Assessing Coagulation
The Coagulation System

The Platelet

1. Vascular injury allows reflex **vasoconstriction** with exposure of the subendothelial matrix and reduced local blood flow.
2. The starting point is the **attachment** of the soluble protein, **von Willebrand factor**, to the subendothelial matrix.
   Failure of this step may be due to
   1. Absence of von Willebrand factor - Autosomal Dominant and Recessive inheritance
   2. Malfunction of collagen - Scurvy

   Tests

   1. History and examination
   2. Ristocetin cofactor test for vWf
3. **Platelet adhesion**. Normal von Willebrand factor, when bound to the subendothelium, exposes multiple intrinsic binding sites for the platelet specific membrane Glycoprotein Ib (GPIb).
   Failure of this step may be due to
   1. Occupancy of the GPIb receptor. Dextran, multiple myeloma and idiopathic thrombocytopaenia purpura can occupy the GPIb receptor.
   2. The number of platelets - Results of the bleeding time become abnormal when the platelet count falls below $100x10^9$/L, however spontaneous small-vessel bleeding does not increase until the platelet count is less than $5x10^9$/L.
   3. Delivery of the platelets - Platelets are normally concentrated in the peripheral blood stream. A functional dilution of platelets

within the column of blood occurs when the packed cell volume is less than 20%

4. Absence of the GPIb molecule. Proteolytic degradation during Cardiopulmonary bypass and storage of greater than 3 days causes loss of GPIb. The Bernard-Soulier Syndrome is a congenital lack of the protein.

4. **Platelet aggregation**. The bound platelets disintegrate to initiate a platelet binding cascade.
    1. von Willebrand factor-GPIb binding stimulates platelet disintegration which exposes the Glycoprotein IIbIIIa binding site for further attachment of von Willebrand factor and fibrinogen.
    2. Dense granules in the platelets release ADP, enhancing platelet aggregation and disintegration, serotonin and thromboxane A_2 which cause vasoconstriction and Calcium. Calcium is essential in the activation of the soluble proteins of the coagulation pathway.
    3. Alpha granules from the platelets release the coagulation proteins - fibrinogen, thrombospondin, fibronectin, factor V and factor VIII
    4. The phospholipid phosphatidylserine (Platelet Factor 3) is exposed on the surface of the disintegrating platelet, serving as an essential base for the initiation of soluble proteins in the coagulation pathway

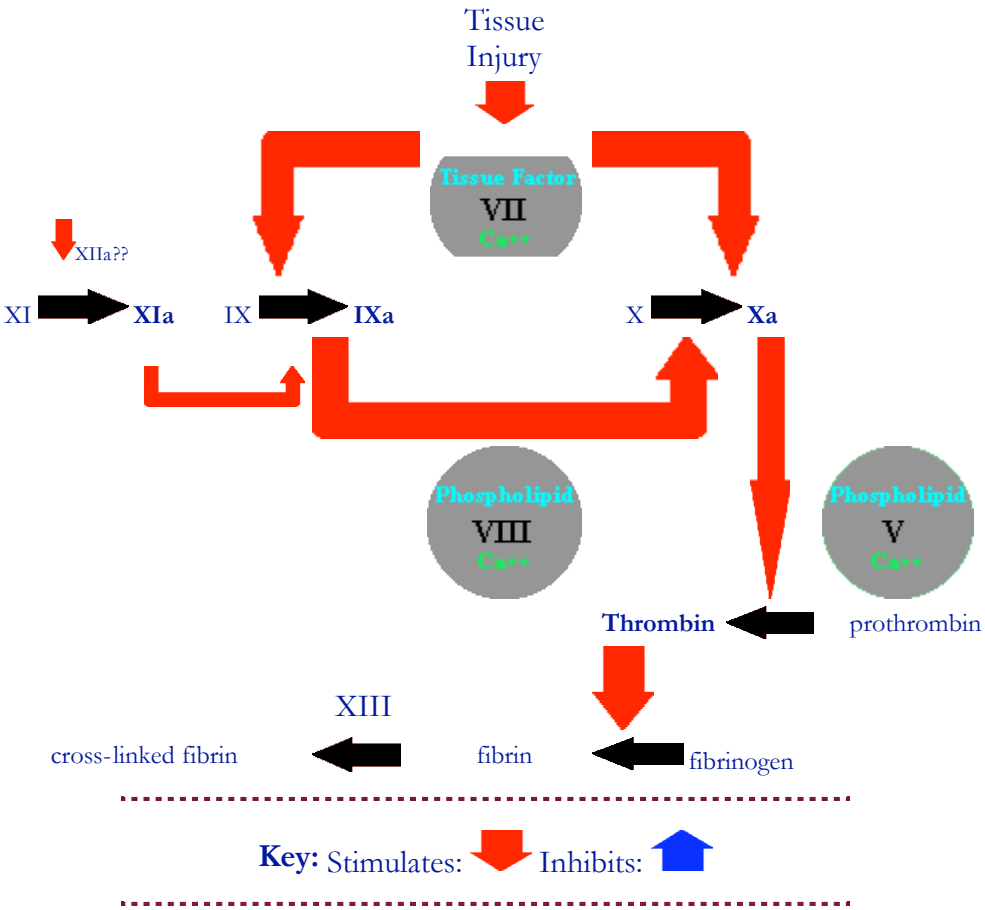
Failure of this step

1. Insufficient number of platelets.
2. Dysfunctional platelets.
    1. Prior activation occurs during cardiopulmonary bypass, storage, exposure to aspirin, uraemia and acute and chronic alcohol exposure.
    2. Congenitally impaired function - absence of Gp IIb-IIIa ("Glanzmann's thrombasthenia")

Tests of the above axis

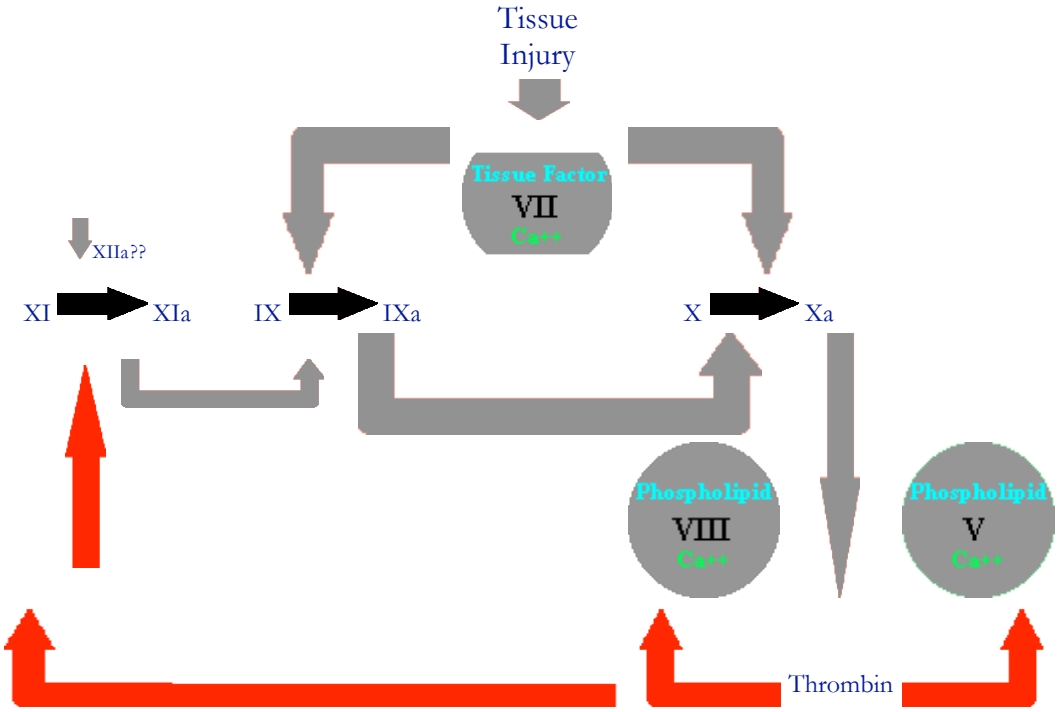
1. History and examination
2. Platelet count
3. Platelet aggregometry
4. Red blood cell count
5. A suggested practical test of the *integrity* of the *entire axis* is a **correctly performed** bleeding time.

The Revised Coagulation Pathway



1. There is a rapid initiation of coagulation when "Tissue Factor" (a protein-phospholipid complex normally present on vascular cells and activated monocytes), is exposed to factor VII in the presence of calcium.
2. The activated Tissue factor-VII complex activates factors IX and X
    1. Factor IXa enhances the production of Xa, especially in the presence of the co-enzyme VIIIa.
    2. Factor Xa converts Prothrombin to Thrombin (factor IIa). This is greatly facilitated by the presence of the coenzyme Va.
    3. **Thrombin enhances its own generation** by
        1. Activating the coenzymes V and VIII
        2. Activating factor XI, this generates more IXa and more XIa by positive feedback.
        3. Encouraging platelet aggregation and disintegration
3. Thrombin cleaves fibrinogen yielding monomers of fibrin which then polymerises to form the fibrin clot. Factor XIII, activated by thrombin and Ca^{2+}, stabilises this clot by forming covalent bonds between the fibrin molecules.

Thrombin's Positive Feedback!



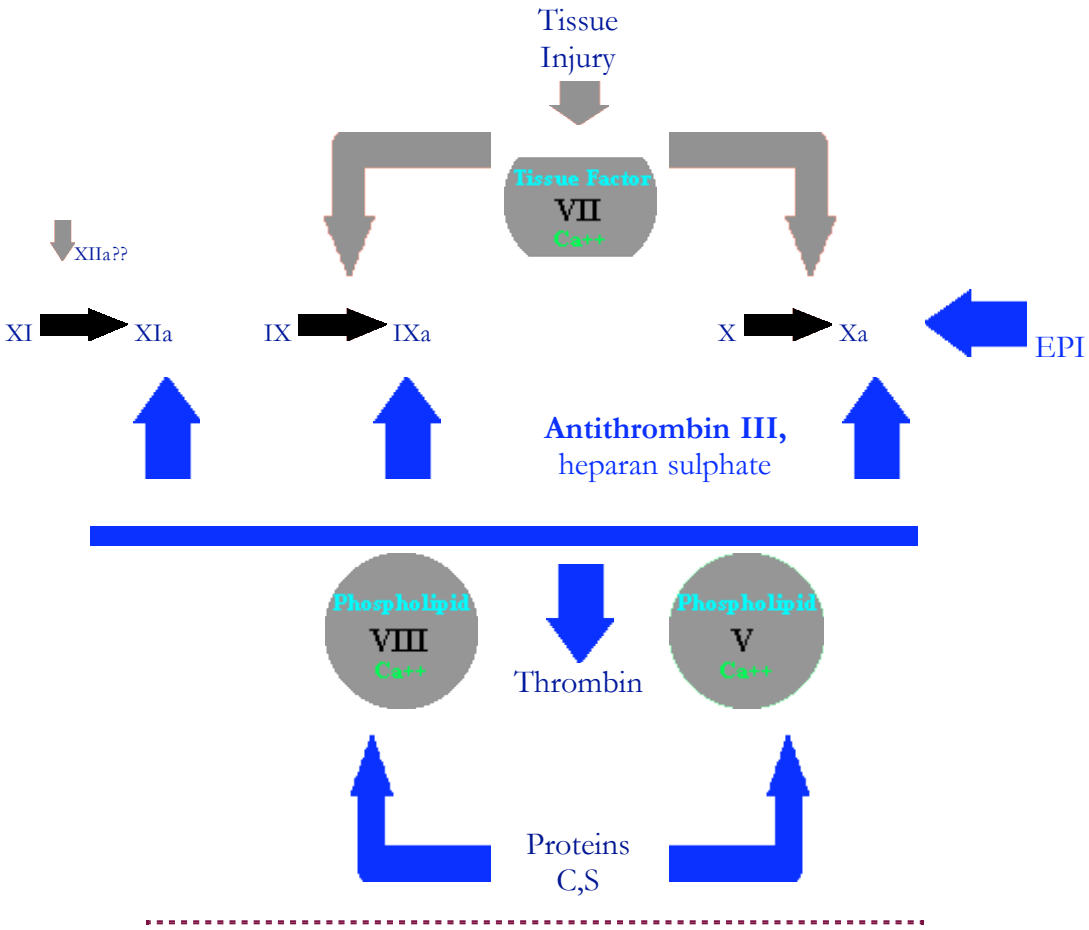
Failure of normal coagulation

1. Inadequate **activity** of a factor - A 30% of normal activity is clinically significant. The actual **concentration** of the proteins in the blood varies considerably and is not important by itself.
    1. Factor VIII - Classical Haemophilia A
        1. Factor VIII deficiency
        2. von Willebrand factor deficiency
    2. Factor IX deficient - "Christmas Disease" Haemophilia B
    3. Factor XI deficient
    4. Factor V deficient
    5. Factor X or II deficient
    6. Factor XIII deficient
    7. Vit K dependant serine proteinases (II, VII, IX and X) deficient
        1. Coumarin anticoagulants
        2. Vit K deficiency
        3. Severe liver disease
2. Presence of an inhibitor
    1. Lupus anticoagulant directed against the phospholipid
    2. Factor V inhibitor
    3. Factor VIII inhibitor
    4. Factor IX inhibitor
3. Inappropriate regulation of the pathway

Tests of normal coagulation

1. History and Examination
2. Whole blood clotting time
3. Prothrombin Time
4. Activated Partial Thromboplastin Time
5. Screening Mixing Test
6. Russel viper venom test
7. Liver function tests
8. Thrombin Time
9. Lupus anticoagulant detection
10. Evaluation of regulation pathway

Regulation of Coagulation



Inherent inhibitors of coagulation control this explosion of coagulation material

1. Intact endothelium secretes Prostaglandin I_2 which prevents platelet activation and causes vasodilatation

2. Antithrombin III, a circulating serine protease inhibitor (serpin) and heparan sulphate from the endothelium inactivate thrombin, IXa, Xa and XIa.
3. Protein C, activated by the thrombin-thrombomodulin complex, inactivates Va and VIIIa in the presence of the activated cofactor Protein S
4. Extrinsic Pathway Inhibitor is a double headed protease inhibitor. One head binds to Xa and the second binds to the Tissue Factor-VIIa. This inhibition is overcome when there is a large amount of Tissue Factor present.
5. Damaged endothelial cells release tissue plasminogen activator, stimulating the fibrinolytic pathway

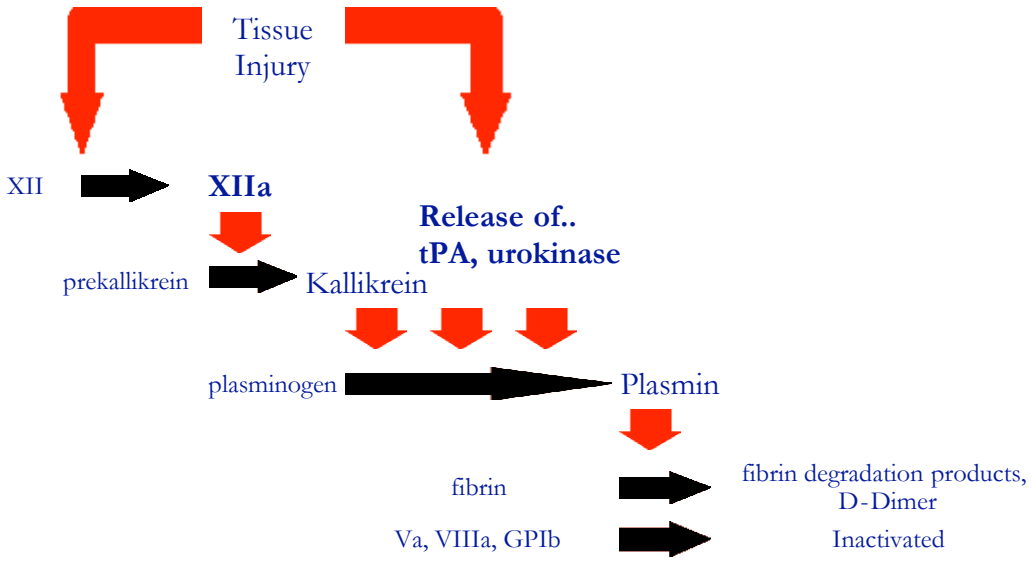
Failure of this pathway

1. Antithrombin III deficiency
2. Protein C deficiency
3. Protein S deficiency
4. Inherited resistance of Va to cleavage by activated Protein C

Tests

1. Specific protein assays
2. Factor V susceptibility test

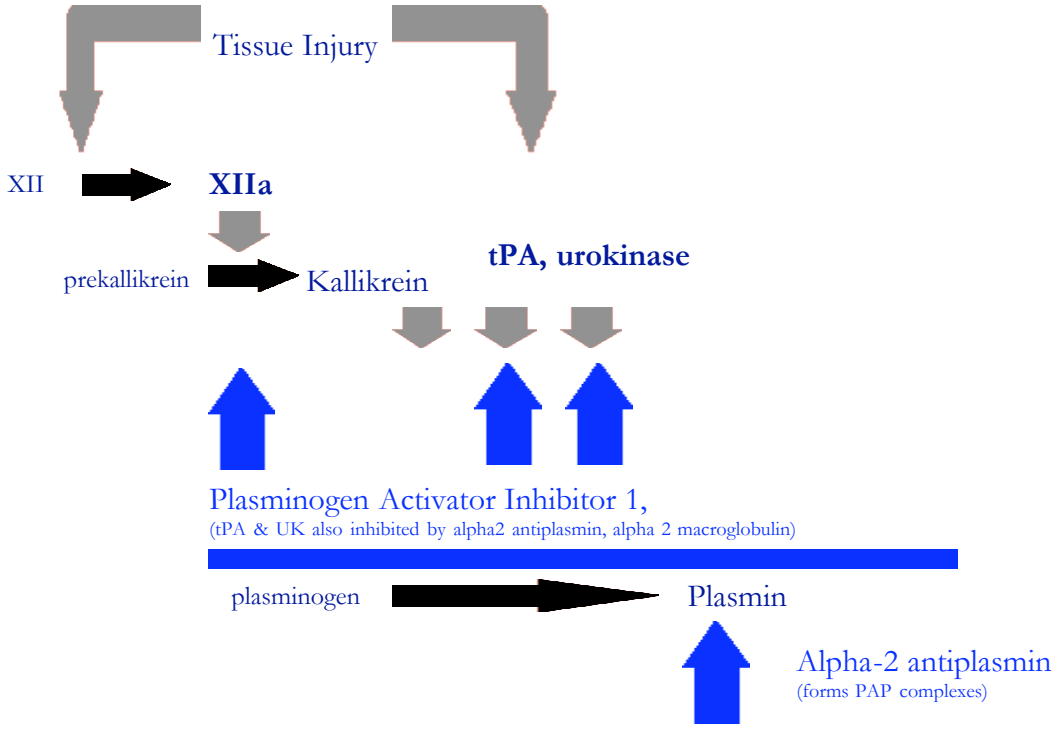
Normal Fibrinolysis



Fibrinolysis is initiated at the time of tissue injury

1. Tissue plasminogen activator and Urokinase are released from endothelial cells following injury and in response to thrombin. They cleave plasmin from plasminogen bound to fibrin within the clot
    1. Plasmin degrades fibrin into D-Dimers and Fibrin Degradation Products.
    2. Plasmin degrades Va, VIIIa and GPIb
2. The negatively charged subendothelium activates factor XII, which then releases kallikrein from prekallikrein, especially in the presence of high molecular weight kininogen.
    1. Kallikrein activates plasmin from plasminogen
    2. Kallikrein releases Bradykinin from kininogen, setting up the pro-inflammatory process.

Regulation of Fibrinolysis



The control pathway is set in motion during platelet disintegration by the release of Plasminogen Activator Inhibitor 1. Inherent inhibitors to the fibrinolytic pathway also exist.

1. Plasminogen Activator Inhibitor 1
    1. Prevents tissue plasminogen activator and urokinase from activating circulating plasminogen to plasmin, and the activation of prekallikrein to kallikrein

    2. Is inhibited by binding with activated protein C
2. Alpha 2 Antiplasmin and alpha 2 macroglobulin
    1. Prevent the formation of plasmin from circulating plasminogen by tissue plasmin activator and urokinase
    2. Bind and inactivate free plasmin, creating a plasmin-alpha2 Antiplasmin (PAP) complex.

Failure of this pathway

1. Deficient Plasminogen Activator Inhibitor 1 or 2
2. Deficient alpha 2 Antiplasmin - Autosomal Recessive
3. Presence of extrinsic plasmin inhibitors - Epsilon aminocaproic acid, tranexamic acid
4. The combination of streptokinase and plasmin is not inactivated by alpha 2 antiplasmin

Tests

1. Specific alpha 2 antiplasmin assay

A Table of Synonyms

Factor	Synonym	Kind of Protein	Function
I	Fibrinogen	Structural	Linkage Strands
II	Prothrombin	Vit K Serine Proteinase	Activates I, V, VII, XIII, Prot C and Plts
V	Proaccelerin	Binding	Helps Xa activate II
VII	Stable Factor	Vit K Serine Proteinase	Activates Ix and X
VIII	Antihaemophilic	Binding	Helps IXa activate X
IX	Christmas Factor	Vit K Serine Proteinase	Activates X
X	Stuart-Prower Factor	Vit K Serine Proteinase	Activates II
XI	Thromboplastin antecedent	Serine Proteinase	Activates IX
	Hageman		Activates Kinin

XII	Hagemann Factor	Serine Proteinase	Activates Kinin system
XIII	Fibrin stabiliser	Transglutaminase	Cross links fibrin
von Willebrand VIII related Ag		Binding	Binds plts and VIII
Extrinsic Pathway Inhibitor		Kunitz inhibitor (2 headed serpin)	Inhibits TF-VIIa and Xa together
Antithrombin III		Serpin	Inhibits Serine Proteinases
Protein C		Vit K serine Proteinase	Inactivates Va VIIIa and PAI-1
Protein S		Vit K protein	Helps Protein C
Plasminogen		Serine Proteinase	Lyses fibrin
Alpha2 antiplasmin		Serpin	Inhibits plasmin
Prourokinase		Serine Proteinase	Activates plasminogen
Tissue plasminogen activator		Serine Proteinase	Activates plasminogen
Plasminogen activator inhibitor 1		Serpin	Inactivates tPA and urokinase
{Whatever happened to III, IV, VI? (heh)}			

On to: **Tests of the Coagulation System**

Date of First Publication: 1999 **Date of Last Update**: 2006/07/26 **Web page author:** Click here