Bleeding Complications Associated With Cardiopulmonary Bypass

By Richard C. Woodman and Laurence A. Harker

CARDIOPULMONARY bypass (CPB) for open-heart surgery (OHS) is commonly performed in hospitals throughout the world. In the United States more than 250,000 OHS procedures are performed annually, primarily for coronary artery bypass grafting (CABG).1 With improvements in surgical techniques and extracorporeal oxygenation, the overall mortality for this procedure is low (1% to 4%).2 However, excessive perioperative bleeding continues to complicate CPB. Management of the abnormal bleeding often requires reoperation and frequently is associated with excessive, and sometimes inappropriate, blood product administration that occasionally exceeds the available blood supply. In some hospitals more than 25% of all blood products are dedicated to OHS.3 A concerted multispecialty approach between cardiac surgery, hematology, and transfusion medicine is required to reduce the need for reoperation and its increased risks2,4 and to minimize the possibility of transmitting transfusion-related diseases.

The actual frequency of severe bleeding with CPB may vary, depending on the criteria used and the patient profile studied.2,4 An incidence of 3% to 5% is commonly reported when abnormal bleeding is defined as comprising more than 10 U of blood transfused in the perioperative period. When these patients undergo reoperation for excessive bleeding, more than half exhibit significant incomplete surgical hemostasis that is, at least in part, corrected by exploration. However, the remaining patients bleed because of various acquired hemostatic defects, most commonly related to acquired transient platelet dysfunction (Table 1).6 An appreciation for the various causes of bleeding following CPB and their incidence is essential for optimal management.

PATHOGENESIS

Platelets

CPB adversely affects both platelet count and function. Hemodilution causes platelet counts to decrease rapidly to about 50% of preoperative levels soon after starting CPB, but usually remain above 100,000/μL throughout bypass.6-9 Of greater significance, however, is the progressive loss of platelet function. Within minutes after starting CPB, the bleeding time (BT) is prolonged significantly and platelet aggregation to adenosine diphosphate (ADP) or collagen is impaired.7,12 The changes in BT are independent of the modest reduction in platelet count. These functional abnormalities worsen throughout CPB, and as the duration of CPB approaches 2 hours the BT progressively increases to more than 30 minutes.1,13 Similar changes in platelet counts, BT, platelet aggregation, and postoperative bleeding occur regardless of whether bubble or membrane oxygenators are used.14 Usually 20 minutes after the discontinuation of CPB and the administration of protamine, the BT shortens to approximately 15 minutes and normalizes by 2 to 4 hours.7 The platelet count usually requires several days to correct.

Platelet dysfunction appears to be dependent on contact of platelets with the synthetic surfaces of the extracorporeal oxygenator and the hypothermia associated with bypass. Studies in primates clearly demonstrate that the prolongation of BT and platelet aggregation are produced by either the oxygenator or by hypothermia.7 Recently it has been suggested that hypothermia induces reversible platelet dysfunction by impairing platelet thromboxane A2 synthesis.13

Although the exact mechanism(s) responsible for this transient platelet dysfunction remains unknown, several lines of evidence suggest that it is consequent to transient platelet activation, similar to the “refractory state” induced in vitro by ADP.9,13,16 First, CPB causes progressive increases in the plasma and urine levels of several biochemical indicators of platelet activation in vivo, including platelet factor 4 (PF4), β-thromboglobulin (β-TG), and thromboxane B2.7,16-22 Platelet functional abnormalities have also been attributed to α-granule depletion.7,16 Second, after exposure to the extracorporeal oxygenator, platelets undergo transient morphologic changes consistent with primary reversible aggregation and platelet activation.12,22 Finally, several investigators have demonstrated in both nonhuman primates and patients undergoing CPB that prevention of platelet activation by PGF, or prostacyclin (PGI2) infused into the bypass circuit abolishes the development of platelet dysfunction.16,19-21,23-25

Complete normalization of plasma PF4 and β-TG usually occurs within the first 2 to 4 postoperative hours, although the reduction in the number of platelet α-granules persists despite the improvement in platelet function, thereby suggesting that α-granule depletion and platelet dysfunction are independent consequences of CPB. Additionally, changes in the concentration of platelet adenine nucleotides, serotonin, and the number of dense granules are unaffected by CPB.7 Therefore, it is unlikely that selective release of either platelet α-granules or dense granules is responsible for the transient platelet dysfunction associated with CPB.

Platelet dysfunction after CPB also has been attributed to temporary depletion or modification of some functional platelet membrane component(s), although there is considerable controversy about these findings. Several studies have reported significant decreases in the amount of membrane antigen for glycoproteins (GP) Iib, IIb, and IIIa on circulating platelets following CPB.26-29 Platelet α2-adrenergic recep-
BLEEDING AFTER CARDIOPULMONARY BYPASS

Several mechanisms, alone or in combination, may be responsible for these membrane abnormalities. Mechanical trauma due to shear stress, surface adherence, and turbulence within the extracorporeal oxygenator may cause fragmentation of platelet membranes with a loss of surface receptors. Plasma concentrations of platelet membrane microparticles unrelated to α-granule secretion are increased after CPB and suggest membrane damage. Another consideration is the proteolytic removal of platelet membrane GP by plasmin. In vitro the incubation of platelets with plasmin (and other proteases) causes the degradation of platelet membrane GP Ib with associated loss of von Willebrand factor (vWF)-dependent, ristocetin-mediated agglutination. Plasmin also impairs ADP-induced aggregation in vitro; however, the exact mechanism has not been determined. Evidence for plasmin-mediated alterations in platelet behavior in vivo is not convincing, although the ability of the protease inhibitor aprotinin to minimize GP Ib loss after CPB does provide further evidence to implicate plasmin in the development of platelet dysfunction. Despite these observations, no correlation between bleeding and platelet activation or platelet membrane abnormalities has been established.

Coagulation Factors

Shortly after starting CPB, predictable reductions in the plasma concentration of coagulation factors II, V, VII, IX, X, and XIII occur, primarily due to hemodilution. For reasons that are unclear, only factor V levels decrease more than can be predicted by dilution alone. Nonetheless, all coagulation factors, including factor V, remain well above levels normally considered to be adequate for hemostasis (ie, ≥15% for factor V and ≥30% for all other clotting factors), even in patients with excessive bleeding following CPB. In contrast to the other coagulation factors, plasma factor VIII levels remain within normal limits during and after CPB despite hemodilution. Generally, all coagulation factors (with the exception of fibrinogen) normalize by the first 12 hours after CPB. The prothrombin time (PT) and activated partial thromboplastin time (APTT) are usually normal following discontinuation of CPB and protamine administration.

A complex and poorly understood relationship exists between CPB and the concentration and multimeric composition of vWF. During bypass, and unrelated to hemodilution, the plasma concentration of vWF generally decreases but usually remains well above levels normally considered adequate for hemostasis. Indeed, increased functional activity by ristocetin cofactor measurements has been reported in vitro. Despite the reduction in plasma vWF concentration during CPB, some investigators but not all have demonstrated an increase in the proportion of high-molecular-weight multimers (HMWM), suggesting the release of stored vWF, possibly from platelet α-granules. Although patients who had a preoperative vWF level of less than 1.8 U/mL had a tendency toward excessive postoperative bleeding, neither the pre- nor the postoperative vWF levels or multimeric patterns are clinically useful as predictors of bleeding. After CPB there is an increase in the total plasma concentration of vWF (characteristic of an acute-phase reactant) and the proportion of lower-molecular-weight multimers. The post-bypass concentration of vWF appears to be adequate for hemostasis.

An acquired deficiency of HMWM has been described in association with valvular heart disease and noncyanotic congenital heart disease. Although the mechanism responsible for the loss of HMWM remains unknown, proteolysis or turbulence may both be contributing factors. In children with noncyanotic congenital heart disease, the reduced HMWM are sometimes associated with bleeding symptoms, prolonged BT, decreased vWF concentrations, and diminished ristocetin cofactor activity. In adults, it has been suggested that the reduced HMWM may contribute to the increased incidence of gastrointestinal mucosal bleeding reported in association with aortic stenosis. These patients generally require no special management before OHS; surgery is usually followed with correction of the vWF multimeric pattern and improvement in hemostasis.

Heparin Rebound and Protamine Excess

Heparin is administered during CPB to prevent clotting in the extracorporeal oxygenator. Its administration is usually adjusted to maintain an activated clotting time (ACT) of 350 to 500 seconds (normal ≤130 seconds). After returning blood from the extracorporeal oxygenator to the patient at the end of CPB, heparin is routinely neutralized by the administration of protamine sulfate. Different reversal protocols are used, but usually about 1 mg of protamine is given for every 100 U of heparin administered throughout the operation. (Several investigators recommend protamine dosages based on total milligrams of heparin given during the intraoperative period, usually trying to achieve a protamine-to-heparin ratio of ≥1:1. This approach is not recommended because [1] heparin is almost always administered in terms of units; [2] there is an imprecise and variable
relationship between units and milligrams; and [3] present-day purified heparin preparations contain variable amounts of low- and high-molecular-weight heparin forms. Adequacy of protamine neutralization may be monitored by whole blood clotting times, occasionally with protamine titration or plasma heparin levels.

Heparin rebound has been proposed as one cause of bleeding after CPB. This diagnosis is based on the reappearance of a prolonged ACT, often performed in conjunction with protamine titration. However, its exact frequency, pathogenesis, and role in CPB-related bleeding remains poorly established. Obviously the ACT is prolonged by other factors, including hypofibrinogenemia, coagulation factor deficiencies, or the presence of acquired inhibitors. Although excess protamine sulfate has been reported to produce anticoagulant and antiplatelet effects, these phenomena are probably in vitro artifacts without clinical significance. Thus, a second dose of protamine sulfate for the management of excessive post-CPB bleeding is generally safe, but indicated only when the first dose of protamine is less than the ratio of 1 mg protamine per 100 U heparin. However, protamine injections also have occasionally been associated with mild transient thrombocytopenia, increases in the ACT and PTT, and a spectrum of allergic reactions. For example, skin rash, urticaria, bronchospasm, increased pulmonary artery pressure, hypertension, cardiogenic shock, and anaphylaxis have been reported to occur occasionally within 10 to 20 minutes of protamine administration. Mild hypotension has been attributed to transient peripheral vasodilation. Patients suggested to be at risk for the life-threatening allergic reactions include vasectomized men, patients with fish allergies, diabetics with impaired platelet function, and IgE. The incidence of protamine-mediated anaphylaxis is low, occurring in 0.6% to 2% of neutral protamine Hagedorn insulin-dependent diabetics compared with 0.6% in the general OHS population.

The usefulness of preoperative screening of patients at risk for protamine-induced allergic reactions remains unverified, and at present these risk factors do not constitute contraindications to protamine administration. Other potential heparin antagonists include hexadimethrine bromide and methylene blue. Unfortunately, the availability and clinical characterization of these agents is extremely limited. Spontaneous reversal of heparin anticoagulation is another alternative to protamine that has been used successfully in OHS. However, in patients with excessive bleeding after CPB, this approach may not be appropriate and more rapid neutralization of heparin with protamine sulfate may be required.

Consumptive Coagulopathy and Fibrinolysis

Historically, bleeding after CPB has been attributed to excessive fibrinolysis beginning after sternotomy, increasing throughout CPB, and persisting for up to 2 hours after CPB. Hypothermia and prolonged pump times were considered to aggravate hyperfibrinolysis. It has been suggested that pleural, pericardial, and periosteal surfaces contain plasminogen activator-like substances that initiate fibrinolysis. However, the findings implicating fibrinolysis, ie, a shortened euglobin lysis time, a prolonged PT and APTT, hypofibrinogemia, and elevated fibrinogen-degradation products (FDP) have probably reflected dilution by non-blood-priming solutions, inadequate heparinization, consumption of platelets and fibrinogen by surgically damaged tissue, and secondary fibrinolysis. Nonetheless, hyperfibrinolysis emerged as a perceived cause of bleeding after CPB and prompted the common surgical practice of administering antifibrinolytic agents such as epsilon aminocaproic acid (EACA) to patients undergoing OHS.

Subsequent and more detailed studies of fibrinolysis during and after CPB have shown that increased fibrinolysis is usually not the principal cause of bleeding. Both plasma fibrinogen and plasminogen levels decrease during CPB not due to consumption but primarily due to hemodilution. Generally, fibrinogen and plasminogen normalize by 12 and 24 hours after CPB, respectively. α2-Antiplasmin and antithrombin III undergo similar changes due to hemodilution. Moreover, total clottable fibrinogen levels do not change detectably with CPB, thus excluding a significant defect in fibrin polymerization due to FDP.

Although consumption is generally not significant, there are circumstances such as cardiogenic shock, sepsis, or crush injury when consumptive coagulopathy may produce thrombocytopenia and hypofibrinogenemia during or after CPB.

Aspirin-Related Bleeding

Patients taking aspirin before CABG have excessive and prolonged mediastinal bleeding complicating CPB. To illustrate, a recent large prospective multicenter randomized study reported that aspirin (325 mg) administration 12 hours before CABG was associated with significantly increased postoperative bleeding, transfusion requirements, and reoperation rates. Importantly, initiating aspirin therapy early postoperatively (6 hours) obviates the bleeding complication while preserving aspirin’s beneficial effects on increasing graft patency. In view of these results, aspirin should not be administered preoperatively. When possible, aspirin should be discontinued at least 5 days before CPB. The management of aspirin-related post-CPB bleeding is similar to that for other acquired platelet defects, consisting of monitoring the BT, administering desmopressin, and transfusing platelets.

MANAGEMENT OF CPB-RELATED BLEEDING

The management of CPB-related bleeding begins with its recognition. Although most of the recent studies regarding CPB and hemostasis have used blood loss or transfusion requirements during the first 24 postoperative hours to define excessive bleeding, these criteria may not be useful for immediate bedside evaluation and early intervention. A more practical clinical definition may be postoperative chest tube drainage of ≧ 100 mL/h. A common cause of bleeding following CPB is a localized defect in surgical hemostasis. However, it may be difficult to distinguish bleeding due to an acquired systemic coagulopa-
thy from a localized surgical problem unless the patient has obvious evidence of a generalized bleeding tendency such as epistaxis or oozing from catheter sites. In the absence of a coagulopathy, bleeding that exceeds 10 mL/kg in the first postoperative hour or an average of ≥5 mL/kg in the first 3 postoperative hours has been suggested as a guideline for reoperation. Any sudden bleeding after chest tube drainage has stopped is also considered an indication for reoperation. Patients who undergo reoperation through a previous sternotomy, regardless of the indication, often experience excessive bleeding, particularly in the intraoperative period. Aspirin administration, infective endocarditis, and prolonged pump times may be important risk factors. The need for reoperation due to hemorrhagic complications has decreased over the past decade and is currently reported to be approximately 5%. A suspicious history for a bleeding disorder or a documented bleeding disorder are at high risk of surgical bleeding. A schema for preoperative hemostatic evaluation has been proposed by Rapaport (Table 2). To identify the rare patient with a mild undiagnosed congenital bleeding disorder and no prior bleeding history, it recommends preoperative evaluation for all patients undergoing CPB, including a platelet count, template BT, PT, APTT, factor XIII screen (urea clot lysis), and a whole blood clot lysis. Because this screening approach has a low yield of detecting abnormalities compared with the number of tests performed and the number of artifactually abnormal test results, many centers have discontinued routine screening. However, the proposed screening serves the following purposes: (1) safeguarding against an inadequate history or an unreliable historian; (2) detecting coagulopathies that only present postoperatively or that are mild and present only postoperatively; and (3) uncovering acquired hemostatic defects that have developed since the last hemostatic challenge. In any event, for patients with a bleeding history the screening evaluation is indicated, and if the screening tests are negative additional evaluation is required to identify abnormalities not always detected by the initial elevation, including a thrombin time (TT), plasma a2-antiplasmin activity, assays for circulating inhibitors, factor VIII and IX activity levels, and platelet aggregation studies. The aspirin tolerance test, vWF levels, and vWF multimers are not recommended as preoperative tests in patients undergoing CPB.

**BLOOD ADMINISTRATION**

Although perioperative blood loss has decreased little over the past 2 decades, transfusion practices associated with CPB have changed dramatically. Since 1972 the total average blood loss in adults after CPB has remained at about 1,000 mL, whereas total postoperative administration of homologous red blood cells (RBC) has decreased from greater than 8 U to less than 3 U. The factors primarily responsible for this trend have been an acceptance of lower postoperative hematocrits and an awareness of the risks associated with blood transfusion.

**Homologous Blood Transfusion**

Conventional practice after CPB involves transfusion of RBC to maintain hematocrits ≥30% (or hemoglobins ≥10.0 g/dL). Although earlier data suggested that decreased tissue oxygenation occurs in surgical patients with hematocrits less than 30%, there is no other available evidence to support this guideline. For example, patients with myocardial infarction, congestive heart failure, or neurologic complications tolerate hematocrits of less than 28%. In general, blood products should be administered for specific clinical indications and in the presence of bleeding.

Transfusion-transmitted viral diseases have become the most significant complication of CPB and underscore the need for appropriate and judicious blood product administration. Cardiac surgery patients account for 27% of individuals contracting transfusion-transmitted acquired immunodeficiency syndrome (AIDS), a risk that is directly related to their exposure to homologous blood products. Although the use of human immunodeficiency virus (HIV) seronegative

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Screening History</th>
<th>Proposed Surgery</th>
<th>Recommended Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>Negative</td>
<td>Minor (eg, dental extraction)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>± Prior surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Negative</td>
<td>Major (eg, cholecystectomy)</td>
<td>Platelet count, APTT</td>
</tr>
<tr>
<td></td>
<td>Prior surgery</td>
<td></td>
<td>As above plus</td>
</tr>
<tr>
<td>Moderate</td>
<td>Possible bleeding disorder</td>
<td>CNS, CPB, Prostatectomy</td>
<td>BT, PT, Urea clot lysis, Whole blood clot lysis</td>
</tr>
<tr>
<td>High</td>
<td>Highly suspicious or documented bleeding disorder</td>
<td>Major or minor</td>
<td>As above plus, if negative, FVIII–FIX levels, Thrombin time, a2 antiplasmin, Platelet aggregation</td>
</tr>
</tbody>
</table>

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**Table 2. Preoperative Hemostatic Evaluation**

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viral hepatitis after CPB occurs in 6% to 10% of patients undergoing cardiac surgery with a mortality rate approaching the number of units administered or with the transfusion of fresh frozen plasma (FFP). These patients are also at risk for developing chronic hepatitis and cirrhosis.82~88

In addition to the other well-recognized complications of transfusion therapy,88 transfusion-associated graft-versus-host disease has recently been reported in patients undergoing cardiac surgery with a mortality rate approaching 90%.91,92 This complication appears to be related to the administration of fresh, nonirradiated whole blood from a blood donor homozygous for one of the recipient’s HLA haplotypes. In view of these findings, packed RBC are probably preferable to fresh whole blood during CPB.

**Autologous Blood Transfusion for Elective CPB**

The risk of alloimmunization and transfusion-transmitted viral diseases may be avoided by transfusing previously deposited autologous blood. Unfortunately, this service remains an underutilized source of blood for patients undergoing elective CPB.93,94 Although initially there was concern that donations could precipitate myocardial ischemia if vasovagal reactions occurred, several studies have clearly shown that preoperative phlebotomy is well tolerated by the majority of patients with underlying cardiovascular disease,52,95~98 and rarely induces angina.52,95,96 Vasovagal reactions occur in about 4% of autologous donations, equivalent to that for homologous donations.97 Patients with unstable angina, left main coronary artery stenosis, and critical aortic stenosis have generally been excluded from autologous blood donation programs.96

Phlebotomies are frequently scheduled at 4- to 7-day intervals, with the last donation occurring at least 72 hours before the operation.83,98,99 Usually a hematocrit of ≥ 34% (or hemoglobin >11 g/dL) is required before each donation. About two thirds of the patients scheduled for elective OHS have donations deferred because of anemia.97 Oral iron supplementation, started before phlebotomy and continued postoperatively, has been recommended to minimize the development of anemia.97,99 Recombinant erythropoietin with preoperative autologous blood collection is an alternative that has not yet been reported in patients undergoing OHS. The insertion or crossover of unused autologous blood into the homologous blood pool remains controversial.99 If autologous blood is crossed over, it must meet the standard donor criteria, including testing for ABO and Rh type, alanine aminotransferase (ALT) level, crossmatching, antibodies, syphilis, hepatitis B surface antigen, HIV, and human T-cell leukemia virus (HTLV-III).97,99

In patients undergoing elective CPB who are capable of donating more than 2 U of autologous blood, the administration of homologous blood can be completely avoided in 65% of cases compared with 20% for patients unable to deposit autologous blood.97 Furthermore, 100% of patients donating only 1 U of blood and 71% of patients donating 2 U of autologous blood subsequently required homologous blood products. A preoperative donation of 3 U is associated with only a 4% reduction in hematocrit.95,97 In the complex OHS cases (CABG plus valvular replacement) in which bypass times often exceed 120 minutes, it has been recommended that 4 U of autologous blood be collected preoperatively.82 Therefore, it appears that a donation of at least 3 U is preferable. Although the preoperative collection of autologous platelets and FFP by apheresis before CPB is under investigation, the guidelines for patient selection are variable and have not yet been standardized.

**Reinfusion of Intraoperative and Postoperative Autologous Blood**

Other techniques to reduce the requirement for homologous blood transfusion following CPB, have included: (1) intraoperative phlebotomy followed by hemodilution and autotransfusion; (2) intraoperative reinfusion of blood salvaged from the surgical field using the cell separator; (3) postoperative reinfusion of shed mediastinal blood (SMB); and (4) more extensive use of bloodless volume expanders.98,93,95 Intraoperative salvage and reinfusion practices have had variable and uncertain benefits on homologous blood requirements and obviously are not useful in patients with excessive bleeding postoperatively.68,98,99~103 Although the postoperative reinfusion of SMB can be given without significant risks of infection, microemboli, or coagulopathy,68,100,104,105 it has had variable success in reducing the need for homologous RBC transfusions and obviously does not affect platelet requirements.68,83,100,105 The hematocrit of unwashed SMB varies from 20% to 30%83,101,105 but can be increased with hemoconcentration after washing.68 Other features of SMB include reduced clotting factors with the exception of factor IX,68 and in vitro the platelets have abnormal aggregation.58,106 Unwashed SMB also contains high titers of FDP and infusion results in elevated plasma FDP levels.68 Although elevated FDP theoretically may cause platelet dysfunction and impair fibrin polymerization, more importantly it may lead to an incorrect diagnosis of consumptive coagulopathy or fibrinolysis with the institution of inappropriate therapy, especially in patients with bleeding complications.68 Despite the safety of SMB, the benefits are unproven and the postoperative reinfusion of SMB, particularly unwashed, does not appear warranted.

**Platelet Transfusions**

Because CPB causes transient platelet dysfunction, some centers have routinely provided random donor platelets for CPB patients.107 To test the usefulness of administering prophylactic platelet transfusions, two prospective randomized studies have been performed.107,109 In both studies 4 U of random donor platelets were infused immediately after discontinuation of the extracorporeal oxygenator and after protamine injection. No clinically significant benefit with respect to transfusion requirements, blood loss, platelet counts, bleeding times, or postoperative hospital stay was demonstrated by either study. Although beneficial effects of transfusing more platelets was not excluded by these studies, a recent National Institutes of Health consensus conference109...
recommended that prophylactic platelet transfusions not be routinely administered following CPB.11,111

Obviously, platelet transfusions are indicated for patients with excessive bleeding caused by thrombocytopenia who are receiving blood replacement after CPB. In this setting both platelet dysfunction, as measured by a prolonged BT, and platelet count should determine the need for platelet transfusions. Normally in patients without bleeding complications the BT shortens significantly (<15 minutes) 20 minutes after CPB and has returned almost to normal (<9 minutes) 2 hours after CPB. In patients with excessive bleeding the BT remains prolonged (>22 minutes) for several hours after CPB, and the bleeding is controlled and the BT shortened (<15 minutes) by platelet transfusions. Transfusion of 1 U of random-donor platelets per 10 kg body weight has been recommended. Clinical response, platelet counts, and possibly BT measurements should be used to monitor the efficacy of platelet transfusions. The BT measurement generally provides useful diagnostic information but may be variably affected by the complexities of bypass. Single-donor HLA-compatible plateletapheresis units may be required for patients in whom alloantibodies have previously formed to random donor platelets.

Transfusion of FFP and Cryoprecipitate

The indications for the administration of FFP or cryoprecipitate in CPB are specific and limited. There is no evidence to support the prophylactic transfusion of either FFP or cryoprecipitate during or after CPB.108,111-114 Particularly, FFP administration is not indicated for volume expansion, nutritional support, wound healing, or factor replacement in patients receiving massive transfusions, because in general none of the coagulation factors decrease to levels sufficient to cause abnormal bleeding or require replacement.

Administration of FFP during CPB should generally be reserved for patients with acquired deficiencies of vitamin K-dependent coagulation factors caused by warfarin or congestive hepatomegaly. FFP may rarely be required for patients with inherited deficiencies of factor V, VII, X, or XI who are undergoing cardiac surgery. If a high concentration of fibrinogen (90 mg/mL) is used, local hemostasis may be successfully achieved in more than 95% of patients despite the presence of systemic heparinization.11 The fibrin glue has been claimed to be particularly useful in OHS associated with internal mammary grafts, reoperations for bleeding, and vascular prostheses. Although intravascular coagulation has not been reported by the use of the fibrin glue, infusion of the thrombin and cryoprecipitate directly into the vascular space or bypass pump must be avoided. Other potential complications of this material include tamponade due to adhesions and transfusion-transmitted viral infections, although the risk does not exceed that associated with plasma transfusion.112,114

**DRUG THERAPY**

Aprotinin

Infusion of the protease inhibitor aprotinin (Trasylol; Bayer AG, Leverkusen, West Germany) during OHS greatly decreases blood loss and normalizes bleeding time (Table 3). This naturally occurring polypeptide inhibits serine proteases, including trypsin, kallikreins, plasmin, and plasmin-streptokinase by reversibly complexing the active site serine. Whereas aprotinin given as a bolus injection after CPB produced no obvious benefit, continuously infused aprotinin therapy, initiated before and maintained for up to 12 hours, was effective in reducing bleeding and transfusion requirements.3

**Table 3. Usual Dosage of Hemostatic Agents Used in CPB**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Routine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>IV bolus 300 IU/kg followed by CII to maintain intraoperative ACT between 350 and 600 s or PTT 1.5-2.0 times normal</td>
<td>38</td>
</tr>
<tr>
<td>Protamine</td>
<td>Administered after CPB at ~1 mg/100 U of total perioperative heparin</td>
<td>38, 41, 42</td>
</tr>
<tr>
<td>Aprotinin</td>
<td>Preoperative IV loading dose of 280 mg followed by CII of 70 mg/h during CPB. Just before termination of CPB, a second loading dose of 280 mg is added to the blood in the pump.</td>
<td>84, 126, 127</td>
</tr>
<tr>
<td><strong>Therapeutic</strong></td>
<td></td>
<td></td>
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<tr>
<td>Desmopressin</td>
<td>0.3 µg/kg IV (maximum 21 µg) over 15–30 min for excessive postoperative bleeding</td>
<td>11, 36, 132, 133, 135</td>
</tr>
<tr>
<td>EACA</td>
<td>Preoperative IV loading dose of 5–10 g followed by CII of 1 g/h until completion of surgery</td>
<td>3, 125, 139</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; CII, continuous IV infusion.
throughout OHS, produced substantial reductions in BT, perioperative bleeding, and transfusion requirements for patients undergoing first-time elective CABG (20% of the aprotinin-treated patients required homologous blood transfusion compared with 95% of the control patients). Patients undergoing repeat CABG also showed considerable reduction in postoperative blood loss (approximately 1,500 mL) and transfusion requirements (8 of 35 aprotinin-treated patients required a total of 10 homologous U of blood compared with a total of 41 U for the 11 untreated patients) after prophylactic aprotinin therapy. Additionally, in an uncontrolled study of 15 patients undergoing OHS for bacterial endocarditis, similar reductions in perioperative blood loss and transfusion requirements were achieved with prophylactic aprotinin therapy. The results of these studies are summarized in Table 4.

In all of these studies a dosage of aprotinin was used that maintained a constant intraoperative plasma aprotinin concentration of approximately 4 μmol/L. This concentration has been reported to inhibit plasmin in vitro, and has been reported to prevent platelet activation and aggregation and to block the loss of platelet membrane GPIb during CPB. However, it is not clear how these effects of aprotinin on normalizing hemostatic function might be related to inhibition of plasmin or coagulation cascade serine proteases. Unraveling the mechanism whereby aprotinin acts may provide some important clues regarding the acquired platelet defect associated with CPB.

Aprotinin clearly represents a promising prophylactic agent in the management of CPB-related bleeding. It may be particularly beneficial for patients at high risk for CPB-related bleeding (bacterial endocarditis and reoperations) or those patients who will not accept blood transfusions. At present, a past history of known or suspected pancreatitis, allergic reactions, or previous exposure to aprotinin constitute contraindications to aprotinin therapy.

Desmopressin

The hemostatic properties of the synthetic vasopressin analogue desmopressin acetate (desmopressin; 1-deamino-8-D-arginine vasopressin) were first demonstrated in patients undergoing dental extractions with mild or moderate hemophilia and vWD. Over the past decade desmopressin has proven to be useful as a relatively nonspecific hemostatic agent for a variety of surgical and clinical bleeding problems, including CPB. The reductions in blood loss often have been associated with a shortening of the bleeding time.

In a randomized double-blind trial of patients undergoing CPB for valvular heart disease alone or in conjunction with CABG, a significant reduction in perioperative blood loss (900 mL over 24 hours) was achieved when desmopressin was administered immediately after protamine infusion. In a second prospective study, desmopressin reduced bleeding and RBC and platelet transfusion requirements in patients experiencing excessive postoperative CPB bleeding. In these patients a significant improvement in bleeding time, vWF, factor VIII, and PTT followed desmopressin administration. Detailed analyses of perioperative vWF levels and vWF multimers, particularly HMWM, demonstrated that the hemostatic benefits of desmopressin in CPB were not explained by increases in HMWM or vWF levels. Although it has been suggested that desmopressin may cause premature saphenous vein graft occlusion, three prospective studies reported no increase in the frequency of graft occlusion. In general, desmopressin administration has been well tolerated without episodes of perioperative hypotension or acute myocardial infarctions.

In a recent randomized double-blind study of 150 consecutive patients undergoing elective CPB, Hackmann et al found no significant difference in blood loss or postoperative transfusion requirements in the patients receiving desmopressin at the end of CPB. They also failed to detect any difference in ristocetin cofactor activity or vWF multimeric patterns with desmopressin administration. Similarly, in another randomized study of 100 patients undergoing OHS for atrial septal defects or valvular heart disease, Rocha et al reported no significant reduction in postoperative blood transfusion requirements by prophylactic desmopressin, although a marginal reduction in blood loss (60 mL/m²) was found in treated patients. On the basis of these trials, it appears that desmopressin should not be given routinely, but reserved for postoperative administration in those patients experiencing excessive post–CPB-related bleeding. The results of the above studies are summarized in Table 5.

### Table 4. Aprotinin-Induced Reductions in Blood Loss and Transfusion Requirements After CPB

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>Average Postoperative Blood Loss (mL)</th>
<th>Postoperative Homologous Transfusion Requirements</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary elective CABG</td>
<td></td>
<td></td>
<td>Postoperative Homologous Transfusion Requirements</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>37</td>
<td>573</td>
<td>35 (96)</td>
<td>75</td>
</tr>
<tr>
<td>Aprotinin</td>
<td>40</td>
<td>309*</td>
<td>8 (20)</td>
<td>13</td>
</tr>
<tr>
<td>Complex CABG (reoperation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>11</td>
<td>1,509</td>
<td>11 (100)</td>
<td>41</td>
</tr>
<tr>
<td>Aprotinin</td>
<td>11</td>
<td>286†</td>
<td>4 (36)</td>
<td>5</td>
</tr>
<tr>
<td>Aprotinin</td>
<td>24</td>
<td>245</td>
<td>4 (16)</td>
<td>5</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aprotinin</td>
<td>15</td>
<td>388</td>
<td>6 (40)</td>
<td>11</td>
</tr>
</tbody>
</table>

*P > .01.
†P > .001.
Table 5. Controlled Trials Using Desmopressin With CPB

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Patient Population</th>
<th>N</th>
<th>Blood Loss/24 h</th>
<th>BT</th>
<th>Transfusion/24 h</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Randomized</td>
<td>Repeat CABG</td>
<td>70</td>
<td>900 mL</td>
<td>NS</td>
<td>NS</td>
<td>133</td>
</tr>
<tr>
<td>Double-blind</td>
<td>Valvular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonrandomized</td>
<td>CABG</td>
<td>39</td>
<td>1,700 mL</td>
<td>&gt;4.0 min (P &lt; .05)</td>
<td>7 U platelets/patient (P = .004)</td>
<td>11</td>
</tr>
<tr>
<td>Therapeutic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized</td>
<td>Valvular</td>
<td>100</td>
<td>NS</td>
<td>&gt;4.0 min (P &lt; .001)</td>
<td>NS</td>
<td>135</td>
</tr>
<tr>
<td>Double-blind</td>
<td>ASD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized</td>
<td>CABG</td>
<td>150</td>
<td>NS</td>
<td>ND</td>
<td>NS</td>
<td>36</td>
</tr>
<tr>
<td>Double-blind</td>
<td>Valvular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.3 μg/kg desmopressin given IV over 15–30 minutes after CPB and protamine. Abbreviations: NS, not significant; ND, not done; ASD, atrial septal defect.

*Transfusion requirements in first 24 postoperative hours.

Table 6. Controlled Trials Using Prophylactic EACA in CPB

<table>
<thead>
<tr>
<th>Reference</th>
<th>Condition</th>
<th>N</th>
<th>Placebo</th>
<th>EACA</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>138</td>
<td>Cyanotic</td>
<td>30</td>
<td>62*</td>
<td>35*†</td>
<td>Significant reduction in bleeding greatest immediately after CPB and for patients with bypass times &gt;60 min</td>
</tr>
<tr>
<td></td>
<td>Acyanotic</td>
<td>26</td>
<td>29*</td>
<td>26*</td>
<td></td>
</tr>
<tr>
<td>139</td>
<td>Elective CABG</td>
<td>60</td>
<td>332‡</td>
<td>272‡‡</td>
<td>2 EACA-related acute MI Controls lower preoperative plasma fibrinogen levels Postoperative platelet counts slightly higher with EACA</td>
</tr>
<tr>
<td>3</td>
<td>Elective CABG</td>
<td>350</td>
<td>883§</td>
<td>617§§</td>
<td>Reduction in transfusion requirements exceeded blood loss No increase in postoperative thrombotic complications with EACA</td>
</tr>
</tbody>
</table>

Abbreviation: MI, myocardial infarction.

*μL/kg body weight.
†P < .02.
‡μL for the first 12 postoperative hours.
§μL for the first 24 postoperative hours.
†P < .05.
The minimal benefit of EACA with respect to bleeding and the uncertainty regarding risk for increasing thrombotic events have generally discouraged its clinical use.

The effect of other lysine analogues such as the longer acting tranexamic acid (AMCA; Cyclokapron Kabivitrum, Alameda, CA) on CPB-related bleeding has recently been evaluated in a randomized double-blind trial with results similar to that described previously with EACA.145

Prostaglandins

The capacity of PGI₂ and its analogues to protect platelets from activation and subsequent destruction during CPB have been studied extensively. PGI₂ inhibits platelet activation by stimulating adenyl cyclase to increase intracellular cyclic adenosine monophosphate levels.146 Its immediate potent but reversible inhibition of platelet activation, together with its rapid clearance in vivo (~3 minutes), characterize PGI₂ as an attractive agent for protecting platelets during CPB without affecting coagulation processes.19 Initial studies in experimental animals undergoing CPB demonstrated that PGI₂ preserved circulating platelets and decreased blood loss.24,147 Using a baboon model, Malpass et al also demonstrated that PGI₂ prevented prolongation of the bleeding time when administered within the therapeutic window of 40 to 80 ng/kg/min.16 However, experimental animal studies also demonstrated that CPB performed with PGI₂ alone without heparin anticoagulation produced depletion of the consumable clotting factors and excessive thrombosis within the extracorporeal circuit.24

Randomized double-blind trials of prophylactic PGI₂ administration in humans undergoing CPB have been performed without conclusive evidence for benefit.19-21,23,25,148,149 Although there were differences in (1) PGI₂ dosages (ranging from 10 to 100 ng/kg/min); (2) site of administration; (3) initiation of therapy; and (4) duration of the PGI₂ infusion, the most consistent finding among all studies was the dose-dependent production of vasodilation and hypotension requiring aggressive management. Despite a modest improvement in perioperative platelet counts by PGI₂ in some studies, there was no significant associated reduction in postoperative blood loss or transfusion requirements.19,21,149 Thus, there are no demonstrated clinical indications for using PGI₂ in CPB. Iloprost (Berlex Laboratories Inc, Cedar Knolls, NJ), a stable potent PGI₂ analogue, has similarly been reported to preserve platelet counts and produce hypotension during extracorporeal circulation.22 At present there is no clinical evidence to support the routine use of Iloprost during CPB. However, of some clinical relevance, Iloprost therapy may protect the platelet count in patients with heparin-induced thrombocytopenia (HIT) who receive heparin during CPB despite the presence of heparin-associated platelet antibodies.

SPECIFIC HEMOSTATIC COMPLICATIONS DURING CPB

HIT

Patients undergoing CPB necessarily require heparin anticoagulation during CPB. Thrombocytopenia complicates heparin therapy in about 2% to 5% of these patients.150 The onset and severity of HIT is variable, usually occurring within 6 to 12 days of heparin administration but occasionally beginning earlier in patients who have had previous exposure.150,151 HIT occurs independent of dose or route of heparin administration, but does not always recur with heparin rechallenge and may even resolve during heparin therapy. In most patients the thrombocytopenia is mild and not associated with bleeding; however, occasionally it may be complicated by life-threatening bleeding and acute arterial thrombosis, including myocardial infarction, stroke, and limb ischemia.152-154 Unfortunately, at present there is no reliable method for predicting which patients develop HIT.190,151,154-156

It recently has been shown that a specific antiheparin IgG antibody binds to repeating antigenic determinants in heparin, which in turn bind to the surface of the platelet through an unidentified 82-Kd platelet membrane protein.157 Immune platelet destruction results. It has also been determined that platelet membrane GP Ib, IIb, IIIa, or IX are not involved in the pathogenesis of HIT.156 The heparin–platelet interaction may be influenced in vitro by such factors as the molecular weight and sulfation of heparin, antithrombin III binding, and the presence of the platelet α-granule proteins thrombospoindin and histidine-rich GP.158 When the heparin–antibody complex forms, the IgG binds to the platelet Fc receptor and initiates platelet activation with serotonin release and subsequent platelet aggregation.150,158,159 This activation process is independent of complement fixation, occurs in vitro at therapeutic heparin concentrations (but not at higher concentrations), and forms the basis for the serotonin platelet-release assay.154,155 Unbound immune complexes in the plasma of patients with HIT have not been detected and it is unclear why the heparin–IgG complexes preferentially bind to platelet Fc receptors as opposed to granulocyte/monocyte high-affinity Fc receptors. The relationship between heparin–IgG complexes and thrombotic complications also remains unexplained. Assays of heparin-dependent platelet aggregation or the presence of platelet-associated IgG are of limited diagnostic value because of their lack of specificity and sensitivity.154,160-162 However, improved sensitivity and specificity for detecting HIT has been achieved by measuring platelet serotonin released by heparin at high (100 U/mL) and therapeutic (0.1 U/mL) concentrations.153,160

In the postoperative period HIT is often a diagnosis of exclusion and must be distinguished from other potential causes of postoperative thrombocytopenia such as sepsis, disseminated intravascular coagulation, posttransfusion purpura, hemodilution, fat emboli, use of an intra-aortic balloon pump, or medications other than heparin. In this context a diagnosis of HIT necessitates immediate discontinuation of any heparin administration. Platelet transfusions should not be given prophylactically and are only indicated for bleeding complications. Acute arterial thrombosis occasionally has been precipitated by platelet transfusions.153,163

The management of patients with HIT associated with CPB is influenced by whether they present pre-operatively or postoperatively (Fig 1). It has been recommended that patients with known or suspected HIT may safely undergo a
bleeding after cardiopulmonary bypass

Fig 1. Management approach for patients developing HIT during or after CPB. Currently Iloprost, Ancrod, and Heparinoid (ORG 10172) are investigational in the United States.

The appropriate management of patients with HIT who must undergo emergency CPB remains uncertain, but several alternatives to standard heparin anticoagulation have been suggested. Warfarin, low-molecular-weight dextran, low-molecular-weight heparins (LMWH), heparinoids, and ancrod (Arvin) have all been considered as possible anticoagulant regimens to heparin anticoagulation during CPB. The prostacyclin analogue Iloprost has also been reported to protect platelets during heparin anticoagulation for CPB. Clearly no optimal alternative to heparin during CPB has been demonstrated. Some success has been reported with heparinoid when prescreening with the heparinoid by in vitro tests for heparin antibody is negative. At present Iloprost, ancrod, or hirudin are investigational agents. When possible it may be more prudent to postpone surgery until the heparin-specific IgG has disappeared. One approach reported to be successful involves a continuous intraoperative infusion of Iloprost administered concurrently with a porcine heparin preparation. The perioperative bleeding, transfusion requirements, BT, and platelet counts were comparable with historical controls and the hypotension often associated with the prostacyclins was adequately managed by intraoperative phenylepinephrine infusions. The dose of Iloprost varied between 3 and 36 ng/min/kg and is difficult to determine preoperatively and to titrate intraoperatively.

The defibrinating agent ancrod (Arvin) has also been reported to be successful during CPB, although others have recommended that surgery is contraindicated with ancrod therapy. Preoperative fibrinogen levels of 0.4 to 0.8 g/L are required for successful anticoagulation during CPB; reduced levels will persist for several days. Ancrod also has been proposed as an alternative to heparin during CPB for patients with protamine-induced allergic reactions or antithrombin III deficiency. Currently ancrod is under investigation in the United States for stroke and HIT.

Heparinoid (ORG 10172), composed of heterogeneous porcine polysulfated heparin and nonheparin glycosaminoglycans, has been used in a limited number of cases of HIT, including CABG. Although heparinoid provided adequate anticoagulation and stabilized or improved platelet counts, significant postoperative bleeding requiring discontinuation of the drug and administration of FFP occurred in some patients. LMWH have also been used in HIT when the assay for heparin-dependent platelet aggregation was negative to LMWH. In the presence of a positive assay for platelet aggregation, 4 of 11 patients had an unfavorable clinical outcome.

Hirudin, a specific potent polypeptide inhibitor of thrombin, has recently been cloned and sequenced. Recombinant
hirudin is a theoretically attractive but untested alternative to heparin anticoagulation during CPB.

**Inherited Disorders of Coagulation Factors**

CPB and OHS for congenital heart disease, acquired valvular heart disease, and coronary artery disease have been performed successfully in patients with hemophilia A, hemophilia B, vWD, factor VII deficiency, and factor XI deficiency (Table 7). The management of these patients is similar to the standard recommendations given for patients with inherited coagulopathies undergoing other kinds of major surgery. Complete replacement of the missing clotting factor and maintenance at therapeutic levels throughout surgery and 2 weeks postoperatively using appropriate concentrates is required. It is important to appreciate that replacement therapy for patients with mild deficiencies undergoing CPB must be as vigorous as for severely deficient patients. The presence of inhibitors to factor VIII or factor IX is presently considered to be an absolute contraindication to elective OHS, although the availability of activated factor VII concentrates may influence this guideline. During CPB, heparin anticoagulation followed by protamine neutralization is required in the conventional dosages, and EACA therapy is generally not used.

There are a number of special considerations in OHS. First, at the completion of CPB, additional factor may need to be administered to achieve appropriate therapeutic levels. Second, desmopressin administration in patients with hemophilia A and vWD undergoing OHS has not been emphasized, although the usual recommendations regarding a test dose, tachyphylaxis, contraindications (type Ib and pseudo-vWD) and its use for the treatment of excessive CPB-related bleeding still apply. Obviously, desmopressin alone will not provide adequate hemostasis during CPB in any patient with hemophilia A or vWD regardless of their underlying factor VIII levels. Third, the use of either activated or unactivated prothrombin complex concentrates (PCC) in OHS for factor IX replacement have been associated with thrombotic complications, including acute myocardial infarction and pulmonary embolism. Liver disease, prolonged administration, and excessive doses of PCC appear to increase the risk of developing thrombotic complications. The addition of heparin to the PCC (60 U per vial) has been recommended to cover the period immediately after administration while activated species of clotting factors are being cleared. Fourth, nonsteroidal anti-inflammatory drugs are avoided after OHS in patients with hereditary bleeding disorders. Finally, to avoid the risk of systemic emboli arising from implanted heart valves without using oral anticoagulation, bioprostheses are preferable in patients with underlying inherited bleeding disorders.

**Emergency CABG After Unsuccessful Thrombolytic Therapy and Angioplasty**

Between 5% and 15% of patients receiving thrombolytic therapy for evolving acute myocardial infarction may develop either coronary reclosure or cardiogenic shock and require emergency coronary angioplasty or CABG. Because streptokinase, urokinase, and to a lesser extent tissue-type plasminogen activator (tPA) destroy fibrinogen and coagulation factors V and VIII, thrombolytic therapy greatly compounds the hemostatic problems in these patients during CPB. In one retrospective study, about 19% of patients who had emergency CABG after receiving thrombolytic therapy and angioplasty developed perioperative bleeding complications. In addition to hypofibrinogenaemia and the depletion of factors V and VIII, defective fibrin polymerization and platelet dysfunction are produced by high levels of FDP during thrombolytic therapy. Although there is no in vivo evidence for direct plasmin-induced platelet dysfunction, platelet aggregation in vitro has been inhibited by: (1) plasmin-mediated proteolysis of platelet GP Ib and IIb/IIIa, (2) plasmin-mediated FDP elevation, (3) plasmin-mediated degradation of platelet-bound fibrinogen, and (4) plasmin-mediated inhibition of thromboxane A2 synthesis.

In one series of 24 patients undergoing emergency CABG after unsuccessful streptokinase therapy and angioplasty, an average perioperative blood loss of more than 1,400 mL was observed and all 24 patients required substantial postoperative transfusion with RBC, FFP, and platelets. Surprisingly, only 11 of the 24 patients had abnormal postoperative coagulation parameters (PT, PTT, platelet count, fibrinogen level, and FDP; PT not obtained), which were often attributed to inadequate heparin neutralization. A reptilase time

---

**Table 7. Patients With Inherited Deficiencies of Hemostasis Undergoing CPB**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>No. of Cases</th>
<th>Factor Replacement</th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>Duration of Replacement Therapy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>vWD</td>
<td>6</td>
<td>Cryoprecipitate</td>
<td>&gt;80</td>
<td>40–200</td>
<td>4–10</td>
<td>80, 81, 117–119, 185</td>
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<tr>
<td></td>
<td></td>
<td>FFP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>4</td>
<td>Cryoprecipitate</td>
<td>22–190</td>
<td>30–100</td>
<td>7–42</td>
<td>120, 182–184</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FVIII concentrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Megadoses of FVIII concentrate preoperatively then CII of FVIII intraoperatively</td>
<td>600</td>
<td>&gt;40</td>
<td>8</td>
<td>185</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>4</td>
<td>FIX concentrate</td>
<td>23–90</td>
<td>12–90</td>
<td>7–14</td>
<td>120, 186–188</td>
</tr>
<tr>
<td>Factor XI deficiency</td>
<td>1</td>
<td>FFP</td>
<td>22</td>
<td>20–26</td>
<td>8</td>
<td>116</td>
</tr>
<tr>
<td>Factor VII deficiency</td>
<td>1</td>
<td>FFP</td>
<td>ND</td>
<td>50–100</td>
<td>2</td>
<td>115</td>
</tr>
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</table>
may be helpful in distinguishing fibrinolysis from inadequate protamine administration. Based on various thrombolytic trials, it appears unlikely that FDP or fibrinogen would be useful as predictors of perioperative bleeding due to thrombolytic therapy.48 Significant perioperative bleeding and increased transfusion requirements were reported in 2 of 24 patients (8%) undergoing emergency CABG after unsuccessful thrombolysis with recombinant tPA (r-tPA).198 Although no randomized study has directly compared hemorrhagic complications after thrombolytic therapy with either streptokinase or r-tPA, the transfusion requirements and the fibrin-specific effects of r-tPA suggest that r-tPA might result in less bleeding after emergency CABG.48,198

Thus, emergency CABG may be safely performed after thrombolytic therapy, although the exact management of postoperative hemostasis has not been established. Prophylactic aprotinin is most likely to be beneficial in this setting, although it has not yet been formally tested in this subset of patients undergoing CABG. The indications for the use of intraoperative and postoperative EACA therapy remains uncertain,46,196 and the routine preoperative administration of replacement blood products such as cryoprecipitate or FFP has not been studied and currently cannot be recommended.

Total Artificial Hearts and Ventricular Assist Devices

Bleeding is a common cause of morbidity and mortality in patients with ventricular assist devices (VAD) and total artificial hearts (TAH).136 In one report, 22 of 30 patients on VAD required a total of 24 reoperations for hemorrhagic complications.49 An acquired platelet defect appears to be the most frequent cause of bleeding.136 It has yet to be determined whether this defect is the same as that associated with CPB. Effective management usually requires: (1) prolonged systemic anticoagulation with heparin or warfarin; (2) platelet inhibition with dextran, aspirin, and dipyridamole; and (3) liberal administration of platelets and FFP. In at least one center, aprotinin also has been routinely used during TAH implantation.200 Desmopressin has been used empirically to control bleeding in patients with VAD; however, the effectiveness of this approach remains to be established.136

Cryoglobulinemia

Because moderate systemic hypothermia (25 to 28°C) is routinely used during OHS, it may present special risks for patients with cryoglobulinemia and cold agglutinin disease if the thermal amplitude of the cryoprotein falls within the range of the anticipated surgical temperatures. Thus, it becomes important to determine the thermal amplitude in patients with established disease, because preoperative plasmapheresis203 and regional pericardial-myocardial hypothermia20,204 have been reported to provide effective management in a limited number of instances.

SUMMARY

Bleeding after CPB has been difficult to characterize and its treatment equally difficult to standardize. The complexity of this problem is related to the hemostatic process, the technical variations in the operative procedures, and the many uncontrolled variables associated with CPB, including the effects of anesthetic or pharmacologic agents, the nature of the priming solution, hemodilution, hypothermia, the type of oxygenator, and the use of transfused blood products. Although there are multiple and generally predictable complex changes in the hemostatic mechanism during CPB, the temporary loss of platelet function is the most common and clinically relevant. This transient platelet dysfunction occurs in all patients undergoing CPB; however, it only causes excessive bleeding in a small percentage of patients. Unfortunately, it has not yet been possible to predict which patients will develop hemorrhagic complications, although prolonged pump times are a contributing risk factor.

Over the past decade there has been extensive investigation into the management of bleeding associated with CPB, provoked primarily by the increased awareness of transfusion-transmitted viral diseases and the inappropriately excessive use of homologous blood products. Several approaches to autotransfusion of shed blood and autologous blood donation have been developed to minimize perioperative homologous blood transfusion. Pharmacologic agents such as desmopressin, aprotinin, and topical fibrin glues have also been introduced to improve hemostasis during CPB. The protease inhibitor aprotinin is particularly promising in the reduction of bleeding associated with CPB when given prophylactically. Aprotinin may provide new insights into the mechanism of CPB-induced platelet dysfunction. Desmopressin is indicated only for the treatment of bleeding after CPB. The management of bleeding associated with CPB will undoubtedly continue to improve.

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BLEEDING AFTER CARDIOPULMONARY BYPASS


Bleeding complications associated with cardiopulmonary bypass

RC Woodman and LA Harker