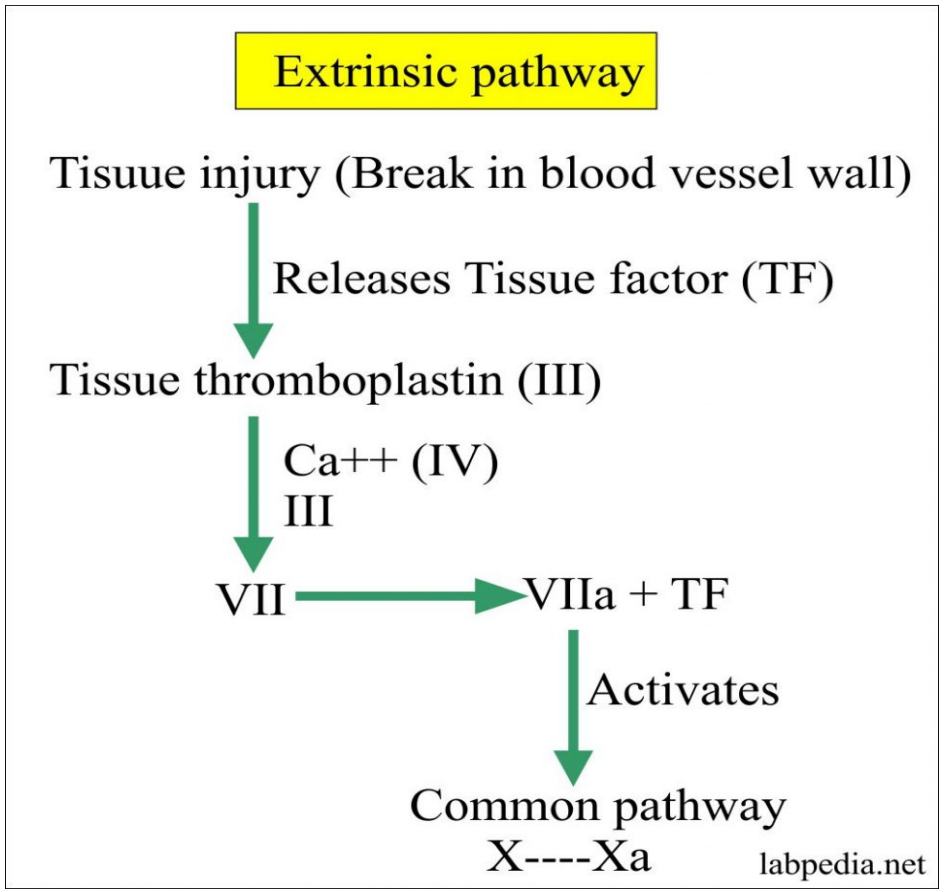
Extrinsic Pathway

The extrinsic pathway is the shorter pathway of secondary hemostasis. Once the damage to the vessel is done, the endothelial cells release tissue factor which goes on to activate factor VII to factor VIIa. Factor VIIa goes on to activate factor X into factor Xa. This is the point where both extrinsic and intrinsic pathways become one. The extrinsic pathway is clinically measured as the prothrombin time (PT).

The extrinsic pathway where there is a complex formation between Tissue factor (factor III or thromboplastin) and factor VII.

1. Activated factor VIIa forms which stimulate factor X.
2. 2. Alternately factor VIIa activates factor IX and X.





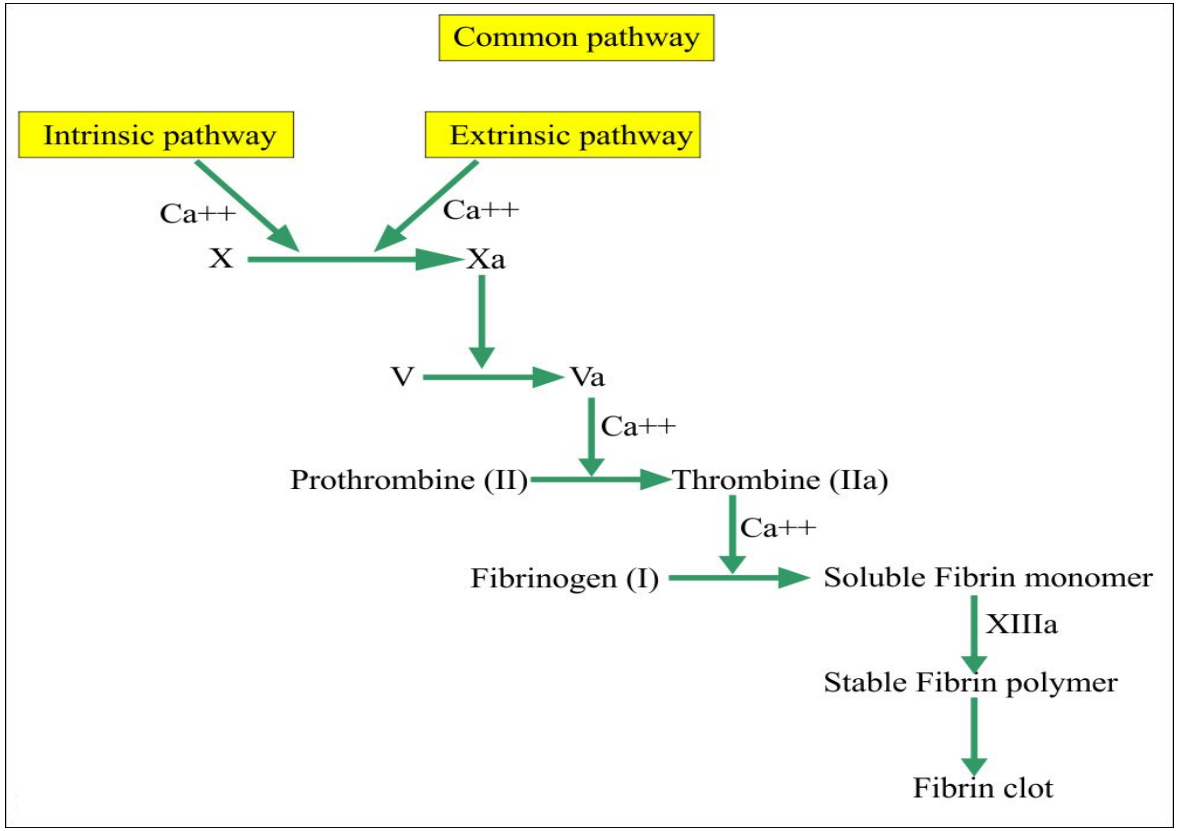
Common pathway

Common pathway Xa → Prothrombin to Thrombin in the presence of factor V, calcium, and phospholipids on the surface of platelets.

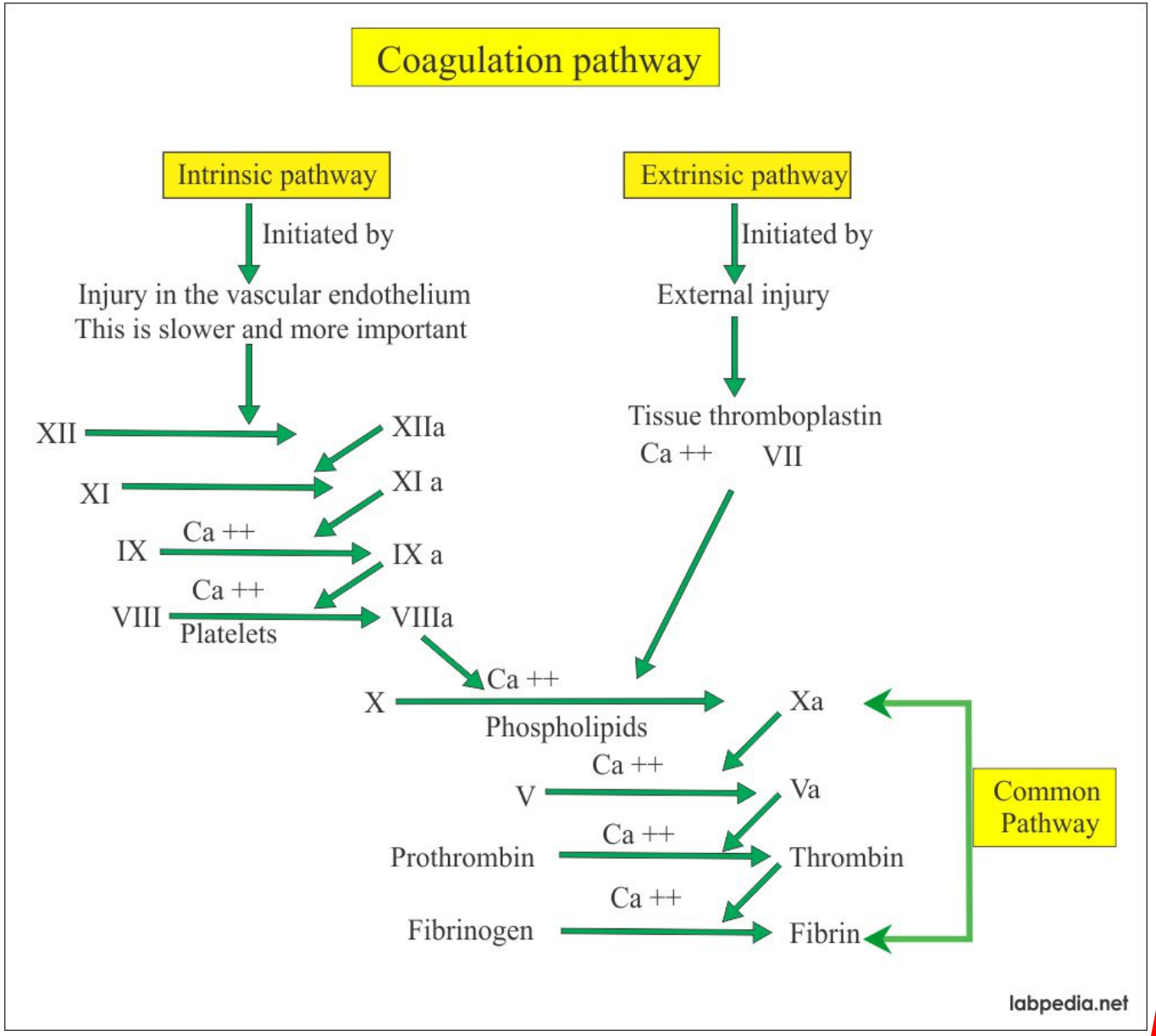
1. Thrombin → Fibrinogen → Fibrin → is polymerized into the **stable clot.**
2. Thrombin also activates factor VIII to stimulate platelet aggregation and fibrin polymerization.
3. Prothrombin is Vit K dependent factor.

Common Pathway depends upon:

1. Factor X
2. Prothrombin to Thrombin
3. Calcium
4. Factor XIII
5. Fibrinogen to Fibrin
6. Fibrin to stabilize the clot



Coagulation Pathway



Negative Feedback

To prevent over-coagulation, which causes widespread thrombosis, there are certain processes to keep the coagulation cascade in check. As thrombin acts as a procoagulant, it also acts as a negative feedback by activating plasminogen to plasmin and stimulating the production of antithrombin (AT). Plasmin acts directly on the fibrin mesh and breaks it down. AT decreases the production of thrombin from prothrombin and decreases the amount of activated factor X.

Normal Values Of Clotting Factors

Factors	Normal value Source 1	Normal value Source 2	Normal value Source 3
Fibrinogen	Adult = 200 to 400 mg/dL Newborn = 125 to 300 mg/dL		200 to 400 mg/dL
	Quantitation minimum hemostatic level mg/dL		**Plasma concentration mg/dL**
Factor II (Prothrombin)	10 to 15 mg/dL	80 to 120 % of normal	10 to 15
Factor III (Thromboplastin)			
Factor IV (Ionized calcium)	4.60 to 5.08 mg/dL		
Factor V (Labile Factor)	5 to 10 mg/dL	50 to 150% of normal	0.5 to 1.0
Factor VI	Not existing		
Factor VII (Stable factor)	5 to 20 mg/dL	65 to 140% of normal	0.2
Factor VIII (Antihemophilic factor)	30 mg/dL	55 to 145% of normal	1.0 to 2.0
Factor IX (Christmas factor)	30 mg/dL	60 to 140% of normal	0.3 to 0.4
Factor X (Stuart factor)	8 to 10 mg/dL	45 to 155% of normal	0.6 to 0.8
Factor XI (Plasma thromboplastin)	25 mg/dL	65 to 135% of normal	0.4
Factor XII (Hageman factor)		50 to 150% of normal	2.9
Factor XIII (Fibrin-stabilizing factor)			2.5
Von Willebrand factor			1.0

Fibrinogen

1. **Fibrinogen Level Increased Is Seen In:**
    1. Acute inflammatory reactions.
    2. Trauma.
    3. Coronary heart disease.
    4. Cigarette smoking.
2. **Fibrinogen Decreased Level Is Seen In:**
    1. Liver diseases like hepatitis and cirrhosis.
    2. DIC (disseminated intravascular coagulopathy).
    3. Fibrinolysis.

Prothrombin

1. **The Decreased Level Is Seen In:**
    1. Vit.K deficiency.
    2. Liver disease.
    3. Oral anticoagulants.
    4. Circulating inhibitor or lupus-like anticoagulants.
    5. Decreased synthesis.

Factor V Deficiency:

1. Liver diseases.
2. Factor V inhibitor.
3. Myeloproliferative disorders.
4. DIC and fibrinolysis.
5. Mild decrease in the newborn.

Factor VII Deficiency:

1. Liver diseases.
2. Kwashiorkor.
3. Normal newborn.
4. treatment with coumarin-like drugs.

Factor VIII

1. **Factor VIII increased in:**
    1. Late normal pregnancy.
    2. Thromboembolic conditions.
    3. Liver diseases.
    4. Post-operative patients.
    5. Normal newborn.
    6. Rebound phenomenon after sudden stoppage of coumarin-like drugs.
2. **Factor VIII deficiency:**
    1. due to the presence of factor VIII inhibitors.
    2. DIC.
    3. Von Willebrand disease.
    4. Myeloproliferative disorders.

Factor IX Deficiency:

1. Liver diseases and cirrhosis.
2. Nephrotic syndrome.
3. Anticoagulant antibody formation.
4. Normal newborn.
5. Drugs like Dicoumarol.
6. DIC.
7. Vit K Deficiency.

Factor X Deficiency:

1. Vit K deficiency.
2. Liver Diseases.
3. Oral anticoagulants.
4. DIC.
5. Amyloidosis.
6. Normal newborn.

Factor XI Deficiency:

1. Liver diseases.
2. Intestinal malabsorption leading to Vit K deficiency.
3. DIC.
4. Newborn.

Factor XII Deficiency:

1. Nephrotic syndrome.
2. Liver diseases.
3. Chronic myelocytic leukemia.
4. Normal newborn.

Factor XIII Deficiency:

1. Postoperative patients.
2. Liver diseases.
3. In persistent increased fibrinogen level.
4. Acute myeloid leukemia.
5. DIC.
6. circulating anticoagulants.

Organs Involved

One of the organs intimately involved in the coagulation process is the liver. The liver is responsible for the formation of factors I, II, V, VII, VIII, IX, X, XI, XIII, and protein C and S. Factor VII is created by the vascular endothelium. Pathology to the liver can cause lack of coagulation factors and lead to hemorrhage. A decrease in coagulation factors typically means severe liver damage. Factor VII has the shortest half-life, leading to elevated PT(partial thromboplastin) first in liver disease. Coagulopathy in liver disease is treated with fresh frozen plasma.

Pathophysiology

Hemophilia A and B are inherited in an x-linked recessive pattern. In hemophilia A there is a deficiency in factor VIII. In hemophilia B there is a deficiency in factor IX.

Hemophilia C is an autosomal recessive mutation, where there is a deficiency in factor XI.

Factor V Leiden is a genetic mutation more prevalent in people European descent. This defect causes a state of hypercoagulability. The genetic mutation causes a defect in factor V such that protein C cannot inactivate it, allowing factor V to continuously activate downstream factors.

Deficiencies in protein C and S also can lead to hypercoagulable states due to an inability to appropriately inhibit factors V and VIII respectively.

Clinical Significance

PT and PTT evaluate the time it takes for the extrinsic and intrinsic pathways to take effect, respectively.
Mixing studies are done to determine whether a PT or PTT is elevated due to a factor deficiency or a factor inhibitor (antibodies to specific factors). It is done by mixing the patient's plasma with a control plasma. If the mixed plasma PT and PTT normalize, the PT and PTT prolongation is due to a factor deficiency. If they do not normalize, the prolongation is due to a factor inhibitor. An example of an inhibitor is lupus anticoagulant.

Vitamin K deficiency can lead to elevated PT and PTT. It can present as hemarthrosis, intramuscular bleeding, or gastrointestinal bleeding. Vitamin K deficiency is commonly seen in newborns due to the lack of gut colonization by bacteria. It also can be seen in malabsorption (cystic fibrosis, celiacs disease, Crohn disease).

Heparin is an anticoagulant used in hospital settings for deep venous thrombosis prophylaxis. Heparin binds and activates AT. AT goes on to inactivate thrombin and factor Xa.

Warfarin is used for long-term therapy in patients with atrial fibrillation to prevent a thrombus from forming in the left atrium. It acts by inhibiting epoxide reductase. Epoxide reductase is a critical component in coagulation factor production because it helps recycle Vitamin K. Without vitamin K more coagulation factors cannot be produced by the liver.

Clotting factors function

Clotting factor number	Clotting factor name	Function	Plasma half-life (h)	Plasma concentration (mg/L)
I	Fibrinogen	Clot formation	90	3000
II	Prothrombin	Activation of I, V, VII, VIII, XI, XIII, protein C, platelets	65	100
III	TF	Co factor of VIIa	-	-
IV	Calcium	Facilitates coagulation factor binding to phospholipids	-	-
V	Proacclerin, labile factor	Co-factor of X-prothrombinase complex	15	10
VI	Unassigned			
VII	Stable factor, proconvertin	Activates factors IX, X	5	0.5
VIII	Antihaemophilic factor A	Co-factor of IX-tenase complex	10	0.1
IX	Antihaemophilic factor B or Christmas factor	Activates X: Forms tenase complex with factor VIII	25	5
X	Stuart-Prower factor	Prothrombinase complex with factor V: Activates factor II	40	10
XI	Plasma thromboplastin antecedent	Activates factor IX	45	5
XII	Hageman factor	Activates factor XI, VII and prekallikrein		-
XIII	Fibrin-stabilising factor	Crosslinks fibrin	200	30
XIV	Prekallikerin (F Fletcher)	Serine protease zymogen	35	
XV	HMWK- (F Fitzgerald)	Co factor	150	
XVI	vWf	Binds to VIII, mediates platelet adhesion	12	10 μg/mL
XVII	Antithrombin III	Inhibits IIa, Xa, and other proteases	72	0.15-0.2 mg/mL
XVIII	Heparin cofactor II	Inhibits IIa	60	-
XIX	Protein C	Inactivates Va and VIIIa	0.4	-
XX	Protein S	Cofactor for activated protein C		-

HMWK – High molecular weight kininogen; vWf – Von Willebrand factor; TF – Tissue factor