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, either in the preoperative or the intraoperative time frames.

The Hemostatic Mechanism.

The hemostatic mechanism includes three process, 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 other. 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 TxA_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 Coagulation.

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 form 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 PF#.

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 liver. 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 factors, 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 large 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 homeostasis 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 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 has 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 phospholipids 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 mechanisms. 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 AT III 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 many fold. 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, alph2-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

protected 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 for some types of Von Willebrand's disease, 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 transfusion with colloids or crystalloid or blood 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 aspirin who present for coronary artery bypass surgery.

Hereditary Factor Deficiencies

Hemophilias A & B. 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 episodes of spontaneously bleeding.

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 Transfusion. 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. It 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 been diagnosed. Severe factor 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 (DIC). DIC is characterized by excessive deposition of fibrin throughout the vascular tree, with simultaneous depression of the normal coagulation inhibitory mechanisms and impaired fibrin degradation. It is triggered by the appearance of procoagulant material (tissue factor or equivalent) in the circulation in amounts sufficient to overwhelm the mechanisms that normally restrain and localize clot formation. That appearance may be the result of either extensive endothelial injury, which exposes tissue factor of fibroblastic origin, or the release of TF into the circulation as occurs with amniotic fluid embolus, extensive soft tissue damage, severe head injury or any cause of a systemic inflammatory response. For reasons not entirely clear, the native pathways that inhibit coagulation, antithrombin III and the protein C pathway are simultaneously inhibited. The accelerated process of clot formation causes both tissue ischemia and, ultimately, critical depletion of platelets and factors. Simultaneously, the fibrinolytic system is activated and plasmin is generated to lyse the extensive fibrin clots. Fibrin degradation products (FDPs) appear in the circulation. FDPs stimulate release of plasminogen activator inhibitor, type 1 (PAI-1) from the endothelium and thrombolysis becomes impaired. The FDPs also inhibit platelet aggregation and prevent the normal cross-linking of fibrin monomers. Depleted of platelets and clotting factors and inhibited by FDPs, the coagulation system fails and the patient bleeds. Simultaneously, the microvascular occlusion by fibrin causes tissue ischemia contributing to multi-organ failure.

Several clinical entities encountered frequently in anesthetic and critical care practice are associated with the development of DIC. Sepsis is the most common cause. Endotoxins or lipopolysaccharide breakdown products from gram negative and positive bacteria respectively incite an inflammatory response that includes the generation of cytokines (tumor necrosis factor alpha, various inter-leukins). These cytokines in turn stimulate the release or expression of TF by endothelial cells, macrophages and monocytes and the DIC sequence is initiated.

Several obstetric conditions can cause DIC. Amniotic fluid embolism, placental abruption, and fetal death in utero result in the direct release of TF-equivalent material into the circulation. Pre-eclampsia is characterized by a systemic vasculitis. The associated endothelial damage causes an initially low grade DIC that accelerates as vasculitis-related damage leads to release of TF from ischemic tissues, in particular placenta.

Large burns, extensive traumatic soft tissue injuries, severe brain injury and hemolytic transfusion reactions can also liberate TF-equivalent material into the circulation and incite DIC. Certain malignancies, most notably promyelocytic leukemia and adenocarcinomas, are associated with DIC. However, with malignancy–associated DIC, thrombotic manifestations are more likely to appear first, whereas with the others mentioned above, the hemorrhagic diathesis is often the first clinical manifestation.

A few general conditions such as acidosis, shock, and hypoxia are associated with DIC. Shock promotes coagulation because one of the control mechanisms (rapid blood flow) is compromised. Clearance of activated

clotting factors is reduced when blood flow is decreased. Acidosis and hypoxia may contribute to both tissue and endothelial damage.

The clinical manifestations of DIC are a consequence of both thrombosis and bleeding. Bleeding is a more common clinical presentation in patients with acute, fulminant DIC. Petechiae, ecchymoses, epistaxis, gingival/mucosal bleeding, hematuria, and bleeding from wounds and puncture sites may be evident. With the chronic forms of DIC, thrombotic manifestations are more likely. Organs with the greatest blood flow, e.g., kidney and brain typically sustain the greatest damage. Pulmonary function may deteriorate as a consequence microthrombus accumulation.

Diagnosis of DIC. There is no absolutely consistent constellation of laboratory findings among routine tests. Increased PT, aPTT, thrombocytopenia, a decreased fibrinogen level, and the presence of FDPs and D-dimer may all be noted. The peripheral smear may reveal schistocytes (fragmented RBCs reflecting the microangiopathy that occurs as a consequence of widespread fibrin deposition). Thrombocytopenia (<100,00/uL) is not always evident early in the process, but true DIC without sequential reduction in platelet count is very unlikely. PT and aPTT may remain normal in spite of decreasing factor levels because of the presence of high levels of activated factors including thrombin and Xa. Fibrinogen level may not be decreased, i.e., <100 mg/dL, initially. Fibrinogen is an "acute phase reactant" which increases in response to stress and the early consumption of fibrinogen may simply reduce its levels to "normal". FDPs are a sensitive measure of fibrinolytic activity although they not specific for DIC. D-dimer (which is a breakdown product of the cross-linked fibrin in a mature clot) is somewhat more specific for DIC, but not entirely so, and should be measured when that diagnosis is suspected.Various other laboratory assays have been employed to support a diagnosis of DIC, but should probably not be considered part of the anesthesiologist's routine. They include levels of: prothrombin fragments F1+F2 (a marker of prothrombin conversion to thrombin-increased), thrombin-ATIII (TAT) complexes (increased), ATIII (decreased), alpha2-antiplasmin (decreased by binding to excess plasmin), protein C (decreased), plasminogen (decreased), and Factor VIII (decreased in DIC but normal with hepatic failure without DIC).

Treatment of DIC. Treatment should focus on management of the underlying condition. Septicemia will require antibiotic therapy. The obstetric conditions are frequently self-limited, although evacuation of the uterus or hysterectomy may be warranted. Hypovolemia, acidosis and hypoxemia should be corrected to prevent their contribution to the DIC process. When bleeding is or may become life threatening, the consumptive coagulopathy must be treated. Platelets will be required for thrombocytopenia, e.g., < 50,000/mm3. FFP will replace the clotting factor deficiencies. Fibrinogen level should be raised to >100 mg/dL. When hypofibrinogenemia is severe (<50 mg/dL) cryoprecipitate may be required. Six units of cryoprecipitate will increase fibrinogen level by approximately 50 mg/dL in a 70 kg patient. Heparin has been advocated. However, the contemporary practice is to restrict its use to only those situations where thrombosis is clinically problematic, principally DIC associated with malignancies. There is no proven benefit in situations in which bleeding is the predominant manifestation. Antifibrinolytics have been considered. However, their use in the face of widespread thrombosis is potentially disastrous and they should not be used. Antithrombin III concentrates have been administered. The hope is that its administration will serve to slow the runaway coagulation process. However, a beneficial effect on outcome from DIC has not been confirmed and its use should be viewed as experimental. An insufficiency in the protein C endogenous coagulation inhibition system is thought to contribute to the prothrombotic state in DIC. Activated protein C has been shown to decrease mortality and organ failure in patients with sepsis and that improvement is also evident among patients with sepsis with overt DIC. Its use should be considered in any sustained episode of DIC.

Reference: Additional detail and an extensive reference list can be found in: Drummond JC, Petrovitch CT: "Hemostasis and Hemotherapy". Chapter 10, In, *Clinical Anesthesia*, 5th Edition, Eds.: P. Barash, B. Cullen, R. Stoelting; Lippincott, Williams & Wilkins, Philadelphia, 2005.