PHTX 441

Drugs that affect Coagulation and Clot Integrity

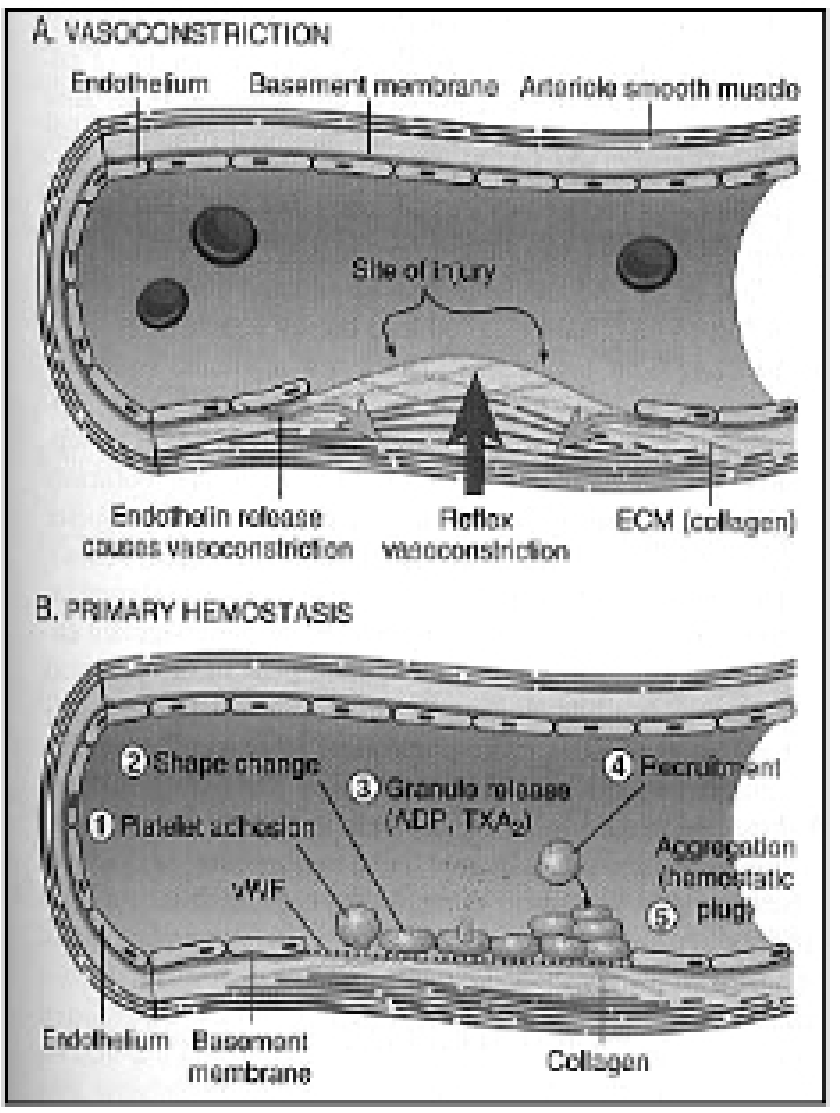
Steve Sawyer

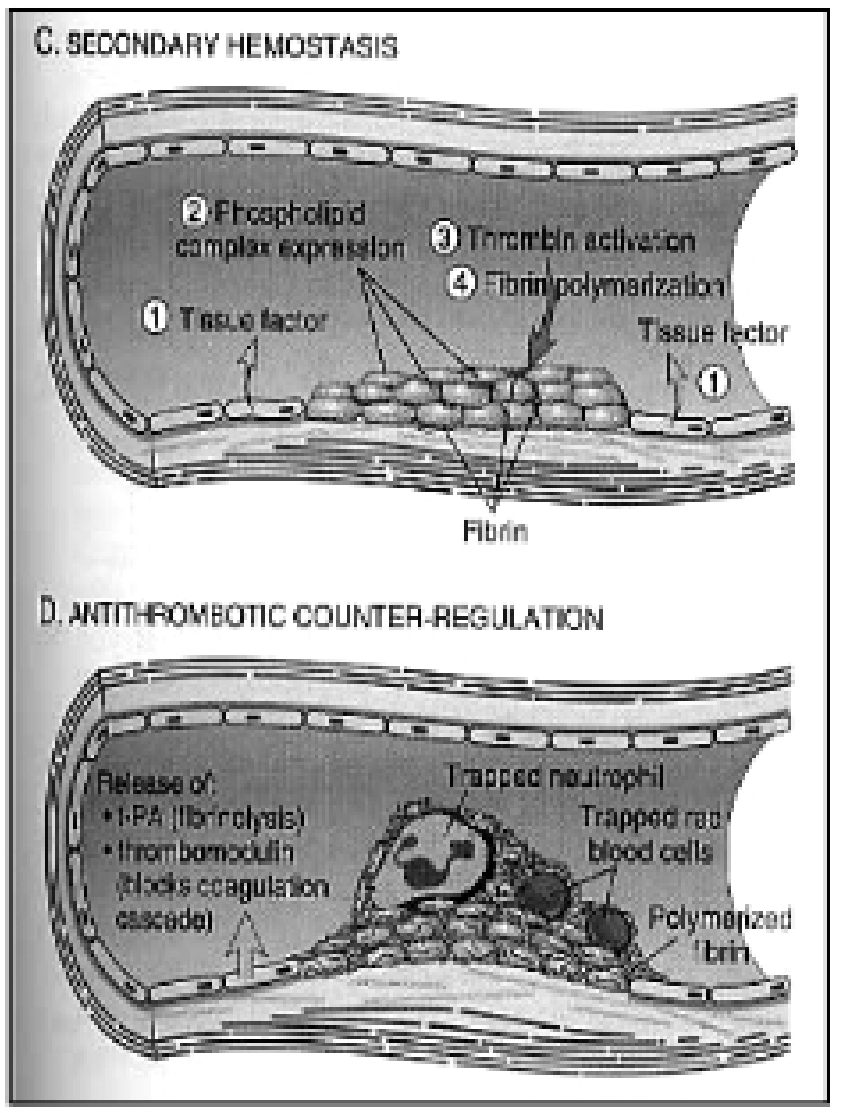
Sept 28, 2004

Anticoagulants and Thrombolytic Agents

Learning Objectives:

1. Coagulation cascade- learn in vivo pathway and key steps in blood coagulation and platelet reaction in both hemostasis and thrombosis.
2. Injectable anticoagulants- mechanism of heparin and hirudin action
3. Oral anticoagulants- warfarin and related compounds-action in Vitamin K-dependent reactions
4. Vitamin K mechanism of action
5. Agents that accelerate and suppress Fibrinolysis- TPA, streptokinase, transexamic acid
6. Agents that promote clotting- Vitamin K, Clotting factors for replacement, Desmopressin





Hemostasis

· Hemostasis is the arrest of blood loss from damaged vessels and is essential for survival.

•The main phenomena are:

1) platelet activation,

2) blood coagulation and

3) vascular contraction.

•The lecture is primarily focused on blood coagulation.

Blood Clot formed by Fibrin

Fibrin forms framework of clot: fibrin acts to traps blood cells that form bulk of clot

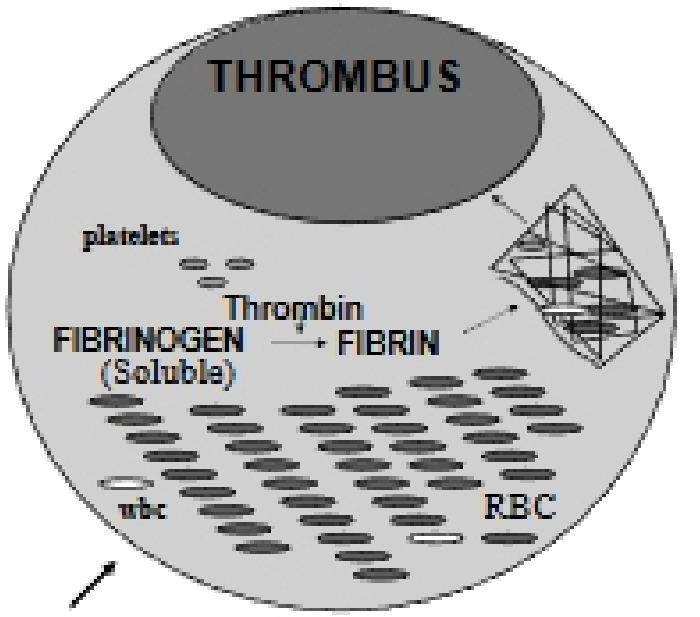
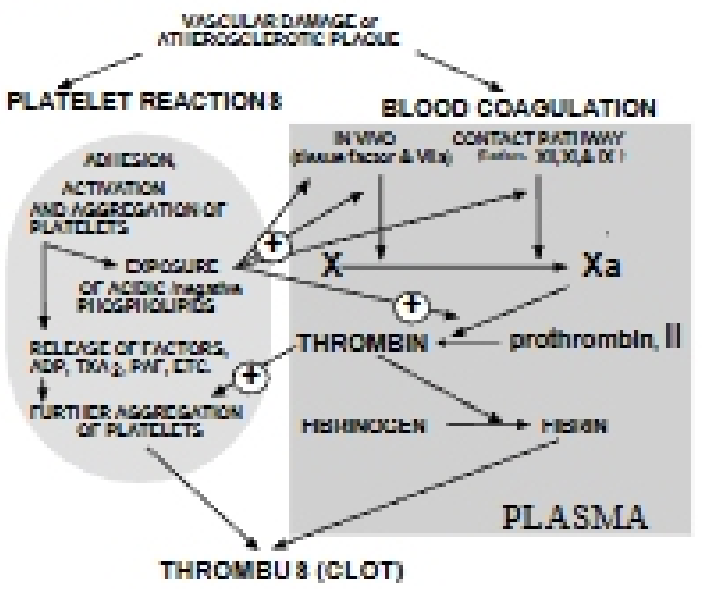


FIGURE 1. Simplified version of coagulation that results in clot formation or thrombus from either vascular damage or atherosclerotic plaque



HEMOSTASIS AND THROMBOSIS

1. Hemostasis is the arrest of blood loss from damaged vessels and is essential for survival. The main phenomena are i) platelet adhesion and activation and ii) blood coagulation (fibrin formation), and iii) vascular contraction.

2. Thrombosis is a pathological condition. Venous thrombosis usually results from slow blood flow and coagulation without significant initial platelet activation. Arterial thrombosis usually is associated with arteriosclerosis and platelet activation. Thrombus may break away from vessel wall becoming an embolus. Embolus is a major cause of death.

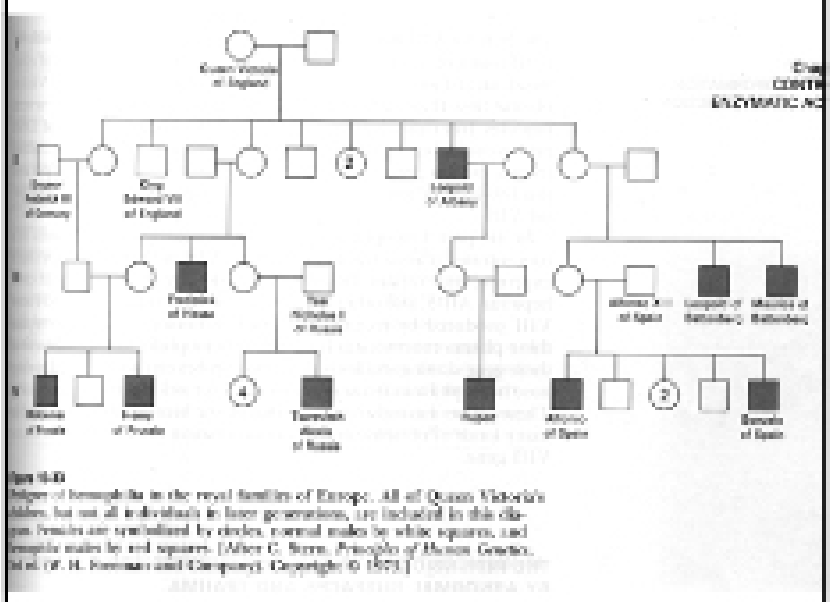
Thrombosis

Thrombosis is the pathological condition of (unnecessary) clotting

1. Venous thrombosis due to slow circulation without significant platelet activation. Thrombus may break away from vessel wall forming an embolus. Emboli clogging vessels in the heart, lungs and brain results in tissues deprived of circulation (oxygen) and are a major cause of death.

2. Arterial thrombosis usually associated with arteriosclerosis and inappropriate platelet activation. Heart Attack and Stroke result primarily from arterial thrombosis in either heart or brain.

Much of knowledge of the molecular / biochemical basis of Blood Coagulation comes from the study of genetic diseases that affect coagulation. An example is as classic hemophilia which results from a mutation of Factor VIII on the X chromosome.



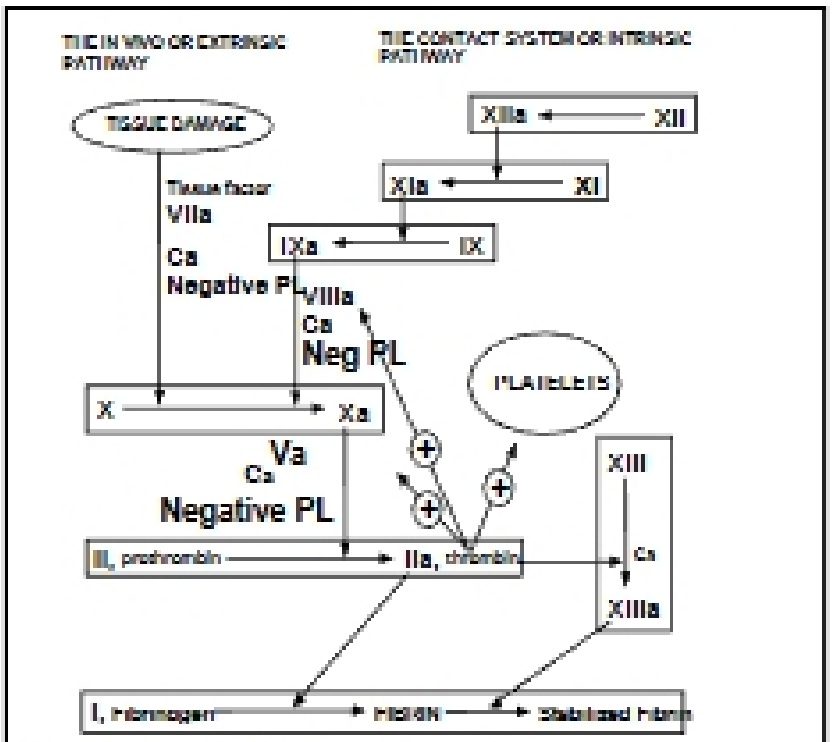
In Vivo Pathway of Blood Coagulation

i. Tissue factor exposed by vessel damage-the binding site of VIIa located at the wound site, additional binding sites (acidic phospholipids) provided by activated platelets.

ii. Common pathway after factor X.

Factor Xa cleaves factor II (prothrombin) to IIa (thrombin) in the presence of factor Va bound to membranes.

iii. **Thrombin, IIa, is central in control of coagulation**-acts to cleave factor I, fibrinogen, to insoluble fibrin. Fibrin meshwork traps blood cells to form the clot. Also converts XIII to XIIIa to stabilize the fibrin meshwork, activates factors V, VII, VIII, & XI, activates platelets, and acts on endothelial cells.



BLOOD COAGULATIN- fibrin formation

1. Clotting system is a cascade of enzymes and cofactors- factors I through XIII.
2. Inactive precursors are activated in series, each giving rise to the next.
3. The last enzyme, thrombin, derived from prothrombin, converts soluble fibrinogen (factor I) into insoluble meshwork of fibrin in which blood cells are trapped, forming the clot.
4. There are two pathways to the cascade: the extrinsic is apparently the in vivo pathway while the intrinsic apparently is triggered in the test tube.
5. Both pathway activate Factor X, which converts prothrombin to thrombin.
6. Calcium and negatively charged phospholipids are required in three enzymatic cleavage steps: IX on X, VII on X, and X on II.
7. Negative phospholipids are provided by activated platelets that have adhered to the site of injury. This localizes the site of clot formation.
8. Binding proteins as well as enzymes are used, i.e. factor V in X cleaving II.

A. Hemostasis- physiological arrest of blood loss

1. **Platelet Reactions**

a. Adhesion, activation, and aggregation of platelets

b. Exposure of acidic (negatively charged) phospholipids that are binding sites for coagulation factors

c. Release of factors: [ADP, TXA2, PAF]

d. Further Aggregation of Platelets