Hematologic Issues in Cardiovascular Surgery Patients

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Introduction
The hematologic management of the cardiac surgical patient entails a complex balance between extreme degrees of anticoagulation and the restoration of normal hemostasis after the procedure. These two opposing processes must be managed carefully and modified with respect to preoperative disease state, duration of cardiac surgery, use of extracorporeal circulation, and the desired hemostatic outcome. During cardiopulmonary bypass (CPB), optimal anticoagulation dictates that coagulation is minimized and platelets are kept quiescent, so that microvascular clots do not form in the extracorporeal circuit. The dramatic increase in interventional cardiology procedures to treat coronary artery disease (stents, lasers, etc.) have made anticoagulation mandatory during these procedures and anti-thrombotic therapy essential afterward.

The increase in heparin exposure has heightened our awareness of heparin resistance and heparin-induced thrombocytopenia. Following CPB, coagulation abnormalities, platelet dysfunction, and fibrinolysis occur and render the patient hemostatically impaired. Bleeding should be managed using careful hemostasis monitoring. Fibrinolysis can be prevented and transfusions minimized by the use of antifibrinolytic therapy. Proper use of these agents and their safety will be discussed. Uncontrolled hemorrhage has been anecdotally treated with success using activated Factor VII, yet the safety of this agent has not been confirmed in large scale trials. The increased complexity of the cardiac surgery patient population has made the treatment of hemorrhage an area of research for new pro-coagulant therapies. This complex hemostatic picture is coupled with the concurrent use of anti-thrombotic medication in the cardiovascular patient in both the preoperative and the postoperative periods. The frequent and prevalent use of multiple anti-platelet medication is of great concern to the cardiovascular anesthesiologist as they increase bleeding after surgery and they increase bleeding-related complications.

Heparin Resistance
Heparin resistance is marked by the inability to raise the activated clotting time (ACT) to therapeutic levels after the administration of heparin. Acquired resistance to heparin occurs in patients who have been treated with heparin.1 These patients were initially responsive to heparin as evidenced by an elevated ACT, but with continued treatment with heparin, resistance to its anticoagulant effects occurs. Patients on preoperative heparin therapy traditionally require larger heparin doses to achieve a given level of anticoagulation. Possible etiologies for this resistance include AT3 depletion, enhanced factor VIII activity, platelet activation, or any combination of these factors. Heparin is known to activate platelets which will shorten ACT values. The direct thrombin inhibitors do not activate platelets, an attribute that will be discussed later in this chapter. Data now suggest that LMWH also contributes to platelet activation and heparin resistance.2 Non-responsiveness to heparin can be due to a congenital deficiency or abnormality of the activity of antithrombin III (AT3). In congenital states, the only way to elicit a response to heparin therapy is to administer exogenous AT3, either in the form of plasma or a factor concentrate. In vitro addition of ATIII enhances the ACT response to heparin. Further, low levels of AT3 are associated with negative outcomes in cardiac surgery.3 But it is unclear if a low AT3 level portends adverse outcomes because of the diminished anticoagulant response to heparin, or because it serves as a “marker” for a patient with a more advanced risk profile (on preoperative heparin). The true heparin requirements during CPB in patients with acquired heparin resistance is not known because the ideal ACT and its correlation with outcomes has not yet been demonstrated.4,5 The administration of fresh frozen plasma as a source of AT3 for heparin resistance is not recommended due to the risks of allogeneic transfusion of blood products. A stable heat-treated AT3 concentrate is available and its use has been shown to minimize the activation of the coagulation system in patients undergoing CPB.6 A recombinant form of AT3 (Atryn®, GTC Therapeutics) has been approved in 2009 by the US Food and Drug Administration. It is approved for the prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient or hemodialysis patients. Atryn is
being studied as a method of treating heparin resistant cardiac surgical patients and can and will probably be used off-label for this purpose until such studies are completed.

**Heparin Induced Thrombocytopenia Syndrome (HIT, HITS)**
The syndrome known as HITS develops in anywhere from 5% to 28% of patients receiving heparin. There is a general reduction in platelet count due to platelet membrane increased adhesiveness, that occurs when platelets are exposed to heparin. This is a benign situation and is characterized by an early and mild decrease in platelet count. HITS or HITT (with thrombosis) is a pathologic condition that most often occurs after more than 5 days of heparin administration (average onset time, 9 days), and it is mediated by antibody binding to the complex formed between heparin and platelet factor 4 (PF4). Among patients developing HIT II, the incidence of thrombotic complications approximates 20%, which in turn may carry a mortality rate as high as 40%. A highly specific enzyme-linked immunosorbent assay for the heparin/PF4 complex has been used to delineate the course of IgG and IgM antibody responses in patients exposed to unfractionated heparin during cardiac surgery. Bedside antibody tests that utilize ELISA techniques or particle gel immunoassays are being used in Europe and soon in the US. These tests may speed the diagnosis of HITT and allow functional testing to be performed more rapidly.

Demonstration of heparin-induced proaggregation of platelets confirms the diagnosis of HIT type II. This can be accomplished with a heparin-induced serotonin release assay, or a specific heparin-induced platelet activation assay. The risks and appropriate courses of action in patients with HIT II are unclear because the antibodies associated with heparin-induced thrombocytopenia often become undetectable several weeks after discontinuing heparin. Also the clinical syndrome does not always recur upon reexposure to the drug and sometimes resolves despite continued drug therapy. Many patients never develop thrombosis and disseminated intravascular coagulation despite positive laboratory testing. Heparin-induced thrombocytopenia should possibly be considered in the differential diagnosis of intraoperative heparin resistance in patients receiving preoperative heparin therapy. The options for treating these patients are few. If one has the luxury of being able to discontinue the heparin for a few weeks, often the antibody will disappear and allow a brief period of heparinization for CPB without complication. Supplementing heparin administration with pharmacologic platelet inhibition using prostacyclin, iloprost, aspirin, or tirofiban have been reported, all with favorable outcomes. Plasmapheresis may be used to reduce antibody levels. The use of heparin could be avoided altogether by anticoagulating with a direct thrombin inhibitor. See Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Heparin</th>
<th>Direct Thrombin Inhibitors</th>
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<tbody>
<tr>
<td><strong>Mode of action</strong></td>
<td>Indirect</td>
<td>Direct</td>
</tr>
<tr>
<td><strong>Catalyst needed</strong></td>
<td>Yes- anti-thrombin 3</td>
<td>No</td>
</tr>
<tr>
<td><strong>Inhibits clot-bound thrombin</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Activates platelets</strong></td>
<td>Yes (LMWH moderately yes)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Antigenicity</strong></td>
<td>Yes</td>
<td>No (bivalirudin) Yes (hirudin)</td>
</tr>
<tr>
<td><strong>Antidote drug</strong></td>
<td>Yes- protamine</td>
<td>No</td>
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Hirudin and Congeners
Hirudin is a coagulation inhibitor isolated from the salivary glands of the medicinal leech (Hirudo medicinalis), hirudin is a potent inhibitor of thrombin. Currently available via recombinant genetics, this substance is a polypeptide (molecular weight of approximately 7,000 Daltons). The APTT prolongation correlates well with plasma hirudin concentrations but does not correlate well with chromogenic antifactor II levels. For this reason, a surrogate APTT using the snake venom ecarin for activation has been described. 10,11 Platelet aggregation is also better preserved with hirudin than with heparin. Hirudin does not activate platelets nearly as much as unfractionated heparin does. This property of direct thrombin inhibitors makes them more “bio-friendly” than unfractionated heparin. Using direct thrombin inhibitors preserves platelet activity and reduces release of platelet activation markers as compared to unfractionated heparin.

Bivalirudin is a synthetic peptide formerly known as Hirulog® and currently marketed as Angiomax® (The Medicines Company, Parsippany, NJ, USA). A bivalent thrombin inhibitor, bivalirudin consists of one moiety that binds thrombin on its active-site cleft, and a second hirudin-like C-terminal region that binds thrombin at its positively charged surface groove known as the anion-binding exosite. Bivalirudin is a synthetic derivative of hirudin and thus acts as a direct thrombin inhibitor. Thrombin itself cleaves the part of the bivalirudin molecule that binds to it, so bivalirudin activity elimination is independent of specific organ metabolism. Bivalirudin has been used successfully as an anticoagulant in interventional cardiology procedures as a replacement for heparin. In fact, in interventional cardiology, bivalirudin has been associated with less bleeding and equivalent ischemic outcomes when compared to heparin plus a platelet inhibitor. Bivalirudin anticoagulation induces less P-selectin expression than do either UH or LMWH, indicating less platelet reactivity and possibly platelet protection. In off-pump coronary artery bypass surgery, Merry et al. found equivalent bleeding outcomes with bivalirudin and heparin, and the bivalirudin patients exhibited higher graft flows.12 A prospective randomized trial in 150 patients undergoing CPB surgery demonstrated similar procedural outcomes adverse event rates with bivalirudin and heparin.13 This CPB trial dosed bivalirudin at 1 mg/kg as an intravenous bolus followed by 2.5 mg/kg/hr as in infusion. When bivalirudin is used, care must be exercised to ensure the absence of stasis in the CPB circuit lest thrombin be formed and metabolize bivalirudin.

Desirudin, a new injectable direct thrombin inhibitor that is now available for subcutaneous injection in patients who cannot receive heparin. New oral direct thrombin inhibitors are also coming to the commercial market as a replacement for warfarin in the treatment of patients with atrial fibrillation.

Monitoring the direct thrombin inhibitors is one of the current challenges in the use of these agents. The ecarin clotting time better correlates with anti-IIa activity and plasma drug concentrations than does the ACT, and it is available using the Cascade POC Testing Device (Helena Inc, Beaumont TX). Modified ACT (1 to 1 dilution of patient blood with FFP) and the standard ACT have also been used safely to monitor the anticoagulant effects of bivalirudin. In multicenter clinical trials using bivalirudin during CPB, an ACT of two and one half times the baseline value was accepted as therapeutic.

Argatroban (MW 527 Daltons) is a synthetic derivative of arginine that inhibits thrombin by binding only to its catalytic site. It is approved for use as an alternative anticoagulant to heparin for patients with HIT and it is frequently the drug of choice for the treatment of medical (non-surgical) patients who cannot receive heparin. Like hirudin and bivalirudin (and unlike heparin), argatroban inhibits both circulating and fibrin-bound thrombin. The plasma elimination half-life is approximately 40 minutes, and the agent is metabolized by the liver with biliary elimination. Thus, argatroban offers appeal in patients with severe renal insufficiency or renal failure. Argatroban anticoagulation for CPB is initiated (with or without a loading dose) with a bolus of 0.1-0.2 mg/kg followed by an intravenous infusion at 5-10 µg/kg/min (less if there is hepatic insufficiency), and the dose is then adjusted to maintain the aPTT 1.5 – 3 times normal. The ACT may also be used to guide therapy, in which case the optimal ACT level appears to be 300-400 seconds. Argatroban has been used safely as a heparin substitute for CPB, however many bleeding complications have been reported. Argatroban has also been used successfully for anticoagulation during pediatric cardiac surgery with CPB and for extra-corporeal membrane oxygenation. Problems with both bleeding and clotting (even in the same patient) have been reported, so the drug may be unsatisfactory for CPB, or alternatively the optimal dosing and monitoring may have not yet been determined.
Antifibrinolytic Therapy
Prophylactic use of synthetic antifibrinolytic agents aminocaproic acid (EACA), tranexamic acid (TA), and the serine protease inhibitor aprotinin has been shown to reduce bleeding and transfusion requirements after CPB in randomized trials and in multiple meta-analyses. Presumably these effects are a result of the inhibition of fibrinolysis and the indirect inhibition of plasmin’s anti-platelet effects. Aprotinin has not been commercially available since November 2007 when it was removed from the market due to adverse effects published in observational trials. These data described an increased occurrence of renal dysfunction using aprotinin in non-randomized patients using a propensity score matching procedure to eliminate confounding variables. The preponderance of prospective randomized evidence suggested that aprotinin treatment was not associated with adverse end-organ outcomes. The BART trial, a prospective randomized trial of excessive bleeding comparing aprotinin with EACA and TA found an increase in all cause mortality in the aprotinin group despite a reduction in the incidence of bleeding. Until the causes of death in the aprotinin-treated patients can be found to be related to or unrelated to the drug and its actions, aprotinin is no longer available for commercial use, though this may be revisited.

Anti-Platelet Therapeutics in Cardiovascular Patients
Anti-thrombotic therapy for the treatment of acute coronary syndromes and interventional cardiology procedures is increasing and the development of new drugs continue. Treatment of patients after implant of a drug-eluting stent includes 12 months of anti-thrombotic therapy which poses a risk for patients who require surgery in that time period. Cardiovascular patients who are maintained on drugs such as clopidogrel and prasugrel, have increased bleeding complications and morbidity after cardiac surgery. There is evidence that an increased risk of infection exists in cardiac surgical patients who have taken clopidogrel and aspirin prior to surgery. This may be a result of an increased volume of transfusion, an increase in bleeding itself, or an independent effect. These drugs (thienopyridine agents) act by non-competitive antagonism at one of the platelet ADP receptors, the P2Y12 receptor. The P2Y12 receptor inhibits cyclic AMP production and potentiates platelet aggregation. The duration of anti-platelet activity is the life-span of the platelet because the P2Y12 receptor is permanently altered. The effects of clopidogrel plus aspirin are not just additive, they are synergistic and this may explain why cardiac surgical patients having received this combination of drugs seem to have excessive postoperative bleeding. Ticagrelor, a new anti-thrombotic agent with reversible inhibition of platelet aggregation is a more attractive alternative for patients who may be at high risk for requiring a surgical procedure. Specific monitoring of the platelet defect induced by these anti-thrombotic drugs would be advantageous for a number of reasons. For therapeutic efficacy, the degree to which patients are protected from thrombotic events is related to the degree of platelet inhibition. Thus platelet function monitoring can be used for titrating drug effect. However, when patients present for surgery after discontinuation of clopidogrel, specific platelet function testing is useful in order to determine the risk of bleeding need for transfusion. A number of point-of-care platelet function assays have been developed that utilize ADP and can assess the degree of platelet inhibition with some degree of accuracy as compared with standard aggregometry. Platelet function tests are listed in Table 2.
Table 2

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Mechanism/Agonist</th>
<th>Clinical Utility</th>
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<tbody>
<tr>
<td>Thromboelastograph®</td>
<td>Viscoelastic/Thrombin (native), ADP, arachidonic acid (AA)</td>
<td>Post-CPB, liver transplant, pediatric, obstetrics, drug efficacy</td>
</tr>
<tr>
<td>ROTEM®</td>
<td>Viscoelastic/Thrombin</td>
<td>Post-CPB?, drug efficacy</td>
</tr>
<tr>
<td>Sonoclot®</td>
<td>Viscoelastic/Thrombin</td>
<td>Post-CPB, liver transplant</td>
</tr>
<tr>
<td>PlateletWorks®</td>
<td>Platelet count ratio/ADP, AA, collagen</td>
<td>Post-CPB, drug therapy</td>
</tr>
<tr>
<td>PFA-100®</td>
<td>In vitro bleeding time/ADP, epinephrine</td>
<td>vWD, congenital disorder, aspirin therapy, post-CPB</td>
</tr>
<tr>
<td>VerifyNow®</td>
<td>Agglutination/TRAP, AA, ADP</td>
<td>Drug therapy</td>
</tr>
<tr>
<td>Clot Signature Analyzer®</td>
<td>Shear-induced in vitro bleeding time/Collagen</td>
<td>Post-CPB, drug effects</td>
</tr>
<tr>
<td>Whole blood aggregometry Multiplate analyzer</td>
<td>Electrical impedance/Many</td>
<td>Post-CPB, drug effects</td>
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Many of the POC tests listed in Table 2 can also be used in transfusion algorithms used to treat bleeding patients in the perioperative period. Many of the platelet function assays are useful to detect patients who have residual antithrombotic therapy on board and those that have CPB-induced bleeding. Specific transfusion algorithms and their efficacy and applicability to clinical practice will be discussed.

Recombinant Activated Factor VII

Recombinant Factor VIIa (rVIIa) has been reported to be effective in restoring hemostasis that results from severe hemorrhagic complications after CPB. Originally this drug was prescribed for patients with specific factor deficiencies such as Hemophilia A with inhibitors. rVIIa induces hemostasis directly at the site of bleeding by binding to locally expressed tissue factor. This activated Factor VII then activates Factor X of the common coagulation pathway and Factor IX of the intrinsic coagulation pathway. Thrombin generation is enhanced but without systemic activation of coagulation. Occasional case reports indicate that in severe uncontrolled hemorrhage, after other possible therapeutic modalities were exhausted, recombinant factor VIIa was effective in attenuating bleeding after CPB and in other surgical settings. A small randomized trial in 20 cardiac surgical patients demonstrated significantly fewer transfusions in the rVIIa group. Observational data indicate a higher incidence of adverse events who receive rVIIa late rather than early in the course of hemorrhage. A multicenter trial of rVIIa in cardiac surgery revealed that patients who received rVIIa versus placebo had a higher incidence of adverse events, including stroke, but this difference was not statistically significant. Mechanistically, rVIIa may reduce the bleeding due to platelet inhibitor therapy. The thrombin burst that is created during the propagation phase of coagulation may augment platelet function to a degree that is clinically acceptable and restores hemostasis. rVIIa use may have enjoyed a transient increase when aprotinin was withdrawn from clinical use and synthetic antifibrinolytic agents became the standard treatment even for high risk patients. This is another area of potential study for the clinical use of rVIIa. In addition to rVIIa, new methods of delivering thrombin, fibrinogen, and procoagulant factors are being investigated for the treatment of bleeding in cardiac surgical procedures.
Summary
The hematologic abnormalities of CPB result from contact with extracorporeal surfaces and the resultant abnormalities of coagulation, fibrinolysis, and inflammation. These abnormalities are not solely due to CPB as they exist in off-pump cardiac surgical patients as well. Concomitant anti-thrombotic drug therapy has increased bleeding in cardiac surgery and further underscores the need for point of care testing of the hemostatic system. Combinations of therapies (antifibrinolytic therapy plus rVIIa) require further investigation in cardiac surgery to assess the benefit and risks.

References:

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