The differential diagnosis of a long APTT with a normal prothrombin time can be due to either a clotting factor deficiency or the presence of an inhibitor, which can be distinguished by using a plasma-mixing study. The various clotting factor deficiency states are reviewed. Clinical bleeding following cardiac bypass surgery due to acquired factor V and thrombin antibodies is also reviewed.

In this brief review, a few selected topics on evaluation of bleeding diathesis in either a preoperative or postoperative setting will be discussed.

Evaluation of a Prolonged APTT before Surgery
It is fairly common that a hematologist is asked to see a patient, sometimes urgently, for evaluation of a long APTT discovered in a pre-operative setting. The anticipated surgery may vary from a relatively minor procedure to a major operation such as open-heart surgery or CNS surgery.

The differential diagnosis of a long APTT with a normal prothrombin time is quite extensive, but can be divided into two groups, due to either a clotting factor deficiency or the presence of an inhibitor. The patient’s history and physical examination are obviously important in considering the various possibilities. In eliciting a bleeding history, one should recognize its limitations. Mild bleeding symptoms are astonishingly common in the general population—epistaxis, easy bruising, and gum bleeding are reported in up to 25-45% of apparently healthy people, many of whom do not have any identifiable bleeding disorders. Conversely, many patients with von Willebrand disease (VWD) fail to identify their bleeding symptoms. Patients with very mild hemophilia A, with factor VIII generally in the 20-30% range, may not manifest any serious bleeding in childhood and remain undiagnosed until their early adulthood. On the other hand, patients with a negative past history of clinical bleeding may have a newly acquired bleeding diathesis due to an inhibitor. Thus one should ask specific informative questions, especially related to prior surgeries, childbirths, and dental extractions.

The first order of laboratory evaluation is a mixing study, which is generally performed by mixing equal volumes of the patient’s plasma with normal plasma and then repeat the APTT. If the prolonged APTT is corrected in the mixing study, the diagnosis is clotting factor deficiency, which can be confirmed by assays of specific clotting factor levels. If the prolonged APTT is not corrected, then it indicates the presence of an inhibitor (with the exception of an anti-VWF inhibitor, please see acquired VWD below). This can be clinically serious, such as an antibody against factor VIII or von Willebrand factor (VWF) (see below), or more commonly a lupus anticoagulant (LA). The diagnosis of LA needs to be confirmed by additional tests to show that the anticoagulant is phospholipid-dependent. LA is not associated with any bleeding but may represent a potent hypercoagulable risk factor (as part of the antiphospholipid antibody syndrome), and prophylaxis against postsurgical thrombosis should be considered in the appropriate clinical setting.

In terms of the mixing study, it is notable that an acquired inhibitor (IgG) against factor VIII typically has a slow onset of action such that a mixing study done after 5
minutes of incubation may show correction of the prolonged
APTT. The presence of the inhibitor is only revealed after a
prolonged incubation of the plasma mixture (generally 60
minutes). Thus both short and long incubation times should
be employed in the mixing study.

Deficiency of Contact Phase Factors
The contact system, consisting of three serine protease zymogens, factor XII, prekallikrein (PK), factor XI, and a non-
enzymatic cofactor high-molecular-weight kininogen (HMWK), is required for the initiation of the clotting cascade via the intrinsic pathway. Exposure of plasma to kaolin or ellagic acid (providing a negatively charged “activating surface”) and negatively charged phospholipids (such as cephalin serving as a “partial thromboplastin”) activates the contact system. This leads to reciprocal activation of factor XII and PK to factor XIIa and kallikrein, in the presence of HMWK. Factor XIIa then activates factor XI with further propagation of the clotting cascade.

A large part of the contact activation (or intrinsic) pathway appears to be physiologically irrelevant because patients deficient in factor XII (Hageman factor), PK (Fletcher factor), or HMWK (Fitzgerald factor) do not have any clinical bleeding. These patients are entirely asymptomatic in terms of bleeding, and replacement with fresh frozen plasma (FFP) prior to surgery is not indicated. Deficiency of factor XII should be confirmed by direct measurement of plasma factor XII level, which is readily accomplished in most clinical coagulation laboratories. Determination of PK or HMWK may require additional time. However, a good tip-off to the diagnosis of PK or HMWK deficiency is that the prolonged APTT is significantly shortened by prolonged incubation of the plasma mixture (generally 1 minute), which allows sufficient auto-activation of factor XII, thus bypassing the requirement of PK or HMWK.²

Interestingly, while factor XII–deficient mice (similar to factor XII–deficient patients) do not exhibit spontaneous or excessive bleeding after surgical challenges, thrombus formation following arterial injury in these mice is unexpectedly and severely impaired.³ It raises the intriguing possibility that factor XII might not be necessary for normal hemostasis but is required in thrombosis.

Factor XI within the contact system does play an important role in physiological blood clotting. Activation of the clotting cascade is initiated by the exposure of blood to tissue factor, which serves as an obligate cofactor for factor VIIa. The initial burst of thrombin leads to feedback activation of factor VIII, amplifying the cascade and accounting for the clinical importance of factor VIII and factor IX. In addition, thrombin can activate factor XI, which in turn activates factor IX. Thus, activation of factor XI by thrombin should be regarded as a tertiary pathway of thrombin generation within the clotting cascade. It is required primarily in situations that call for a significant and rapid production of thrombin. This additional production of thrombin activates the thrombin-activatable fibrinolysis inhibitor (TAFI), which serves to stabilize the fibrin clot from premature lysis.⁴ The role of factor XI in this revised clotting cascade⁵ thus explains nicely the clinical observation that, in contrast to hemophilia A and B, factor XI–deficient patients seldom bleed spontaneously and their bleeding usually occurs with trauma or surgery. The diagnosis of factor XI deficiency should be confirmed by direct determination of factor XI level, and the type of surgical procedure contemplated should determine the level of factor XI replacement by FFP (or factor XI concentrates in Europe).

Prolonged APTT Due to Passovoy Factor Deficiency
Passovoy factor deficiency refers to a rare autosomal dominant clinical bleeding disorder characterized by prolonged APTT which is corrected by mixing with normal plasma but not correctable by Passovoy factor deficient plasma. This disorder was initially described about 30 years ago,⁶ but the missing Passovoy factor has never been identified. Recent studies suggest that the commercially available Passovoy factor–deficient plasma may have a low titer LA7 and that some of the patients who satisfy the criteria of having the Passovoy defect have other identifiable bleeding disorders such as VWD.⁸ It raises the question of whether Passovoy factor deficiency should be regarded as a distinct coagulation disorder.

Hereditary or Acquired Deficiency of Factor VIII
The classic hemophilia A or B patients usually have the typical bleeding history of recurrent joint bleeds since childhood, although a mild hemophiliac, with clotting factor > 10-15%, may not have significant spontaneous bleeding. Also, about one-third of hemophilia A cases arise from spontaneous mutations in the factor VIII gene and therefore do not have associated family history of bleeding.

Spontaneously acquired factor VIII inhibitor (IgG) is the most common acquired inhibitor among the clotting factor inhibitors. It generally occurs in pregnant women or in elderly patients without any apparent underlying disease. The clinical presentation is similar to hereditary hemophilia A except that the patient has no prior history of clinical bleeding. The inhibitor is confirmed by mixing studies and its titer expressed in Bethesda units (one unit of inhibitor inhibits all the factor VIII in one mL of blood). Depending on the inhibitor titer and the clinical bleeding phenotype, activated prothrombin complex (or FEIBA), porcine factor VIII (sometimes difficult to obtain) or recombinant factor VIIa (extremely expensive) can be used acutely and judiciously. Management generally requires short-term immunosuppression, which gives excellent long lasting control. In general, elective surgery should be postponed until the inhibitor is under good control.
Hereditary or Acquired Deficiency of von Willebrand Factor

Deficiency of von Willebrand factor (VWF) can lead to a prolonged APTT because VWF functions as a carrier molecule for factor VIII and prolongs its plasma half-life. VWD is generally perceived as one of the most common hereditary bleeding disorders. However, because of the very broad distribution of VWF levels and the common prevalence of mild bleeding symptoms in the general population, many diagnoses of type I VWD may be false positives, reflecting a coincidental association between a low VWF level and a mild bleeding history. It has been suggested that type I VWD should be reserved for severe, dominant, symptomatic VWF deficiency, generally less than 20 IU/dL.1 In these patients, intragenic VWF mutations can usually be identified, which cosegregate with both low VWF levels and bleeding symptoms. On the other hand, a modestly low VWF level, from 30 to 50 IU/dL, does carry a modest bleeding risk, which is partly dependent on the particular surgical procedures being considered, and thus whether VWF replacement is required should be made on an individual basis.

Acquired VWD is a rare bleeding disorder, the diagnosis of which appears to be made more frequently in the past few years, perhaps due to increased awareness of this condition. It is most frequently associated with lymphoproliferative or myeloproliferative disorders, accounting for ~50-60% of cases, while severe aortic stenosis with a history of gastrointestinal bleeding due to underlying angiodysplasia is found in ~15-20% of cases. Solid tumors, especially with the results of prior surgeries, is extremely useful, but the available history is often inadequate or incomplete. Depending on the clinical setting, the following questions should be considered: Does the patient have underlying renal, hepatic, or malignant disease? Has the surgery required pump bypass or the induction of hypothermia? Has the patient been in shock? How many units of blood and blood products have been given, and over what period of time? Were baseline coagulation screening tests obtained before surgery and is the patient’s frozen plasma still available? The initial laboratory evaluation should include thrombin time, fibrinogen level, and a well-stained blood smear for evaluation of platelet and red cell morphology. More specific tests can be obtained if there is evidence of a specific disorder. The differential diagnosis of postoperative hemorrhage varies according to the clinical setting but may include disseminated intravascular coagulopathy (DIC), coagulopathy caused by shock liver and undiagnosed VWD. Postoperative bleeding following cardiopulmonary bypass (CPB) will be discussed in more detail here.

Despite the routine use of high-dose heparin, a wide variety of derangements in blood coagulation and platelet function during CPB have been reported. There is significant activation of the contact phase of coagulation, with generation of kallikrein and bradykinin, which presumably leads to enhanced fibrinolysis and the generation of inflammatory mediators. Changes in coagulation factors post-CPB do not correlate with clinical bleeding.14 Extensive platelet contact with the oxygenator membrane causes moderate thrombocytopenia, which generally returns to baseline level by post-operative day 5-6,15 and platelet degranulation and dysfunction, sometimes requiring platelet transfusions.

Evaluation of Bleeding after Cardiopulmonary Bypass Surgery

Postoperative bleeding is a complicated clinical problem requiring rapid diagnosis and prompt intervention. The first question is whether the bleeding has a local anatomic cause (generally confined to the operative area) or is the result of a systemic hemostatic failure (with bleeding at sites outside the surgical wound). The patient’s bleeding history, especially with the results of prior surgeries, is extremely useful, but the available history is often inadequate or incomplete. Depending on the clinical setting, the following questions should be considered: Does the patient have underlying renal, hepatic, or malignant disease? Has the surgery required pump bypass or the induction of hypothermia? Has the patient been in shock? How many units of blood and blood products have been given, and over what period of time? Were baseline coagulation screening tests obtained before surgery and is the patient’s frozen plasma still available? The initial laboratory evaluation should include thrombin time, fibrinogen level, and a well-stained blood smear for evaluation of platelet and red cell morphology. More specific tests can be obtained if there is evidence of a specific disorder. The differential diagnosis of postoperative hemorrhage varies according to the clinical setting but may include disseminated intravascular coagulopathy (DIC), coagulopathy caused by shock liver and undiagnosed VWD. Postoperative bleeding following cardiopulmonary bypass (CPB) will be discussed in more detail here.

Use of Antifibrinolytic Agents in CPB

Aprotinin, ε-aminocaproic acid (EACA) and tranexamic acid have been used extensively in high-risk CPB surgery and have been shown to reduce perioperative blood loss and transfusion requirements.16–18 Aprotinin, a bovine serine protease inhibitor, directly inhibits plasmin, and at high doses, also inhibits kallikrein. Both EACA and tranexamic acid are lysine analogues that function in suppressing fibrinolysis. Recently, in a large multicenter, phase 4 observational study, aprotinin was shown to be associated with a higher incidence of renal dysfunction and cardiovascular thrombosis, as compared to EACA or tranexamic acid, while the efficacy of reduction of postoperative blood loss was equivalent in all three drugs.19
Coagulopathy and Bleeding Following Exposure to Bovine Thrombin in Cardiac Surgery

There is widespread acceptance of the use of topical thrombin for hemostatic control in surgery. It has been estimated that at least 1 million patients in the US are treated with topical thrombin annually, and bovine thrombin is the only thrombin currently approved by the FDA as a stand-alone hemostatic agent. (A human fibrin sealant using a mixture of purified human fibrinogen and human thrombin has been developed but it is expensive and apparently not widely used.) Development of antibodies to bovine thrombin following exposure to topical bovine thrombin in the form of fibrin glue has been recognized since the late 1980s. In many cases, this might cause a prolonged thrombin time (using bovine thrombin to initiate clotting) in vitro, without clinical consequences. However, in a minority of cases, this leads to concurrent antibodies directed against bovine as well as human factor V, in part due to contamination of the bovine thrombin preparation with bovine factor V, causing depletion of factor V, associated with significant coagulopathy and clinical bleeding. A prospective study showed that bovine thrombin preparations are highly immunogenic, with ~50% of patients developing antibodies to human factor V and/or thrombin. These antibodies may persist and may be associated with an increased risk for adverse clinical outcomes during subsequent surgical procedures. Similar acquired thrombin and factor V inhibitors are recently reported in children exposed to topical bovine thrombin.

It is notable that one of the index cases underwent a repeat cardiac valvular replacement procedure 15 years after the initial event. Preoperatively there was no evidence of antibodies against either bovine thrombin or human factor V, but postoperatively, despite stringent avoidance of the use of bovine thrombin during surgery, an antibody against human factor V was again detected (Zehnder JL, Leung LLK; unpublished observation). It suggests that once antibodies to human factor V and thrombin have been detected, careful monitoring of these patients in subsequent cardiac surgery procedures is warranted.

Fresh frozen plasma is generally not useful. Both prednisone and IVIg have been reported to be efficacious. Platelet transfusions, perhaps related to the release of platelet factor V at the vascular injury site to achieve local hemostasis, are successful in some but not others. However, if severe clinical bleeding is associated with a high titer factor V inhibitor, plasmapheresis should be considered.

References