Post Cardiopulmonary Bypass Bleeding: An Introductory Review

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ABSTRACT

Cardiac surgery requiring cardiopulmonary bypass (CPB) has increased in both number and safety over the past four decades. Postoperative bleeding continues to be a major cause of perioperative morbidity. The reported incidence varies from 4-32%.

This paper reviews the preoperative evaluation and specific hemostasis defects associated with cardiac surgery and extracorporeal circulation. Monitoring of anticoagulation and coagulation, methods to decrease the alterations of the coagulation system, as well as the specific therapy for and risks of post-CPB bleeding are also discussed.

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INTRODUCTION

Cardiac surgery requiring cardiopulmonary bypass (CPB) has increased in both numbers and safety over the last four decades. Although tremendous improvements in surgical, anesthetic and perfusion techniques, as well as training of those personnel, have led to the increased safety of cardiac surgery, post-CPB bleeding continues to be a major cause of perioperative morbidity.

This is a major concern to all perfusionists because of the thousands of variables which may occur prior to and during CPB. The decisions the perfusionist makes while conducting CPB will have direct effects on the patient as manifested in the postoperative period.

Hemostasis is dependent on the integrity and normal function of three components. Intact blood vessels or surgical control of bleeding vessels, platelets adequate in both number and activity to form a platelet plug, and a normal coagulation cascade to form a stable clot. A delicate balance exists between the coagulation system and the anticoagulating fibrinolytic system to maintain blood in the liquid form. Activation of any component of hemostasis will enhance clotting, while deficiencies will result in increased risk towards hemorrhage.

Depending on the criteria for excessive bleeding, the incidence of post-CPB bleeding varies from 4-32% (1), with 3-7% incidence of re-exploration for such bleeding (2,3). In 1997-98, over 400,000 cardiac cases were performed in the U.S. (4). As cardiac surgery accounts for over 25% of all donor blood used, there is a tremendous burden on the blood bank supply and resources (5).

The etiologies of non-surgical hemostatic dysfunction are numerous and multifactorial. The effects of hemodilution, interaction of blood with the extracorporeal circuit, effects of heparin and/or protamine, qualitative and quantitative platelet dysfunction, primary fibrinolysis, disseminated intravascular coagulation, coagulation factor deficiencies, transfusion reaction, hypocalcemia, and hypothermia all may contribute to post-CPB bleeding. This paper reviews the preoperative evaluation and specific hemostatic defects associated with cardiac surgery and extracorporeal circulation. Monitoring of anticoagulation and coagulation, methods to decrease the alterations of the coagulation system, as well as the specific therapies for and risks of post-CPB bleeding are also discussed.

PREOPERATIVE EVALUATION

HISTORY

As with all surgical patients, any patient undergoing cardiac surgery requires a detailed history, physical examination, review of drug therapy, and appropriate laboratory tests. Any preoperative coagulation deficit must be thoroughly investigated and its implication during cardiac surgery understood. Hemostasis, renal, and hepatic diseases which may affect hemostatic homeostasis, should also be examined. Many cases of cardiac surgical bleeding may be averted by eliciting a careful history including family history of bleeding diathesis, spontaneous or easy bruising, gingival bleeding with toothbrushing, excessive bleeding with previous surgery, menses or after tooth extraction, or any history of epistaxis, hemoptysis, hematemesis, hematochezia, or melena (6).

DRUG THERAPY

A detailed drug history is of great importance in the cardiac surgery patient as many patients are receiving medications with primary or incidental anticoagulant effects. The medications that affect platelets in a quantitative or qualitative fashion are very important. Cardiac surgery performed on patients taking aspirin is associated with increased blood loss and transfusion requirements. Response to aspirin varies in healthy volunteers and patients, who may be hypo- or hyperresponders. Aspirin resistance has been described not only in single patients but also under certain clinical conditions. Authorities debate whether higher doses of aspirin are needed in patients with cerebrovascular disease than in those with coronary disease and whether some diabetics are more resistant. The COX-2 gene is probably expressed in atherosclerotic vessels leading to a hundred fold expression of prostaglandin synthesis in the vessel wall. Under these conditions a retrograde transfer of precursors from the vessel wall to the platelets adhering to it may increase their thromboxane synthesis. This mechanism may explain the generally increased thromboxane synthesis in cardiovascular diseases.

High doses of aspirin (500 mg/day) inhibit thrombin formation in whole blood. Lower doses (300 mg/day) inhibit thrombin formation in platelet rich plasma (PRP) with a marked intra-individual variation. How such mechanisms correlated with the inhibition of thromboxane synthesis in platelets and to what extent they may explain aspirin resistance in a clinical setting need further evaluation (7). As most drugs which inhibit platelets have a duration of 7-10 days, elective cardiac surgery should be delayed for 10-14 days.

Warfarin depletes the vitamin K dependent coagulation factors II, VII, IX, and X. Although clinical anticoagulation effects of warfarin diminish in 48 hours, the effects may last as long as five days with increased bleeding even with normalization of the prothrombin time. Therefore, warfarin should be discontinued preoperatively. For emergent situations, the effects of warfarin may be reversed by administering vitamin K intravenously for six hours, or via the infusion of two units of fresh frozen plasma. For patients on intravenous heparin for unstable angina, the heparin is continued until the patient arrives into the operating room.

Patients may present for emergency myocardial revascularization after thrombolytic treatment of acute coronary thrombosis and myocardial infarction. Streptokinase and tPA increase plasmin induced lysis of fibrinogen and fibrin to arrest and dis-
solve intravascular fibrin formation by primary fibrinolysis. Thrombolytic therapy depletes factors V, VIII:C, IX, X, and fibrinogen for 12-24 hours.

**PHYSICAL EXAMINATION**

Obvious physical signs of hemostatic defects include petechiae, ecchymoses, hematomas, hemarthroses, bruises, splenomegaly, and hepatomegaly. Careful examination of the skin, mucous membranes, nailbeds, and sublingual areas may reveal evidence of thrombocytopenia or platelet dysfunction. Since many hereditary and acquired connective disorders are associated with vascular defects and platelet dysfunction, the signs of these disorders must be sought.

**PREOPERATIVE LABORATORY STUDIES**

In many institutions a satisfactory and economical laboratory workup for patients without positive findings on history and/or physical is limited to a platelet count, prothrombin time (PT) and an activated partial thromboplastin time (aPTT) (8). However, since the majority of bleeding post cardiac surgery is due to platelet dysfunction, some institutions include a more thorough presurgical hemostatic screen. Patients who are taking platelet inhibiting medication should have a template bleeding time (TBT). Any positive history and/or physical findings of hemostatic defects may require any combinations of the following tests: thrombin time (TT), fibrinogen level, qualitative platelet screen, coagulation factors, and cryoglobulins for hypothermic CPB.

**CARDIOPULMONARY BYPASS**

This section describes the basic physiologic alterations of hemostatic function during CPB and reviews the experiences of different institutions.

Heparin anticoagulation protocols and neutralization with protamine protocols vary among clinicians and institutions. Unless there is pre-existing anemia, most adult extracorporeal circuits (ECC) are primed with 500-2000 ml of crystalloid and colloid solutions. This hemodilution will cause an immediate reduction, approximately 30%, in red blood cells, platelets, and coagulation factors. The extracorporeal circuit surface interface stimulates what has been described as a "whole blood inflammatory response" involving the coagulation, the complement, and the kallikrein/kinin systems (9). Intraoperative blood loss is scavenged and traumatized by cardiotomy suction of varying degree. Varying degrees of hypothermia may be utilized. The above variations in individual and institutional protocols contribute to differences in the etiology and incidence of postoperative bleeding. The same factors make comparative analysis of post-CPB bleeding extremely difficult.

**THROMBOCYTOPENIA**

Platelets initiate the process of clot formation by a variety of mechanisms which include: 1) adhesion to disrupted vascular endothelium, 2) aggregation to form a platelet plug, 3) secretion of pro-coagulating co-factors to facilitate coagulation cascades, and 4) inducing vasoconstriction. Proper platelet activity requires the presence of an adequate number of functional platelets.

A consistent finding of CPB is a reduction of the platelet count. Depending on the preoperative platelet count, decreases of 25-60% from the baseline are seen. Dilution at the initiation of CPB will decrease the platelet count by approximately one third (10). Mammen et al. has shown that dilution accounts for 80-90% of the decrease in the platelet count during CPB (11). The oxygenator, venous reservoir, the extracorporeal circuit, arterial line filters, and surgical wounds are all sources of platelet retention and fragmentation (1).

There appears to be a significant sequestration of platelets in solid organs, especially in the liver, within a few minutes of initiation of CPB (12). Increased platelet turnover and mobilization of platelet reserves from the spleen and marrow occur consistently. In animals, hypothermia causes platelet sequestration in the liver which reverses with rewarming (1). Transient thrombocytopenia due to sequestration occurs below 25° C (13) with in vitro platelet aggregation abolished below 33° C (14). The shear stress of the cardiotomy suction and exposure of blood:air and blood:tissue interfaces cause both destruction and activation of the platelets. The volume and percentage of blood aspirated by cardiotomy suction correlate directly with platelet loss (15,16).

There has been controversy over the effects of bubble oxygenators (BO) versus membrane oxygenators (MO) on thrombocytopenia. There is less initial thrombocytopenia with BO since there is less foreign surface. However, there is a continued decrease in the platelet count with BO, but the platelet count is stabilized with the MO. MO are associated with: 1) less trauma to the blood cells; 2) less thrombocytopenia; 3) a decrease of platelet release product β-thromboglobulin (17); 4) less sequestration of platelets (12,18); 5) reduced particulate microembolization; and 6) preservation of platelet function (19). However, with bypass times less than 2 hours, the difference in bleeding between BO and MO may be insignificant (17,20). Intravenous protamine reduces platelet count by one third within minutes. This effect lasts for less than one hour and probably results from transient sequestration in the liver (21).

**PLATELET DYSFUNCTION**

The interaction of blood and foreign surfaces is complex. Within seconds of contact, plasma proteins adhere to the extracorporeal surfaces, followed by cellular elements within minutes (22). Fibrinogen has a strong affinity to the foreign surfaces and the bound fibrinogen in turn stimulates platelet adhesion via the platelet fibrinogen receptors with resultant loss of platelet membrane glycoprotein IIb/IIIa fibrinogen receptors (23). Albumin coated surfaces reduce the binding sites of fibrinogen, reduce platelet granule release, and preserve the functional and morphologic integrity of the platelets (24).
The activation of platelets occurs shortly after the initiation of CPB, possibly by the release of ADP from hemolyzed red cells, or the release of human neutrophil elastase by activation of the contact pathway (25) and a variety of humoral factors (26). Within a few minutes of CPB initiation, there is no further platelet adhesion, since fibrinogen is covered by platelet fragments or undergoes a conformational change (23), or activation to the foreign surface (27). Activation of platelets causes a discoid to a spherical morphologic platelet shape change (28). With further stimulation, primary platelet aggregates form, which release PF4, B-TG, fibrinogen, and other substances from the alpha granules (29). After the initial activation of primary aggregation, there is recovery of platelet morphology and function during CPB. With strong or continued stimulation, these reversible primary aggregates transform into irreversible secondary aggregates that secrete thromboxanes from the dense granules. Primary aggregation appears to be responsible for the decrease in circulating platelets during the first few minutes of CPB, as there is no release of products in either bubble or membrane oxygenators (27). Once the platelets are activated with loss of surface proteins and/or granules, platelets are no longer able to function.

There is a spectrum of platelet activation. A minority of platelets are fully activated, but the majority circulate with reduced function. Karpadkin reported a marked decrease in larger, younger, and more adherent platelets after CPB (30).

During the first few hours post-CPB, there is recovery of platelet function and volume, indicating entry of young, larger platelets into the circulation (31). Recovery of platelet function and normalization of bleeding times occur when there is adequate replacement of platelets or recovery of platelet morphology.

Platelet aggregation induced by pulmonary artery catheters, heparin (32), protamine (33), and heparin/protamine complex (34) may also cause thrombocytopenia and/or platelet dysfunction. As a rise in intracellular calcium may be the final common pathway mediating platelet granule secretion, a low ionized calcium level may decrease platelet responsiveness to triggering stimuli (35).

COAGULATION FACTORS

A consistent reduction in the levels of coagulation factors, fibrinogen, plasminogen, and antithrombin III (AT-III) occurs during CPB. The primary cause of the reduction is thought to be dilutional, since the decline (approximately 30-40%) parallels the decrease in hematocrit (11). For unknown reasons, factor V levels decrease more than others. The reported range of decrease may be due to differences in priming solutions, flow rates and pumping techniques (20). Levels remained low during CPB, although slight increases were noted for most parameters towards the end of CPB (11). All levels recover to normal within 48 hours.

FIBRINOLYSIS

Primary fibrinolysis is the activation of the fibrinolytic system without the activation of the coagulation system, while secondary fibrinolysis is the activation of the fibrinolytic system secondary to activation of the coagulation system. Primary fibrinolysis involves the primary activation of circulating plasminogen to plasmin, with resultant increase in plasmin induced lysis of fibrinogen to fibrin. The lysis of fibrinogen and fibrin generates fibrin degradation products (FDP).

The fibrinolytic system alters hemostasis by conversion of plasminogen to plasmin, plasminogen depletion, and subsequent fibrinolytic degradation of fibrinogen and factors V, VIII, and IX (36). The resultant degradation products interfere with thrombin activity, fibrin monomer polymerization, and platelet function (2).

Pathogenesis of fibrinolytic activation during CPB remains unclear. It is also unclear whether adequate heparinization alone can completely suppress fibrin formation on foreign extracorporeal surfaces. Primary fibrinolysis may be stimulated by release of thromboplastic tissue substances into the circulation from disruption of vascular endothelium rich in plasminogen activator substances, ischemia, the interface of blood with the ECC, the physiologic alteration associated with CPB, prekallekrein activation by synthetic surfaces, and hypothermia. Tanaka has suggested that the activation of the intrinsic fibrinolytic system is mainly limited to the beginning of CPB, while enhanced fibrinolytic activity during CPB is predominantly of extrinsic origin by the release of t-PA from the vascular endothelium (37). Whatever the exact mechanism, there is an imbalance between the ability to form clots and the stability of the clot once formed.

The incidence of primary fibrinolysis during CPB varies from 0-85% depending on the testing technique. Bick et al. found the presence of FDP in all patients and the appearance of active plasmin in 46% of patients with fibrinogen and plasmin depletion. Conversion of factor XII to Xlla, which activates the intrinsic fibrinolytic system by converting plasminogen to plasmin was noted in 70% of the patients (20,38).

There is controversy regarding the incidence and significance of fibrinolysis during CPB. The clinical and laboratory manifestations of systemic hyperfibrinolysis result from the ability of plasmin to degrade not only established fibrin clots but also fibrinogen and factors V and VIII:C. The differences in the occurrence, and therefore clinical significance, may be the tests used to assess fibrinolysis (39).

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation (DIC) occurs when there is activation of coagulation factors through the intrinsic or extrinsic coagulation system. There is uncontrolled systemic fibrin deposition and coagulation with simultaneous fibrinolysis by intrinsic or extrinsic plasminogen activators introduced into the circulation, or by secondary activation by excessive production of thrombin or fibrin. The result is the combination of intravascular thrombosis, with consumption of platelets, fibrin, and coagulation factors, and liberation of D-dimers, and resultant coagulopathy.
As CPB causes depletion of coagulation factors, thrombocytopenia, and elevation of fibrin split products, many early investigators concluded that DIC occurred during CPB (40,41). With better understanding of the hemostatic changes during CPB, many investigators have shown that the occurrence of DIC during CPB is rare (20). DIC is unlikely to occur with heparinization, absence of significant thrombocytopenia, rapid correction of hypofibrinogenemia and hypoplasminogenemia post-CPB, and lack of massive thrombosis after protamine administration. Only two of several thousand patients have had DIC in association with CPB in Bick’s experience. Both patients developed DIC pre-CPB, one from cardiac arrest and the other from sepsis, and with protamine administration, massive vascular occlusions occurred.

In summary, the effects of CPB (thrombocytopenia, decreased level of fibrinogen and coagulation factor, elevation of fibrin split products) which were thought to be reflective of DIC during CPB, may have been based on isolated measurements reflecting fibrinolysis. Decreased AT-III levels, which are indicative of acute or chronic DIC, have only been shown in one study (42). With acceptance of heparin titration during CPB in the 1970’s (11), there appears to be less chance of low grade coagulation and secondary fibrinolysis.

**DIAGNOSIS OF POST CARDIOPULMONARY BYPASS BLEEDING**

**INCIDENCE, CRITERIA, CLASSIFICATION**

A cause of variability in the incidence of post-CPB bleeding is the different institutional protocols in the type of CPB circuit, priming solutions, type of oxygenators, intraoperative blood scavenging techniques, use of hypothermia, and the duration of CPB times. Variability also depends on the definition of excessive bleeding, with the Kirklin criteria being the most frequently used criteria (43).

The diagnosis and management of post CPB bleeding can be exceedingly difficult due to the tremendous derangement of coagulation during CPB. The alterations in the coagulation system during CPB do not predict excessive post CPB bleeding. Diagnosis of excessive bleeding post CPB is made after protamine reversal of heparin anticoagulation and inspection of the surgical field. The cardiac surgery team should be well versed with the hemostatic derangements of CPB and the diagnosis and management of post-CPB bleeding made with such understanding and with the aid of carefully evaluated coagulation tests. Any medications which affect the coagulation function may give clues to the deficit and therapy directed towards that likely defect. As different institutions may have different protocols resulting in varying defects, no one specific approach is the best for any one institution.

The causes of postoperative bleeding are loosely divided into surgical and non surgical bleeding, although the distinction is often blurred as the associated hemostatic defect in one patient may cause bleeding while not in others. Surgical bleeding is usually defined by specific sites of bleeding, such as anastomotic sites, cannulation sites, or bleeding vessels, that can be controlled by surgical technique. In various studies, the incidence of such surgical bleeding was 33 to 62%, for all cases evaluated(1). Non-surgical bleeding is usually defined as continued, generalized bleeding from multiple sites, such as the intravenous sites, skin edges, sternum, and mammary and saphenous harvest beds, without significant clot in the surgical field after full reversal of heparin with protamine. The treatment of such bleeding causes significant demands on blood product support and blood bank supply. In the 1970s, the average case utilized 6 units per case, with transfusion of 10 units of blood products being not uncommon. In the 1990s, the average case utilized 0-2 units per case (1). However, with the improvements in surgical technique, extracorporeal technology, blood scavenging systems, as well as the acceptance of hemodilution and lower hematocrits, a significant number of patients (greater than 30%) receive no blood products in certain centers (44).

**ACTIVATED CLOTTING TIME (ACT)**

After the administration of protamine, an ACT is performed. If the ACT after protamine administration is within ±10% of the control, then adequate heparin neutralization is likely. The ACT is dependent on many factors and relatively insensitive to low heparin levels. While an elevated post protamine ACT may indicate the lack of heparin reversal, (if there were no technical errors, i.e. heparin contamination), the presence of a normal ACT does not ensure complete heparin neutralization (45). Although ACT may be affected by many factors, including severe depletion of the factors in the intrinsic coagulation system or severe thrombocytopenia due to insufficient platelet factor 3, platelet dysfunction will not elevate ACT. If the ACT is elevated after initial protamine administration, then additional incremental doses of protamine may be required, followed by ACT monitoring. If there is no improvement in the ACT following additional administration of protamine, then questions of inadequate/excess protamine, marked platelet abnormalities, fibrinolysis, or coagulation factor deficiency require further investigation.

**HEPARIN CONCENTRATION ASSAYS**

Due to the limitations of the ACT, direct measurements of the circulating heparin have been developed. Heparin concentration may be measured either by titration methods (by either protamine or polybrene) or by chromogenic assays. The titration method is by far more commonly available and detects the formation of a clot as its end-point in discrete points. The assay takes 2 minutes unless there is severe anticoagulation. The titration method for heparin level is exceedingly accurate. Teien and Lie have shown that only the polybrene titration method gives accurate results at heparin concentrations of 0.05 U/ml of plasma as compared to four other tests which included aPTT and calcium thrombin time (46). The chromogenic substrate assay of heparin may be performed as an assay of heparin activity, or heparin concentration with AT-III added. The different
Laboratory tests had a correlation coefficient of 0.85 when the patients had AT-III levels greater than 1.00 unit/ml versus a correlation coefficient of only 0.36 for patients with AT-III level less than 0.5 unit/ml AT-III level (47).

Therefore, a direct measure of heparin level is an accurate, simple method to determine heparin. However, since it is not a functional test for heparin activity, its use during CPB may not reflect the level of functional anticoagulation (48,49). Its primary use is for guidance of protamine dosage and diagnosis of excessive unneutralized circulating heparin post CPB.

LABORATORY TESTS

If abnormal post CPB bleeding is suspected after complete neutralization of heparin, then a complete laboratory coagulation profile should be performed. Tests include: PT, aPTT, complete blood count (CBC) with platelet count, examination of the peripheral smear, fibrinogen and fibrinogen split products, thrombin or reptilase time, and plasminogen levels.

Adequate protamine reversal of heparin can be assessed by measuring heparin concentration level; an increased thrombin time will also reveal the presence of residual heparin. Platelet count and peripheral smear will reveal thrombocytopenia. A prolonged PT or aPTT may indicate a deficiency in the coagulation factors. The clot from reptilase or thrombin time is observed for 5 minutes for evidence of lysis, which along with the fibrinogen and fibrinogen split products will reveal the presence of hyperfibrinolysis. The absence of significant clot lysis without significant elevation in the fibrin split products strongly suggests against primary fibrinolysis. Euglobin lysis time is a measure of clot lysis in the euglobin fraction of the plasma that contains a portion of the plasma fibrinogen, plasminogen, and plasminogen activator. Increase in the plasminogen activator levels will shorten the euglobin lysis time (normal < 60 min). Plasma plasminogen level will aid in possible antifibrinolytic therapy. TBT(normal 1-8 minutes) is technically difficult to perform intraoperatively and is probably underutilized postoperatively. However, the test is subject to wide variations and lacks correlation with clinically significant bleeding. The platelet aggregation test and tests of platelet dysfunctions are limited by the time required for results.

Laboratory tests of coagulation measure specific coagulation parameters. With hemostatic alterations from CPB, dilution, and platelet dysfunction, the tests’ results are difficult to interpret. Several studies have demonstrated the poor predictability of bleeding by laboratory test. Oh et al have shown prolonged PT and aPTT in pediatric cardiac patients without excessive bleeding (50). Bachmann et al have shown an 80% prolongation of PT, even though the extrinsic coagulation factors were 70-80%, with only a 4% clinically significant occurrence of bleeding (2), while Tuman et al have shown only a 33% overall accuracy by routine coagulation tests consisting of ACT, platelet count, PT, and aPTT in predicting postoperative hemorrhage (51). Therefore, an abnormality of laboratory tests in a patient with adequate hemostasis in not an indication for therapy. Despite the limitations of laboratory coagulation tests with post CPB bleeding, they may serve as a guide to therapy.

THROMBOELASTOGRAPHY

First introduced in 1948 by Hartert (52), thromboelastography (TEG) has gained interest as an intraoperative coagulation monitor for liver transplantation (53) and cardiac surgery (54). TEG is a qualitative viscoelastic measure of clot formation from initial procoagulant activation and fibrin formation through fibrin cross linking and clot retraction to eventual clot lysis over time. The test requires 0.35 ml of blood pipetted into a continuously rotating stainless steel crucible maintained at 37° C. A polished metal piston is suspended by a torsion wire 1 mm from the inner wall of the crucible. Fibrin strands form between the piston and the wall of the crucible, and as the clot matures, the rotational motion of the piston is electronically amplified to create the characteristic TEG tracing.

Characteristic tracings and parameters can be measured. The R value (reaction time: normal 7.5-15 min) is the time from blood placement to 1 mm amplitude and represents the time required for initial fibrin formation. Its prolongation may be due to coagulation factor deficiencies, heparin, or severe hypofibrinogenemia. The K value (coagulation time: normal value 3-6 min) is the time from R value until the amplitude of the TEG is 20 mm. The α value (alpha angle: normal 45-50°) is the angle formed by the upslope of the TEG tracing from the R value. Both K and the α values represent the speed of clot formation, fibrin cross-linking, and platelet-fibrin interaction. Thrombocytopenia or hypofibrinogenemia may decrease the K and α values. MA (maximum amplitude: normal 50-60 mm) represents the maximum clot strength, and depends on platelet number and function, as well as fibrinogen levels. The MA value may be very small with DIC, primary fibrinolysis, and uremia. A60 (normal value MA-5mm) is the amplitude of the tracing 60 minutes after the MA. Ratio of A60:MA (normal value > 0.85) and the F value (time from MA until 0 amplitude: normal value > 300 min) along with A60 is a measure of clot retraction or lysis.

Tuman (51) and Speiss (54) have both shown that TEG monitoring for clinical hemostasis post CPB to be 80-100% accurate in predicting postoperative bleeding and found the TEG to be more sensitive and specific than the ACT or the coagulation profile. TEG showed 88% overall accuracy with 0% false negative and 15% false positive, as compared to only 33% overall accuracy with 44% false negative and 73% false positive rates for routine coagulation testing consisting of ACT, platelet count, PT, and fibrinogen. TEG offers other important advantages compared to the routine coagulation tests, as it is: 1) economical 2) easy to use, 3) available in the operating room and allows intraoperative monitoring of coagulation hemostasis, 4) highly predictive of post- surgical bleeding, 5) able to assess heparinization and platelet-protein interaction, 6) able to easily diagnose fibrinolysis, DIC, and hypercoagulable states, 7) allows assessment of coagulation factor, fibrinogen, and platelet activity, as well as clot maturation and lysis, all from a single blood sample, 8) rapid compared to laboratory coagulation tests. Ini-
tial evaluation of fibrin formation is available within 12-25 min given a normal R and K values. Platelet function may be assessed from the amplitude of the tracing in another 20 min. Evaluation of clot lysis for fibrinolysis requires a variable amount of time.

Thromboelastography data have been shown to be loosely correlated with various coagulation tests. The lack of significant correlation exists because while coagulation tests examine isolated coagulation factors, the TEG examines whole blood coagulation, interaction of the protein coagulation cascade, fibrinogen, and platelet surface. However, there are specific changes in the TEG associated with cardiac surgery. Full heparinization and afibrinogenemia will result in a straight line tracing with infinite value for R and K, with MA value being zero. Near complete heparinization or extremely severe platelet deficiency will result in markedly prolonged R and K values, with MA less than 20 mm. Thrombocytopenia or platelet dysfunction will result in a diminished MA (<50mm) with a normal A60:MA value. With severe platelet deficiency, there may be prolonged R and K values, along with a markedly diminished MA value. Factor deficiency or moderate anticoagulation therapy will result in prolongation of the R value, and possibly prolongation of the K value, with normal MA and A60 values. Primary fibrinolysis will present with a nearly normal R and K values, with diminished MA value, and markedly diminished A60:MA value TEG tracing. Secondary fibrinolysis is contrasted by markedly prolonged R and K values, as well as severely diminished MA and A60:MA ratios. Hypercoagulable states can be determined peroperatively by decreased R and K values with increased a and MA values. This may be seen with patients with DVT (deep vein thrombosis) or excessive transfusion of platelets or coagulation factors.

An exceedingly important advantage of TEG is the ability to test therapeutic interventions in vitro prior to the administration of the drug or blood products. For example, the differentiation of DIC versus fibrinolysis is often difficult as both will yield consumption of protein factors and fibrinogen and production of fibrin split products. Small increments of epsilon aminocaproic acid (EACA) may be added and the TEG repeated. Improvement of the TEG tracing will confirm the diagnosis of fibrinolysis and EACA may be safely administered to the patient. Similar methods can be used for protamine titration of unneutralized heparin, platelet and factor deficiencies. This way, the amount of transfusion and the correct therapy can be improved by a priori in vitro TEG testing. Indeed a 33% reduction in blood and fluid infusion was found using a TEG directed therapy in liver transplantation (53). For patients on urokinase or streptokinase therapy, TEG may be used to monitor and guide dosage of thrombolytic therapy (55).

SONOCLOT

In 1975, von Kaulla described a device that utilizes changes in impedance to assess coagulation (56). The sonoclot uses 0.4 ml of whole blood or plasma with a vertical plastic vibrating (approximately 200 Hz) probe immersed in a fixed depth. The increasing impedance to the vibration by formed fibrin strands is detected by an electronic circuit which converts it into an output signal proportional to the fluid's viscoelasticity. A typical tracing consists of a "signature" of the entire clotting, clot retraction, and the clot lysis process.

The onset time, T1 (normal 3.5 minutes), reflects the initiation of fibrin formation and the primary slope, R1 (normal 2.3 ± 0.5 cm/min), reflects further fibrin formation and the rate of clot formation. In between R1 and the secondary slope, R2 (normal 3.5 ± 0.6 cm/min), which represents further fibrinogenesis and platelet-fibrin interaction, there is often an inflection point, which represents the point at which the platelets begin to contract the fibrin strands. PEAK, is the peak impedance at which there is maximum fibrin formation. The downward slope, R3, is produced as platelets induce contraction of the completed clot.

Sonoclot tracing is dependent on the number and function of platelets. As platelet number increases, the lag time and the shoulder-peak interval decreases, while the slope of R1 and R2 increases. R2 first appears with a platelet count of 30,000, while R3 appears at a platelet count of 60,000. Saleem et al has demonstrated the greater effectiveness of the sonoclot in assessment of excessive bleeding post CPB compared to the template bleeding time or platelet aggregation tests (57).

While the sonoclot tracing is used primarily to assess functional integrity of platelets, it also may be used to aid in the diagnosis of other coagulation deficits. The correlation to coagulation profile has not been demonstrated. Sonoclot tracing can detect the presence of heparin and with celite activation, can monitor heparin therapy. Clot lysis can be determined by measuring the final impedance as a function of time (i.e. severe fibrinolysis results in a final impedance close to that at the onset of clot formation). Peck has shown that the sonoclot and thrombin generation time (TGT) are practical, rapid and useful tests for the detection and monitoring of hypercoagulable states (58).

MANAGEMENT OF POST CARDIOPULMONARY BLEEDING

OVERVIEW OF THERAPEUTIC APPROACH

As discussed in the above sections, CPB creates tremendous alterations in the coagulation system. After successful hemodynamic separation from CPB, heparin is neutralized and surgical bleeding controlled. After satisfactory neutralization of heparin by protamine and surgical hemostasis, the most important monitor of adequate coagulation is the visual inspection of the surgical field. Assessment should include: Is there any active surgical bleeding? Is there continuous pooling of blood in the dependent areas of the surgical field? Is there clot formation? If there is continuous, "non-surgical" bleeding, the cause of bleeding is investigated.

Due to the lack of timely and specific laboratory tests, the "shot gun" approach of empirical transfusion of blood products is often used. However, this nearsighted approach is to be discouraged, as it places unnecessary burdens on the blood supply
and increases the long term complications of transfusions.

While the coagulopathy work-up is in progress, several considerations are addressed. First consideration is the amount of bleeding. Brisk bleeding requiring administration of crystalloids or packed RBCs to maintain an adequate circulatory function and hematocrit will further dilute platelets and coagulation factors. Empiric therapy may be required for hemodynamic instability, to control the hemorrhage, and to prevent further dilution of coagulants. Furthermore, circulatory insufficiency and resultant shock may even cause DIC. Transfusion of platelets is reasonable empiric therapy, as platelet dysfunction appears to be the primary cause of post-CPB bleeding. Fortunately such situations rarely exist and there is time for a diagnostic work-up.

During assessment of coagulopathy, factors such as hypothermia and hypertension need to be avoided and treated as these factors may increase bleeding. The institution of positive end-expiratory pressure may tamponade some mediastinal oozing. With supportive therapy, the bleeding, if not severe, will often resolve spontaneously with a “tincture of time.”

**HEPARIN REBOUND**

Heparin rebound is the reappearance of unneutralized heparin after complete neutralization of heparin after CPB. The proposed etiologies include: the longer elimination time of heparin compared to protamine, greater body stores of heparin, incomplete rearming with delayed heparin release from the tissues, exogenous heparin (heparin flush solutions and pump blood), and re-entry of free heparin into the circulation via the lymphatics system (59).

Heparin rebound is reported to occur in 0-100% of patients post-CPB (60). Most cases of heparin rebound have been reported to occur within 8-9 h post initial heparin neutralization, but delayed heparin rebound has been reported as late as 18 h post heparin neutralization (61). Ellison et al demonstrated there is heparin rebound in all patients who received lower doses (0.56 mg protamine/1 mg total heparin administered) of protamine (60). Others have reported a much lower incidence of heparin rebound (4.5%) without clinical significance (62). Administration of excess protamine at the time of initial heparin neutralization will not prevent heparin rebound and may actually increase bleeding due to detrimental effects on platelets. Zaidan et al have demonstrated that a slow (>30 min) administration of protamine reduced the initial incidence of early (<2 h) heparin rebound (63). Interestingly, the chloride salt of protamine has been suggested to cause less heparin rebound than the commercially available more rapidly metabolized sulfate preparation (64).

Whatever its cause, incidence, or clinical significance, heparin rebound is easily treatable by administration of additional protamine in 25-50 mg increments. Indeed, any diagnostic workup or treatment of post-CPB bleeding should be initiated after elimination of heparin rebound.

**PLATELETS**

As discussed in the section on CPB effects on coagulation, the primary hemostatic derangement associated with CPB is platelet dysfunction (1,2,20,29). The assessment of post-CPB bleeding after documented neutralization of heparin with protamine essentially deals with the adequacy of platelet function. Of primary importance in the evaluation of therapy for platelet dysfunction is the presence of bleeding. Routine prophylactic platelet transfusion is unjustified due to the risks of transfusion and the documented inefficiency of prophylactic platelet administration (65). Simon et al. demonstrated no differences in blood loss, transfusion requirement, or clinical outcome in patients who were given 4 units of platelets prophylactically after protamine administration (66). Furthermore, thrombocytopenia (platelet count 58,000/ul) and transient platelet dysfunction do not require platelet transfusion in coronary artery bypass surgery and uncomplicated valvular surgery as there is recovery of platelets in number and function post CPB. In the absence of bleeding, prophylactic transfusion of platelets should be reserved for platelet counts of < 60,000. Since a single unit of platelets will raise the platelet count by 5-10,000, administration of 4-8 units should raise the platelet count to acceptable levels.

However, in the face of post-CPB bleeding, there may be platelet dysfunction despite adequate platelet count (29) and many have advocated transfusion of platelets regardless of platelet count or documentation of abnormal coagulation tests (20). Indeed, in terms of adequacy of overall platelet function, the TBT is more predictive of postoperative bleeding than platelet count. If the measurements of platelet function. (TBT, TEG, Sonoclot) are abnormal, platelets should be transfused. Any transfusion therapy should be monitored to minimize the amount of transfusion. As platelet concentrates contain 40-60 ml of plasma per unit, there is also replenishment of active coagulation factors (67). Another indication for platelet transfusion is the presence of documented, active DIC.

**FRESH WHOLE BLOOD**

Fresh whole blood administration is gaining popularity to decrease blood loss post-CPB. Mohr et al. compared the hemostatic effects of transfusion of 1 unit of fresh whole blood and 10 units of platelets (68). The whole blood group showed an increase in platelet count as much as 4 units of platelets and normalization of bleeding time. Furthermore, postoperative platelet aggregation to collagen and epinephrine improved after whole blood, but not with platelet concentrates. The 24 hour blood loss was lower in the whole blood group (68). A recent study in children undergoing open heart surgery showed a significant decrease in postoperative blood loss in patients receiving fresh whole blood (69). The benefit appears greatest for children less than two years of age who have had complex surgery. The difference in blood loss is most probably due to better platelet function in fresh whole blood.

**LEUKOCYTES**

Although our own white blood cells (leukocytes) protect us
against invading bacteria, white cells in transfused blood from others produce a reaction that increases the risk of infection following surgery. Dramatic proof of this came in a recent study, by Lone Jensen, a Danish scientist. She reported to the American Society of Colon and Rectal Surgeons, that among 589 colorectal surgery patients, 23% of those receiving whole blood came down with pneumonia vs. only 3% of those receiving blood that had been filtered to remove white blood cells. The figures for wound infection were 12% vs. none, while 16.9% vs. 3.5% needed a re-operation.

In a separate study of 915 cardiac surgery patients, noncardiac postoperative mortality was 7.6% for those receiving whole blood vs. 2.5% for recipients of filtered blood.

Standard care to date has limited leukocyte-reduced blood to the critically ill or those with the highest risk of infection. Removing leukocytes from donor blood can be easily achieved through the use of blood filters. This can be done at the patient’s bedside, in the blood bank, or on CPB (70).

**PROPHYLACTIC PLATELET THERAPY**

Since the major effect of CPB on hemostatic function is platelet dysfunction, pharmacological preservation of platelet function has been studied. Iloprost, a potent synthetic analog of prostacyclin, has been successfully used to prevent platelet activation for patients with heparin-induced thrombocytopenia undergoing CPB cardiac surgery (71). Due to the hypotensive side effects, the routine use of prostacyclin is probably unjustified (1).

**DESMOPRESSIN ACETATE**

1-Deamino-8-D-arginine vasopressin (DDAVP), a synthetic analog of the antidiuretic hormone L-arginine vasopressin, induces release of Factor VIII:C and von Willebrand’s factor (vWF), a large polymeric glycoprotein required for normal platelet adhesion and normal bleeding time (BT). Release from endothelial cells appears to be the major source of vWF, which serves as a bridge for adhesion of platelets to the subendothelium or between platelets (72). However, DDAVP does not affect platelet count nor platelet aggregation (73).

Desmopressin may be administered intravenously, intranasally, or subcutaneously. Intravenously, there is an almost immediate release of Factor VIII:C and vWF which persists for 6 h. The maximal effect is seen with doses of 0.3-0.4 ug/kg (74). In both volunteers and hemophiliacs, DDAVP shortens the aPTT, even if not prolonged, but does not shorten the PT (75).

Side effects of DDAVP appear to be minor (76). Transient mild vasodilatation, 10-20% decrease in systolic blood pressure, with facial flushing is the most frequent side effect and there appears to be less incidence with slow (>15 minute) administration. Tachyphylaxis with therapy every 12-24 h for several days in some patients seems to validate the mechanism of DDAVP release from stored factors. DDAVP also releases tPA accompanied by increased plasminogen activator inhibitor. However, there is no marked increase in plasmin circulation nor are there reports of fibrinolysis. Although DDAVP has a potent antidiuretic effect, there have been no cases of clinical significance and unlike other natural antidiuretic hormones, DDAVP has very little effect on the V-1 vasopressin receptors on smooth muscle and thus does not produce vasoconstriction or contraction of visceral smooth muscles (77).

DDAVP has been shown to shorten BT in certain forms of hemophilia, von Willebrand’s disease, uremia, and other conditions, as well as improve hemostasis in conditions with no known abnormality of Factor VIII:C or vWF (78). Kobrinsky, in a series of studies on the effects of DDAVP in surgical patients, demonstrated that DDAVP reverses the aspirin-induced prolongation of bleeding time in normal subjects and decreases surgical blood loss during spinal-fusion surgery, even in subjects who were hemostatically competent preoperatively (78,79).

In cardiac surgery, Salzman et al. used DDAVP 0.3 ug/kg intravenously post-CPB in 70 patients and found decreased perioperative blood loss of 1317 ± 486 ml as compared to 2210 ± 1415 ml (80). An unexpected finding of their study was the correlation of preoperative plasma vWF levels with subsequent blood loss. Czer et al. found a decrease in bleeding time from 17 min to 12.5 min with administration of 20 µg of DDAVP and decreased blood product usage in the treatment group (81).

Despite the enthusiasm generated after the initial studies, further studies have questioned the value of DDAVP in cardiac surgery. Brown et al. have demonstrated no difference in peroperative bleeding or transfusion requirement in a study of 20 patients undergoing routine coronary artery bypass (82). Furthermore, 4 of the 10 patients in the DDAVP group experienced hypotension with the administration of the drug. In view of the side effects and the cost of DDAVP administration, they concluded that the prophylactic administration of DDAVP in routine coronary artery bypass surgery is unwarranted. Indeed, further studies are required to elucidate the patient group who will benefit from DDAVP therapy. At this time, the only indication for use in cardiac surgery is for deficiency of factor VIII:vWF.

**DIPYRIDAMOLE**

Dipyridamole, a pyridopyrimidine compound, inhibits platelet phosphodiesterase activity, increases platelet cyclic adenosine monophosphate concentrations, and decreases calcium mobilization (83). Clinically, dipyridamole has been used to inhibit venous thrombosis, and improve myocardial and cerebral blood flow. Platelet inhibiting agents may preserve platelet counts during CPB by preventing platelet aggregation on foreign surfaces and at sites of endothelial injury. Although dipyrimadole limits platelet activation, aggregation, and granular release, it preserves platelet adhesion and therefore does not inhibit platelet hemostatic functions unlike other antiplatelet agents such as aspirin which may increase postoperative bleeding (84).

Nuutinen and Mononen found a significantly higher platelet count (129,000 mm m-2 versus 82,000 mm m-2) post CPB in the group treated with 40-80 mg of intravenous dipyridamole during CPB without increased postoperative bleeding (85).
et al. confirmed the preservation in platelet count, with decreased postoperative bleeding (42-46%) in patients treated with dipyridamole during CPB (86). Intravenous administration resulted in higher platelet count and less blood loss than the oral administration. An additional benefit of perioperative dipyridamole is the improved early bypass graft patency (87). A side effect of dipyridamole is a 20-25% decrease in blood pressure due to vasodilation upon rapid intravenous administration (88), which may be eliminated by slow administration over 10 min.

**APROTININ**

The complement system may be activated by the blood: foreign surface interaction through the Hageman Factor or via the alternative pathway by C3b binding on the surface of the extracorporeal circuit (89). The activation of the fibrinolytic and the complement systems may also affect platelets and leukocytes.

Aprotinin is a proteolytic enzyme known to inhibit plasmin and kallikrein. van Oeveren et al. studied the effects of high dose (plasma concentration > 150 kallikrein inactivator units/ml) aprotinin during CPB in 11 patients and found preservation of platelet number, decreased platelet release product Thromboxane B2, and significantly less postoperative bleeding (26). As aprotinin was not successful in preventing complement activation, plasmin appears to play an important role in the prevention of platelet impairment. Plasmin may remove the bound fibrinogen from the platelets, thereby decreasing the postoperative platelet function. Platelets were protected by aprotinin, probably at the molecular level, during CPB against pathologic stimuli, but functioned normally on a physiological basis postoperatively. Royston et al. found an eight-fold reduction in postoperative blood transfusion requirement for patients undergoing repeat cardiac surgery with a similar high dose aprotinin therapy (90). The benefits of aprotinin on platelet function occur only when aprotinin is given pre-CPB.

**COAGULATION FACTORS**

Primarily due to hemodilution, there is a decrease in the levels of coagulation factors during CPB. There is an especially low level of factor V. Rush and Ellis have shown that levels greater than 30% for all coagulation factors and 15% for Factor V, are adequate for normal hemostasis (91). Therefore, even with the lower levels after CPB, bleeding due to inadequate coagulation factors is rare.

Prophylactic therapy with 6 units of fresh frozen plasma after CPB for elective coronary artery surgery in 100 patients did not reduce blood loss or transfusion requirements as body stores and synthesis of coagulation proteins maintain levels above those required for adequate hemostasis (92).

Indications for transfusion of fresh frozen plasma have been delineated by a multidisciplinary panel conference (93). The indications for administration of FFP include 1) replacement of isolated factor deficiencies, 2) reversal of warfarin effect, 3) massive blood transfusion, 4) Antithrombin-III deficiency, 5) treatment of immunodeficiencies, and 6) treatment of thrombotic thrombocytopenic purpura.

However, preoperative coagulation defects or excessive dilution by crystalloid, colloid, or packed RBC infusions may result in bleeding due to factor deficiencies. In the bleeding patient post-CPB with continuing dilution of coagulation factors, the possibility of deficiencies in the coagulation factors need to be addressed. Patients receiving thrombolytic therapy in the immediate preoperative period may require FFP and cryoprecipitate for excessive bleeding.

The laboratory abnormalities post-CPB are difficult to assess. However, the threshold of laboratory parameters that justify FFP transfusion include: PT, aPTT, TT greater than 1.3 x control; fibrinogen level of 100 mg/dl; and ACT greater than 150 s. Furthermore, abnormalities in the TEG or Sonoclot suggestive of coagulation factor deficits merit transfusion of FFP.

Cryoprecipitate (CP) contains a concentrated solution of Factors VIII:C and vWF, XIII, fibrinogen, and fibronectin. CP is indicated in the treatment of hemophilia A, von Willebrand’s disease (types II and III), and deficiencies in Factor XIII or fibrinogen. Excessive use of CP can produce elevation of fibrinogen levels, and increase the risk of thrombosis. There is no indication for use of CP in the absence of documented laboratory data.

**PRIMARY FIBRINOLYSIS**

The occurrence and the clinical significance of primary fibrinolysis during CPB is controversial. Due to early reports of primary fibrinolysis during CPB, the use of empirical antifibrinolytic therapy was advocated (94). Bick found evidence of almost universal fibrinolysis during CPB and postulated that the presence of fibrinolysis and fibrinogen degradation products may be the cause of platelet dysfunction (20). However, there was no correlation between plasmin levels and platelet adhesion. Marengo-Rowe and Levenson, who found only 8 of 774 patients with platelet counts of less than 40,000 with only 3 out of those 8 experiencing abnormal bleeding, consider fibrinolysis as the most common and important cause of bleeding after cardiac surgery (95). They have therefore tailored their treatment of post-CPB bleeding with emphasis on antifibrinolytics as first line therapy.

### Table 1: Anticoagulation protocol

<table>
<thead>
<tr>
<th>With aprotinin</th>
<th>Without aprotinin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin loading dose: 350 U/kg</td>
<td>Heparin loading dose: 200-250 U/kg</td>
</tr>
<tr>
<td>Maintain heparin concentration/Hepcon at 2.7 U/ml</td>
<td>Add 2,000-3,000 U as required to maintain</td>
</tr>
<tr>
<td>ACT (celite) &gt; 750 sec</td>
<td>ACT (celite) above 400 sec</td>
</tr>
<tr>
<td>ACT (kaolin) &gt; 500 sec</td>
<td></td>
</tr>
</tbody>
</table>
Other studies have failed to show any differences in postoperative bleeding with the use of antifibrinolytics, while McGoon and Gomes have shown an increased postoperative bleeding with the empirical use of antifibrinolytic therapy (96). Although fibrinolytic activity is shown to be increased on initiation of CPB, there is prompt resolution within minutes of the end of CPB (97). As the incidence of hypofibrinogenemia or elevated FDP titers post-CPB is low, postoperative bleeding due to fibrinolysis is rare unless there is excessive or persistent plasminogen activation and plasmin generation during or post-CPB.

**ANTIFIBRINOLYSES**

\(\varepsilon\)-aminocaproic acid (EACA), a \(\varepsilon\)-amino-carboxylic acid analog of lysine, binds to the outpouchings of plasminogen at their lysine binding sites and displaces plasminogen from the fibrin surface, thereby interfering with plasminogen’s ability to split fibrinogen. Effective EACA levels are achieved with a loading dose of 100-150 mg/kg followed by an infusion of 10-15 mg/kg/hr (98). Tranexamic acid, a cogener of EACA, is 10 times more potent and appears to have a higher therapeutic index.

Risks of EACA therapy include hypokalemia, hypotension, ventricular dysrhythmias, thromboses, and DIC (99). This agent should only be used in bleeding patients with definitive laboratory evidence of primary fibrinolysis and consultation with a hematologist (20).

**DISSEMINATED INTRAVASCULAR COAGULATION**

Disseminated intravascular coagulation (DIC) is a condition of uncontrolled systemic fibrin formation leading to intravascular thrombosis with simultaneous coagulopathy caused by consumption of coagulation components and presence of D-dimers. The differential diagnosis of DIC with secondary fibrinolysis and primary fibrinolysis may be exceedingly difficult.

Disseminated intravascular coagulation due to CPB appears to be rare, with the wide acceptance of heparin titration during CPB in the mid-1970’s. Earlier reports of DIC may have been due to low grade coagulation from inadequate heparinization. However, DIC may occur during cardiac surgery by activation of the intrinsic or extrinsic coagulation system or fibrinolytic system from shock, transfusion reactions, sepsis, and aortic dissections.

Therapy for DIC requires treatment of the precipitating cause and supportive therapy in terms of hemodynamic support, organ preservation, and transfusion of platelets, FFP, and cryoprecipitates.

**RISKS OF TRANSFUSION THERAPY**

Risks of transfusion therapy during cardiac surgery have been well documented (100). The primary risks of transfusion are transfusion reactions and infectious complications. The risk of hepatitis has been estimated to range from 4% in St. Louis to 18% in Houston (101). Despite the risks, there are certain situations where the benefits of transfusion outweigh the risks. However, one study showed that 22-26% of all intraoperative transfusions were inappropriate (102). Those who are transfusing blood products need to understand the indications and appropriately document them (103).

**CONCLUSION**

This paper has reviewed the etiology, incidence, pathophysiology, diagnosis, and therapy for the altered hemostatic system in patients undergoing cardiac surgery with cardiopulmonary bypass. Although tremendous progress has been made, further research is required to delineate the complex interaction of blood elements with foreign surfaces. With further progress, cardiac surgery may be performed with less bleeding and safer use of blood products.

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