An Approach to the Patient Who May Have a Bleeding Disorder

Charise T. Petrovitch, M.D. Washington, District of Columbia

The intent of this refresher course is to present the basic principles of the hemostatic mechanism, to review some of the common bleeding disorders, and then with these concepts in mind, to develop an approach to the patient who may have a bleeding disorder in the preoperative and intraoperative time periods.

The Hemostatic Mechanism

The *hemostatic mechanism* includes three processes, primary hemostasis, coagulation and fibrinolysis. Primary hemostasis takes place within seconds of vascular injury and involves the action of platelets and blood vessels. In a process called platelet activation, platelets spread along the surface of the denuded blood vessel and adhere to the subendothelial collagen layer via glycoprotein receptors and the von Willebrand factor. The activation process causes the platelets to change shape from a flattened disk to a spheroid and extend multiple pseudopods. The platelets undergo a release reaction, extruding the contents of their alpha and dense cytoplasmic granules, and releasing multiple compounds into the blood, including ADP, serotonin, clotting factors V, VIII, fibrinogen and many other chemical mediators, important to primary hemostasis and the subsequent coagulation process. With sufficient stimulus, the platelets synthesize thromboxane $_{A}2$, a prostaglandin, which stimulates further ADP release and also has potent vasoconstrictor actions. ADP increases platelet activation and leads to the aggregation of platelets to each. Finally, the platelets expose a new phospholipid surface called platelet factor 3, which changes the surface charge of the platelet and creates a "procoagulant" activity. The interaction of clotting factors follows on the phospholipid surface of the activated platelet and culminates with the formation of fibrin, reinforcing the friable platelet plug.

Beyond the site of vascular injury, the intact endothelial lining arrests further platelet aggregation. Endothelial cells secrete prostacyclin (PGI2), a prostaglandin, which has actions opposite those of $Tx_{A}2$. PGI2 inhibits platelet activation, secretion, and aggregation, and prostacyclin is a potent vasodilator. Any imbalance in the production of the two prostaglandins, thromboxane or prostacyclin, can lead to a defect in primary hemostasis or to abnormal coagulation.

Basic Principles of the Coagulation Mechanism

Coagulation involves the interaction of many plasma proteins, called clotting factors, which interact in various reaction sequences to produce fibrin. Most of the clotting factors circulate in *an inactive for*m, called a procoagulant molecule or proenzyme. During the process of coagulation, a portion of this protein molecule is cleaved off and the remaining protein becomes an active cleavage enzyme, called a serine protease. The "activated clotting factor"cleaves off a portion of the next procoagulant clotting factor, which "activates" that factor in succession. In a chain reaction-like fashion, one factor "activates" another, until fibrinogen (factor I) is cleaved to form fibrin.

The proper interaction of many of the clotting factors requires the presence of *a phospholipid surface*. This phospholipid surface can be provided by tissue factor (extrinsic to blood) or by the surface of platelets when they become activated and expose platelet factor 3 phospholipid (intrinsic to blood). Because the process of coagulation

requires a phospholipid surface, the production of fibrin is localized to the site of vascular injury where tissue factor is exposed to blood and where platelets are activated, exposing PF3.

Some of the reactions of the coagulation cascade involve the *formation of a reaction complex* in which two clotting factors are bound in a particular spatial arrangement on a phospholipid surface and together activate the next clotting factor. In the reaction complex, one of the clotting factors serves as a cofactor and is not an actual cleavage enzyme. *Factors V and VIII serve as cofactors* and are also known as *the labile factors* because their coagulant activity does not last long in stored blood. Transfusion of large quantities of PRBCs leads to a deficiency of these labile factors, Va and VIIIa.

Most of the coagulation proteins are *synthesized by the live*r. Their normal structure and function are dependent upon normal hepatic activity. Four of the clotting factors, (II, VII, IX, and X) are *vitamin K dependent factor*s, because they require vitamin K for their proper synthesis in the liver. After these factors have been synthesized, they undergo a final enzymatic reaction which requires the presence of vitamin K. A carboxyl moiety is added to each factor and enables the vitamin K dependent factors to bind via calcium to phospholipid surfaces. Without vitamin K, these proteins are produced in normal amounts by the liver, but are not functional because they cannot bind to phospholipid surfaces. The coumadin-like drugs compete with vitamin K for binding sites on the hepatocyte and in this way coumadin inhibits carboxylation of the vitamin K dependent factors. Of the four vitamin K dependent factors, factor VII has the shortest half-life. It is the first clotting factor to disappear from the circulation when a patient is placed on coumadin.

Only one factor, coagulant factor VIII, is thought to have some extrahepatic origin. *Factor VIII circulates as a huge plasma protein* and is really a complex of two components, each under separate genetic control. The high molecular weight portion (VIIIR:Ag) contains both the factor VIII antigen and the von Willebrand factor (vWF). The vWF has two major functions-- it mediates adhesion of platelets to collagen in the subendothelial layers of blood vessels after they have been injured during the process of primary hemostasis and it serves as a carrier protein for the smaller moiety of the factor VIII molecule. This smaller moiety contains the factor VIII coagulant activity (VIIIC). Absence of the smaller portion of the factor VIII molecule (VIIIC), leads to hemophilia A. Because the vWF also serves as a carrier protein for the coagulant factor VIII portion, deficiencies of vWF make the patient appear to have a both a defect in primary hemostasis and hemophilia A. Restoration of vWF levels returns the level of coagulant factor VIII to normal.

Coagulation Initiated by Tissue Factor

The cascade description of coagulation was proposed in 1964. However, at that time coagulation was thought to proceed via two pathways, the intrinsic and the extrinsic pathways, and these were thought to converge with the activation of factor X to Xa. Then fibrin would be generated through a common pathway of coagulation. This classical understanding had been modified. In contrast to the previous belief that the “intrinsic” pathway of coagulation was primarily responsible for coagulation in vivo, it may be that coagulation is initiated by the exposure of blood to tissue factor (TF) which is “extrinsic to blood” and involves reactions of the classical extrinsic pathway. In this model, when blood is exposed to TF in the subendothelial layers of the blood vessel, the TF binds

factor VII or VIIa which is circulating in the blood. The factor VIIa/TF complex then activates two different substrates, factor X and also factor IX producing some factor Xa and some factor IXa respectively. Factor IXa bound together with cofactor VIIIa can activate X to Xa on the platelet surface. What this means is that the activation of factor X (by the VIIa/TF complex) can occur by two different reaction sequences. Once formed, Xa binds together with its cofactor, factor Va, on the platelet phospholipid surface (PF3) and together they activate factor II, prothrombin, to thrombin (IIa). Thrombin then converts fibrinogen to fibrin.

An inhibitor to the tissue factor pathway has been found called tissue factor pathway inhibitor (TFPI). TFPI inhibits the VIIa/TF complex after the first flurry of thrombin has been synthesized. Xa must then be produced by an alternate series of reactions, the classical intrinsic pathway of coagulation. It is the functioning of TFPI that results in the bleeding seen with the hemophilias because TFPI forces coagulation to proceed via the "intrinsic pathway" of reactions involving factors XIA, IXa, and VIIIa. It is theoretically possible that inhibition of TFPI by another inhibitor could allow the TF pathway to function in hemophiliacs and effectively correct their bleeding problems.

Coagulation is controlled under normal circumstances by several mechanism. First, the clotting factors themselves circulate in an inactive form. Once they do become activated, normal blood flow dilutes their concentration and washes them away from sites of injury. Activated clotting factors are preferentially removed from the circulation by the liver and the reticuloendothelial system. Some of the clotting factors require the presence of a phospholipid surface for their proper interaction and this requirement localizes clot formation to phospholipid surfaces. However, when the blood is exposed to massive amounts of phospholipid, uncontrolled coagulation or disseminated intravascular coagulation (DIC) may be initiated. The phospholipid may be that which is exposed by activated platelets, (PF3), or it may be tissue factor. Coagulation is also controlled by the presence of anticoagulants which circulate in the blood. Antithrombin III (ATIII) is one such naturally occurring anticoagulant. As its name implies, ATIII binds to thrombin to inactivate this master coagulation enzyme. ATIII also binds to factors IXa, Xa, XIA, and XIIa. Under normal circumstances, the binding of ATIII to thrombin and the other activated factors of the "intrinsic pathway"occurs slowly. In the presence of heparin (the man-made drug), the rate of ATIII binding is accelerated manyfold. Without ATIII, heparin has almost no anticoagulant action.

Fibrinolysis

The process of fibrinolysis involves the conversion of plasminogen to plasmin, the active fibrinolytic enzyme. Plasmin does not circulate in the blood freely because it would rapidly be attacked by antiplasmins present in the bloodstream. Instead the precursor to plasmin, plasminogen, circulates in the bloodstream. When plasminogen comes into contact with fibrin, plasminogen preferentially binds to the fibrin clot. Bound to fibrin, plasminogen is converted to plasmin by tissue plasminogen activator (t-PA). The plasmin formed has a specific binding site for fibrin. This same binding site is also involved in the interaction of plasmin with the plasmin inhibitor, alpha2-antiplasmin. As long as plasmin remains bound to fibrin, even though actively involved in degrading the fibrin clot, alpha2-antiplasmin cannot neutralize the enzyme. However, as soon as the binding site is free--when plasmin is released into the bloodstream--alpha2-antiplasmin will rapidly neutralize the plasmin. These antiplasmins which circulate in blood, prevent widespread

fibrinolysis. Only plasmin bound to fibrin is portected from antiplasmin attack. Fibrinolysis is also limited to the site of fibrin formation because t-PA only activates plasminogen which is bound to fibrin.

The primary action of plasmin is to degrade fibrin clots. The degradation products produced are called fibrin degradation products (FDPs) or fibrin split products (FSPs). Their structure varies according to whether plasmin cleaves fibrinogen, fibrin that is cross-linked, or fibrin that is not cross-linked, etc. Under normal circumstances, FDPs are removed from the blood by the liver, kidney, and reticuloendothelial system and have half-lives of about nine hours. If the FDPs are produced at a rate that exceeds their normal clearance, they will accumulate. In high concentrations, FDPs act as anticoagulants. The FDPs impair platelet function, inhibit thrombin, and prevent the cross-linking of fibrin strands. In such high concentrations, the FDPs lead to bleeding which is not due to a coagulation defect, but rather due to the accumulation of FDPs which act as "inhibitors" to coagulation.

Disorders of the Hemostatic Mechanism

The disorders of the hemostatic system may be broadly classified according to whether they involve platelets and/or clotting factors, and/or the presence of inhibitors (such as FDPs). Treatment most often involves transfusion of hemostatic agents--platelets and/or clotting factors--or the use of pharmacologic agents which will affect the function of platelets (desmopressin, antiplatelet drugs) or clotting factors (vitamin K, coumadin, heparin) or inhibitors (antifibrinolytics, protamine, fibrinolytics).

Hereditary Platelet Disorders

Von Willebrand's Disease: Von Willebrand's disease is the most common congenital bleeding disorder in humans. The disease is actually due to a deficiency in plasma of the von Willebrand factor (vWF) and not due to defective or deficient platelets. The disease is usually discussed in the context of platelet disorders because when the vWF is deficient, platelet function is impaired. Likewise, treatment of this disease does not involve transfusion with platelets. Instead, the vWF levels may be increased via transfusion with FFP, cryoprecipitate, or the administration of desmopressin.

Acquired Platelet Disorders

Thrombocytopenia: By definition, when the platelet count falls below 150,000/mm^3, a patient is said to be thrombocytopenic. Thrombocytopenia may result from (1) inadequate platelet production by the bone marrow (2) sequestration in the spleen (3) consumption from tissue injury or platelet activation (4) dilution due to massive transfusions and (5) destruction by immune mechanisms.

Platelet Dysfunction: Myeloproliferative and myelodysplastic syndromes produce intrinsic defects in platelets. Some systemic conditions, renal failure, liver disease, DIC, and cardiopulmonary bypass can produce platelet dysfunction by altering the milieu in which the platelet circulates. The most common cause of acquired platelet dysfunction is due to drug administration, such as ASA or NSAIDs. Platelet dysfunction is observed after platelet storage due to a depletion of energy stores, specifically ATP. Platelet defects can last as long as 8 to 20 hours after they are transfused. Desmopressin is sometimes recommended to treat platelet dysfunction due to uremia, liver disease, and for patients taking aspiring who present for coronary artery bypass surgery.

Hereditary Factor Deficiencies

Hemophilia A is caused by a deficiency of factor VIII activity, whereas hemophilia B (Christmas disease) is due to a deficiency of factor IX, and hemophilia C is due to deficiency of factor XI. Hemophilia A occurs in approximately 1 in 10,000 males. Clinically, hemophilia A can be classified as mild, moderate, and severe. The great majority of hemophiliacs have the severe form of the disease. Their factor VIII levels are less than 1% of normal activity and they frequently experience spontaneously bleeding episodes.

Acquired Factor Deficiencies

Vitamin K Deficiency: Vitamin K deficiency leads to deficiencies of factors II, VII, IX, and X as well as protein C and protein S deficiencies. In the absence of vitamin K, these proteins are synthesized but are structurally abnormal. When vitamin K deficiency develops the "functional" coagulation factors become depleted in a specific order dependent upon their individual half-lives. Factor VII is the first to be deficient--it has the shortest half-life—then factor IX and X and finally factor II.

Vitamin K is a fat soluble vitamin, found in leafy green vegetables, that requires bile salts for absorption from the jejunum. Clinically patients with malabsorption syndromes, pancreatic insufficiency, biliary obstruction, GI obstruction, or conversely a rapid GI transit time can all develop vitamin K deficiency due to inadequate absorption of the vitamin. Treatment of vitamin K deficiency is best done by the intramuscular or intravenous administration of vitamin K (Aquamephyton) in doses of 10 to 20 mg. Within 3-5 hours, the coagulopathy will begin to correct.

Acquired Combined Deficiencies of Platelets and Factors

Massive Transfusions: The transfusion of large volumes of stored PRBCs to correct extreme hypovolemia may result in hemostatic defects similar to the hemostatic defects present in stored blood--the coagulant activity of factors V and VIII are significantly reduced and the great majority of platelets are non-functional.

Platelet Dysfunction, Factor Deficiencies and the Presence of Inhibitors

Liver Disease: Liver disease produces a complex coagulopathy that is multifactorial in nature. The liver synthesizes most of the clotting factors, with the possible exception of factor VIII. The liver also synthesizes the anticoagulants, antithrombin III, protein C and protein S, and the fibrinolytic precursor, plasminogen. The liver is responsible for clearing activated clotting factors and for clearing plasminogen activator (t-PA) as well as the products of fibrinolysis, fibrin degradation products (FDPs). The net effect of the diseased liver on the hemostatic mechanism may be difficult to predict, difficult to diagnose, and difficult to treat.

Treatment of the hemostatic defects associated with liver disease is difficult. In the alcoholic, platelet dysfunction is presumed. If thrombocytopenia is also present, platelet transfusions will more than likely be necessary to prevent bleeding. Vitamin K may be administered even if vitamin K deficiency has not be diagnosed. Severe factors deficiencies are treated with FFP, but volume overload can be a problem if multiple transfusions are required. Cryoprecipitate may be transfused if the patient has hypofibrinogenemia, but cryoprecipitate does not contain the vitamin K-dependent factors.

Disseminated Intravascular Coagulation: Disseminated intravascular coagulation (DIC), is a syndrome involving the formation of multiple thrombi, disseminated throughout the

vascular tree. The syndrome develops whenever some underlying condition presents such a massive stimulus for blood coagulation that the normal mechanisms which localize clot formation are overwhelmed. DIC may also occur when an underlying medical condition presents such a constant chronic stimulation of the coagulation system that over time the factors which normally inhibit and restrain coagulation are consumed. Activation of the fibrinolytic process results in the production of FDPs which in high concentrations act as an anticoagulant. The FDPs inhibit platelet aggregation and prevent the normal cross-linking of fibrin monomers.

Many conditions predispose to the development of DIC, but they all share a final common pathway. Both thrombin and plasmin circulate concurrently resulting in ongoing clot formation and clot lysis. The end result of excess coagulation is tissue ischemia and the end result of fibrinolysis is the production of a bleeding diathesis. The ratio of thrombin to plasmin varies with the different conditions which lead to DIC.

Blood Component Therapy

Our ability to treat coagulopathies remains rather limited. Individual isolated factors, such as factor VIII, can be transfused for the treatment of genetic defects. But otherwise, component therapy for hemostatic disorders usually involves just three choices, the transfusion of platelets, fresh frozen plasma, or cryoprecipitate.

Platelet Transfusions: Platelets are transfused to correct deficiencies in platelet number or platelet function. Each unit of platelets will increase the platelet count approximately 7,500 to 10,000/mm^3. The recommended dose of platelets in adults is 1 unit/10kg of body weight within a 24-hour period. The National Institutes of Health sponsored a consensus conference to develop guidelines for the transfusion of platelets. They concluded that indications for pooled platelet concentrates include: treatment of thrombocytopenia in association with clinical coagulopathy, which often may not occur until platelet counts reach: (1) 10,000/mm^3 in ITP (idiopathic thrombocytopenic purpura), (2) 20,000/mm^3 in bone marrow depression, and 40,000/mm^3 during massive transfusion. Treatment with platelet concentrates was also recommended with a clinical coagulopathy resulting from platelet dysfunction, even with platelet counts over 100,000/mm3 such as occurs: (1) following cardiopulmonary bypass, (2) during surgical procedures in patients taking aspirin or other drugs impairing platelet function, (3) with uremia, and (4) with Glanzmann's thrombasthenia. They go on to state that inappropriate uses include prophylaxis with massive transfusion or following cardiopulmonary bypass.

Transfusion of FFP: In 1984 the National Institutes of Health held a multidisciplinary Consensus Development Panel to discuss the indications and risks of transfusion with FFP. Indications for FFP administration developed by the consensus conference include: (1) replacement of isolated factor deficiencies (documented by laboratory evidence), (2) reversal of coumadin effect, (3) antithrombin III deficiency, (4) treatment of immunodeficiencies, (5) treatment of thrombotic thrombocytopenic purpura, or (6) massive blood transfusion (rarely an indicated cause for the use of FFP). FFP has been found to be the most "over used" blood product. Patients may be incurring infectious risks without indicated benefit. FFP should not be used to treat hypovolemia or nutritional deficiency in the absence of coagulation disorders.

Transfusion of Cryoprecipitate: Cryoprecipitate contains significant levels of factor VIIIC, factor VIII/vWF (von Willebrand factor), XIII, and fibrinogen. This blood component is used for the treatment of hemophilia, von Willebrand's disease, fibrinogen deficiencies and uremic platelet dysfunction.