An Introduction to Thromboembolic Disease

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Abnormal blood clotting (thrombosis) is the major cause of death in the United States and a leading cause of morbidity, with an annual incidence of about 1 case per 1,000 individuals. Nearly 1 million individuals die from thrombosis in the United States each year, in contrast to 500,000 deaths from cancer (Fig. 1).

Many developments during the past decade have led to a greatly improved understanding of the etiology of abnormal blood clotting; improvements in clinical diagnosis and therapy have been reported. Blood clots can develop in the arterial circulation (arterial thrombosis) or venous circulation (venous thrombosis). Arterial thrombi usually develop in arteries diseased by the process of atherosclerosis. The factors that lead to venous thrombosis are less well understood, but inactivity and small injuries to the veins may play a role.

Blood clots that form in the circulation often break off and travel to other areas of the circulation, where they can cause major organ damage or death. Heart attacks and strokes can be caused by these “emboli.” Emboli that lodge in the lungs (pulmonary emboli) can rapidly cause death. Since thrombosis and embolism occur together, the process is usually referred to as thromboembolism. Some of these terms are defined in Table 1.

Most individuals who develop thromboembolism have one or more risk factors. Many of the non-inherited (acquired) risk factors have been recognized for decades, but a rapid series of scientific discoveries over the past two decades have led to the recognition of numerous inherited (genetic) factors that can increase an individual’s risk of developing thromboembolic disease. These inherited factors act in conjunction with acquired risk factors and involve the vessels, blood flow through the vessels, and the blood platelets and chemicals in the blood that are part of the hemostatic system. Thrombophilia refers to individuals who have a tendency to develop thrombosis from either acquired or inherited causes, or both.

In view of the enormous amount of medical resources needed to care for patients with thromboembolic disease, there is a great interest in avoiding acquired risk factors and the identification and early treatment of patients who have a high risk of developing thromboembolic disease. Many new laboratory tests and drugs are available for this purpose.
Introduction to Hemostasis

Hemostasis is a series of physiologic processes that confine blood to the vascular spaces, maintain the fluidity of the blood, and stop bleeding when injury to a vessel occurs.

Hemostasis is a complex process based upon interactions among the blood vessels and supporting tissues, endothelial cells, platelets, plasma coagulation proteins, physiologic protease inhibitors and the fibrinolytic system. Alterations in the hemostatic system can result in significant pathologic bleeding or clotting.

Resistance to bleeding is provided by:
- Extravascular forces (i.e., pressure exerted by the skin and supporting tissue)
- Physical resistance provided by the blood vessel
- Substances present within the blood (e.g., the platelets and coagulation factors)

Vessels constrict when injured, limiting the flow of blood to the injured area. Platelets adhere to collagen fibers exposed by the vascular damage and clump (aggregate) to form a loose, temporary (primary) plug. The plasma protein fibrinogen helps to stimulate platelet aggregation. Aggregated platelets undergo a series of mechanical (shape) and biochemical changes, termed activation. Activated platelets release chemical substances that activate

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**Thromboembolic Disease**

| **Anticoagulants** | Substances that prevent blood clotting. Include both drugs and substances naturally produced by the body |
| **Anticoagulant therapy** | Using drugs to prevent or treat abnormal blood clotting. Anticoagulant drugs are commonly known as “blood thinners” |
| **Coagulation factors** | Circulating blood proteins essential for clot formation, dissolving old blood clots, and preventing unwanted clotting |
| **Coagulation system** | The system that maintains hemostasis, including blood vessels, platelets, coagulation factors, and other factors |
| **Deep venous thrombosis (DVT)** | The formation of blood clots in the deep veins of the legs. May break-off and lead to pulmonary emboli |
| **Embolus** | A blood clot that breaks free from its site of formation |
| **Fibrinolysis** | The natural process to rid the body of old blood clots that have formed |
| **Hemostasis** | The natural process to prevent blood loss from blood vessels and wounds by the formation of blood clots |
| **Homozygous** | Inheriting two copies of the same gene. There are two copies of each gene in the genetic code, one inherited from each parent. |
| **Heterozygous** | Inheriting a single copy of a mutated gene. Heterozygous diseases are usually milder than homozygous diseases. |
| **Hypercoaguable state** | An increased tendency to develop blood clots from hereditary or acquired causes |
| **Mutation** | A change in the DNA of the genetic code from that common in the general population. Mutations can be harmful or helpful |
| **Platelets** | Small cells in the blood which comprise an important part of the clotting system. |
| **Polymorphism** | Common variations in the DNA of the genetic code in a population |
| **Pulmonary embolus** | An embolus, usually from the deep veins in the legs, that breaks free and occludes vessels in the lungs. May cause rapid death |
| **Thrombosis** | A blood clot that forms abnormally within the vessels |
| **Thrombolytic therapy** | Drugs that dissolve blood clots that have already formed. Commonly known as “clot busters” |
| **Thrombophilia** | An increased tendency to develop blood clots from hereditary or acquired causes |
| **Venous thromboembolism** | Deep venous thrombosis + systemic embolism |
other platelets and initiate the coagulation cascade. Coagulation generates a fibrin mesh, which stabilizes the platelet plug. The process of healing and recovery also is initiated to restore normal function to the vessel. The endothelium heals and blood clot is dissolved through the action of plasmin and other components of the fibrinolytic system. The stages of coagulation therefore include:

- Vessel constriction
- Formation of platelet plug (primary hemostasis)
- Coagulation and fibrin generation (secondary hemostasis)
- Fibrinolysis, healing and repair

The body has an efficient system to assure that unneeded blood clotting does not occur. For example, active coagulation substances are effective for only very short periods of time (milliseconds to seconds) and are rapidly diluted by normal blood flow. The liver and other parts of the body remove activated coagulation factors and an elaborate system of chemical substances destroys them. Lastly, the walls of the vessels throughout the body (vascular endothelium) release chemical substances (i.e., anti-thrombin, protein C pathway, etc.) that prevent platelet activation and the activation of chemical mediators.

Normally, these systems work together to assure that bleeding does not occur, but also to prevent thromboembolic disease. Unfortunately, defects in the blood vessels (vascular defects), or in any of the processes leading to defective formation of the hemostatic plug (platelet dysfunction, coagulation defects) may result in a bleeding disorder, while thromboembolic disease may be caused by vascular injury or arterial disease, blood stasis, inappropriate activation of hemostasis, or defective modulation of the mechanisms that normally regulate blood clotting.

The major types of venous thromboembolism, deep venous thrombosis (DVT) and pulmonary embolism are a leading cause of morbidity and mortality in hospitalized patients. They are being seen with increasing frequency in outpatients as well. The discovery of a number of acquired and inherited risk factors for thromboembolic disease has
provided a means to predict the risk of these diseases and institute preventive therapy.\(^5\)

**Acquired Risk Factors**

Acquired risk factors for venous thromboembolism include surgery, smoking, trauma, fractures, immobilization or venous stasis, inflammatory diseases, pregnancy, the use of oral contraceptives containing synthetic estrogens, malignancy, congestive heart failure and other diseases. Venous stasis in the extremities, venous obstruction, increased blood viscosity and direct venous damage may cause or contribute to the development of venous thromboembolism. The increasing trend to early hospital discharge of postsurgical patients may be responsible for the increasing incidence of venous thromboembolism in outpatients.

Venous thromboembolism usually involves the deep or superficial veins of the legs. Blood clots in the superficial veins (superficial thrombophlebitis) leads to localized tenderness, surrounded by an area of redness (erythema), heat and edema. A thrombus can often be palpated in the affected vein. Although usually benign and self-limiting, superficial thromboemboli can cause serious complications if they extend into the other veins. Deep thrombi confined to calf veins rarely cause clinical problems but can lead to pulmonary emboli (PE).

The antiphospholipid syndrome (APS) is another common acquired cause of thrombosis. APS is caused by autoantibodies that form against certain components of the coagulation system. In addition to venous and arterial thrombosis, including strokes, APS is associated with cause bleeding, miscarriages and other medical problems. The long-term use of certain drugs, including chlorpromazine and phenothiazine, may result in APS.

Generally, patients with APS have a six to 10 times risk of developing venous thrombosis than normal individuals; the risk of arterial thrombosis is increased as well.\(^6-9\)
The majority of patients who develop recurrent venous thromboemboli (thrombophilia) have discernable abnormalities of the coagulation system, including factor V Leiden, deficiencies of protein C, protein S, antithrombin III, the prothrombin G20210A gene mutation, homocysteinemia, elevated factor levels, dysfibrinogenemia, or abnormalities of the fibrinolytic system.4,10 Most of these abnormalities cause deficiencies of the regulatory substances of clotting. Genetic abnormalities are especially common in individuals who develop thrombi at an early age (< 40 years) and in those with a family history of thrombosis. Although no genetic abnormality is detectable in about 15 percent to 20 percent of individuals with recurrent thromboembolic disease, research in this area is rapidly proceeding and new genetic abnormalities may be described in the near future.

Individuals with decreased levels or abnormal function of naturally occurring anticoagulants such as antithrombin and protein C are prone to thrombosis that may present as DVT, thrombophlebitis and/or PE. The primary inherited causes of thrombosis include resistance to activated protein C (APCR) and deficiencies of protein C, protein S and antithrombin.

**Factor V Leiden**
Activated protein C (APC) is a major regulator of the coagulation system. It inhibits blood clotting by degrading phospholipid-bound activated factor VIII (VIIIa) and activated factor V (Va). Factor V Leiden, first identified in February 1993,11 is the most common inherited cause of thrombosis known at this time. It is found in about 5 percent of the general population and is responsible for 20 percent to 50 percent cases of inherited thrombosis. Approximately 50,000 individuals die yearly in the United States from this abnormality.12-16 Heterozygous individuals are at five to 10 times greater risk of thrombosis than the general population, while homozygotes are at a 50-100 times greater. The use of estrogen or oral contraceptives increases the risk of thrombosis even further. In 90% to 95% of cases, APCR is a result of a single point mutation in the gene for factor V, inherited as an autosomal dominant trait. This mutation renders activated factor V (Va) resistant to inactivation by APC acquired protein C resistance, APCR). The remaining
five to 10 percent of APCR is due to other genetic abnormalities in the factor V gene.

**Prothrombin G20210A Mutation**

A mutation in the prothrombin gene that produces elevated levels of prothrombin was discovered in 1996. There is increasing evidence that the G20210A mutation is an important risk factor for deep venous thrombosis, myocardial infarction and stroke. The use of estrogen or oral contraceptives increases the risk of thrombosis even further in patients with the prothrombin 20210 mutation.

**Homocysteine Abnormalities**

Hyperhomocysteinemia and homocysteinemia are inherited abnormalities of homocysteine metabolism. Homocysteine is a naturally occurring substance involved in the metabolism of certain amino acids, including cysteine and methionine. Abnormalities in three enzymes—methylenetetrahydrofolate reductase (MTHFR), cystathionine beta-synthase (CBS) and methionine synthase (MS)—associated with homocysteine metabolism in the body can lead to increased homocysteine levels in the body (hyperhomocysteinemia).

Genetic abnormalities in these enzymes, particularly MTHFR mutations, are the second most common risk factors for thrombotic disease, including heart disease and stroke. Hyperhomocysteinemia also may be associated with vitamin deficiency, advanced age, hypothyroidism, impaired kidney function, systemic lupus erythematosus and the use of certain medications, including nicotinic acid, theophylline, methotrexate and L-dopa.

**Protein S Deficiency**

Hereditary protein S deficiency is responsible for 5 percent to 8 percent of cases of inherited thrombosis. This disease typically presents as deep vein thrombosis of the legs, with a median age of onset in the late 20s. The
family history is frequently positive for thrombosis.27-30

Unlike protein C deficiency, in which many families of affected individuals are asymptomatic, no entire kindred with protein S deficiency has been described that is thrombosis free. Acquired protein S deficiency occurs during pregnancy, oral contraceptive usage and nephrotic syndrome. Since approximately 60 percent of circulating protein S is bound to C4b binding protein, elevations in C4b binding protein are believed to cause a deficiency of functional protein S.31

Protein C Deficiency

Heterozygous protein C deficiency occurs with a prevalence of 1 in 200-300; however, associated thrombosis probably occurs in less than 1 in 10,000 individuals (2 percent to 5 percent prevalence in thrombotic patients).30,32,33 Homozygous protein C deficiency, which causes life-threatening thrombosis unless treated, typically appears at birth. Patients with heterozygous protein C deficiency, however, usually present with thrombosis of the leg, mesenteric veins and iliofemoral veins prior to the age of 35. The initial thrombotic episode is spontaneous in approximately 70 percent of patients, while the remaining fraction has other thrombotic risk factors present. Acquired protein C deficiency occurs in liver disease, disseminated intravascular coagulation (DIC), postoperative state, adult respiratory distress, nephritic syndrome and an association with L-asparaginase therapy. L-asparaginase is a drug used to treat certain types of leukemia.

Antithrombin Deficiency

The prevalence of AT deficiency is approximately 1 in 2,000 to 1 in 5,000 individuals.34-37 A positive family history of recurrent thrombosis typically begins in youth and is associated with trauma or surgery. Seventy percent of AT deficient individuals develop thrombosis prior to age 35 and 85 percent develop thrombosis by age 50.

Arterial thrombosis is seen in approximately 20 percent of symptomatic patients. The use of oral contraceptives and pregnancy increases the risk of thrombosis. Acquired AT deficiency may develop in patients following three or more days of intravenous heparin administration and is associated with liver disease, DIC, nephrotic syndrome and following L-asparaginase therapy. Oral contraceptive usage can result in a 10 percent to 20 percent reduction in AT concentration.

Aspirin

Low-dose aspirin (80 mg) is the most commonly used drug for preventing thrombosis, particularly coronary thrombosis in patients with atherosclerosis. Aspirin works by inhibiting an enzyme, cyclooxygenase-1, that is present in platelets and the endothelial cell. A single dose of aspirin works for the life of the platelet (about a week). However, since platelets are continuously produced, aspirin must be taken daily.

Warfarin (Coumadin)

Crystalline warfarin sodium (Coumadin) is the most widely used oral anticoagulant.45,46 Warfarin interferes with the synthesis of the vitamin-K dependent procoagulants (factors II, VII, IX, X) in the liver by inhibiting the reduction of oxidized vitamin K. Since functional circulating clotting factors are not affected by warfarin, a week or more of oral anticoagulation therapy is required to achieve an optimal therapeutic effect. Warfarin is a safe agent for the prophylaxis of thrombosis if the correct dosage is given and the patient is carefully monitored.47-50 However, serious bleeding complications can occur with excessive anticoagulation, while thromboembolic complications are a risk with inadequate coagulation. For this reason, accurate laboratory measurements of the prothrombin time (PT) are critical in the management of patients receiving oral anticoagulation.51-53
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#### Table III
**Properties of Major Anticoagulant Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Most Important Applications</th>
<th>Route of Administration</th>
<th>Laboratory Monitoring</th>
<th>Adverse Effects and Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coumadin (Warfarin)</strong></td>
<td>Thrombosis prophylaxis in outpatients</td>
<td>Oral</td>
<td>Prothrombin time, INR</td>
<td>Bleeding with overdose, skin necrosis and gangrene</td>
</tr>
<tr>
<td><strong>Unfractionated heparin</strong></td>
<td>Thrombosis prophylaxis in hospitalized patients</td>
<td>Intravenous</td>
<td>aPTT, anti-factor Xa assay</td>
<td>Bleeding, thrombocytopenia, acute systemic reaction, skin necrosis, resistance to heparin effect, osteoporosis (long-term use)</td>
</tr>
<tr>
<td><strong>Low Molecular Weight Heparins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ardeparin</td>
<td>Total knee replacement</td>
<td>Subcutaneous</td>
<td>Anti-factor Xa assay</td>
<td>Bleeding, thrombocytopenia, osteoporosis (long-term use)</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>High-risk abdominal surgery</td>
<td>Subcutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Knee or hip replacement, abdominal surgery, DVT treatment, unstable angina, Non-Q wave MIs</td>
<td>Subcutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Treatment of DVT</td>
<td>Subcutaneous</td>
<td></td>
<td></td>
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<tr>
<td><strong>Direct thrombin inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lepirudin</td>
<td>Treatment of HIT</td>
<td>Subcutaneous</td>
<td>aPTT, ACT</td>
<td>Contraindicated in renal disease</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Treatment of HIT</td>
<td></td>
<td>aPTT, ACT</td>
<td>Contraindicated in hepatic disease</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Treatment of HIT</td>
<td></td>
<td>aPTT, ACT, thrombin time</td>
<td>Contraindicated in renal disease</td>
</tr>
<tr>
<td><strong>Anti-platelet agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Thrombosis prophylaxis</td>
<td>Oral</td>
<td>Usually not required. PLT function assays if needed.</td>
<td>Bleeding, Gl hemorrhage Not in pregnancy or hepatic disease, neutropenia (ticlopidine only) Thrombocytopenia, bleeding Headache, Gl upset, dizziness</td>
</tr>
<tr>
<td>Clopidogrel, ticlopidine</td>
<td>Acute coronary syndrome, Coronary intervention, stents</td>
<td>Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIb/IIIa blockers</td>
<td>Same as clopidogrel</td>
<td>Intravenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Strokes</td>
<td>Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Factor Xa inhibitors</strong></td>
<td></td>
<td>Subcutaneous</td>
<td>Usually not required.</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Thrombosis prophylaxis in hip fracture, hip replacement, and knee replacement</td>
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</table>
Heparin

Heparin is the other major anticoagulant used for therapeutic purposes. It is a negatively charged, highly sulfated mucopolysaccharide with a molecular weight between 6,000 and 25,000 daltons. It is not absorbed from the gastrointestinal tract and must be given by injection into the veins (intravenous) or under the skin (subcutaneous). A single intravenous dose has a half-life of approximately 60 minutes. Heparin exerts its potent anticoagulant effect by activating a natural anticoagulant, antithrombin III. Recent drugs derived from heparin and termed “low molecular weight heparin” act in the same way but have fewer side effects and require less frequent injections. A particularly serious complication of heparin anticoagulation is thrombocytopenia induced by an immune reaction against complexes of heparin and platelet factor 4.

Cost-Effective Diagnosis of Abnormal Blood Clotting

The recent identification of inherited and acquired risk factors for thrombosis has greatly improved the ability of doctors to diagnose thrombotic disorders and identify individuals at increased risk of thrombosis. There is a debate regarding whom should be tested for thromboembolic disease, but most doctors feel that individuals with a family history of abnormal blood clotting, as well as those with well-defined acquired risk factors, should be screened for the antiphospholipid antibody syndrome and the common inherited risk factors. This testing can help in estimating the risk of thromboembolic disease and planning long-term anti-thrombotic management.

The coagulation laboratory performs tests that detect the function and amount of various coagulation factors, while the molecular diagnosis laboratory looks for specific abnormalities in DNA. Generally, coagulation tests are used to screen for the presence of disease and to monitor treatment, while the molecular assays are used for confirmation. Since the coagulation system is disrupted by the body’s reaction to thromboembolic disease, coagulation screening in a person who suffers from a blood clot should be delayed for several weeks after discharge from the hospital and the coagulation system returns to a “steady state.”

The molecular assays, however, are not affected by drugs or disease processes and can be performed at any time. In a person with a suspected inherited thromboembolic disease, laboratory testing for the most common abnormalities (i.e., antiphospholipid antibody syndrome, factor V Leiden, prothrombin G20210A mutation, homocysteine abnormality) is usually performed first. If these tests are negative, additional testing for less common deficiency states (i.e., fibrinolytic abnormalities, plasminogen deficiency, etc.) might be considered.

Most deficient individuals presenting with thrombosis are managed acutely with heparin therapy, followed by long-term oral anticoagulant therapy. Commercially prepared concentrates are available for use post-surgically and during parturition in AT III deficient individuals. Protein C concentrates are available on a compassionate use basis.

Summary

Thromboembolic diseases are the leading cause of death and responsible for more than 1 million deaths/year in the United States alone. Fortunately, thromboembolic disease is preventable, and many recent scientific discoveries have led to the ability to estimate a person’s disease risk so that appropriate preventive therapy can be instituted.

References


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