Activation of the Hemostatic System During Cardiopulmonary Bypass

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Cardiopulmonary bypass (CPB) is a unique clinical scenario that results in widespread activation of the hemostatic system. However, surgery also results in normal increases in coagulation activation, platelet activation, and fibrinolysis that are associated with normal wound hemostasis. Conventional CPB interferes with normal hemostasis by diluting hemostatic cells and proteins, through reinfusion of shed blood, and through activation on the bypass circuit surface of multiple systems including platelets, the kallikrein-kinin system, and fibrinolysis. CPB activation of the kallikrein-kinin system increases activated factor XIIa, kallikrein, bradykinin, and tissue plasminogen activator levels, but has little effect on thrombin generation. Increased tissue plasminogen activator and circulating fibrin result in increased plasmin generation, which removes hemostatic fibrin. The nonendothelial surface of the bypass circuit, along with circulating thrombin and plasmin, lead to platelet activation, platelet receptor loss, and reduced platelet response to wounds. In this review, we highlight the major mechanisms responsible for CPB-induced activation of the hemostatic system and examine some of the markers described in the literature. Additionally, strategies used to reduce this activation are discussed, including limiting cardiotomy suction, increasing circuit biocompatibility, antithrombin supplementation, and antifibrinolytic use. Determining which patients will most benefit from specific therapies will ultimately require investigation into genetic phenotypes of coagulation protein expression. Until that time, however, a combination of approaches to reduce the hemostatic activation from CPB seems warranted. (Anesth Analg 2011;113:1319–33)

The hemostatic system consists of 4 integrated components: the coagulation system, endothelium and regulatory proteins, platelets, and fibrinolysis. These elements work together to prevent blood loss from injured vasculature without occluding the entire vessel. In certain situations, however, this activation inappropriately spreads systemically, creating both coagulopathy and thrombotic complications. Cardiac surgery with the use of cardiopulmonary bypass (CPB) is one such scenario that results in widespread activation of the hemostatic system. This can result in micro thrombi during CPB, coagulation defects after its termination, and even hypercoagulability leading to thrombotic complications in the postoperative period. In this review, we examine the current concepts thought to be involved with CPB-induced activation of the hemostatic system, as well as some of the potential interventions to minimize clinical sequelae.

THE IMPORTANCE OF THROMBIN AND ITS MEASUREMENT

At the site of a wound (Fig. 1), platelets bind to collagen through von Willebrand factor, activate and aggregate forming an initial hemostatic plug. Active factor VII (FVIIa) in blood binds wound tissue factor (TF) leading to activation of factor IX (FIXa) and factor X (FXa), which in turn activate prothrombin to thrombin.1,2 Once thrombin is formed, it becomes the key regulatory protein, activating platelets and factors V, VIII, and XI, which accelerates coagulation, while activation of fibrinogen and factor XIII stabilizes the hemostatic clot. Thrombin formed at the site of a wound we term “hemostatic” thrombin because it is participating in normal hemostasis.

Under some conditions, thrombin and fibrin may be generated without wounds. This can occur locally as in deep venous thrombosis or systemically because of widespread organ damage (shock, sepsis) or systemic release of procoagulants such as TF and anionic phospholipids (brain injury). Excessive local or systemic thrombin and fibrin formation are not being made in response to a wound site but represent dysregulation of the coagulation system and may result in consumptive coagulopathy and in some cases disseminated intravascular coagulation, bleeding, and thrombosis. This is termed “nonhemostatic” thrombin and fibrin.

The average amount of thrombin produced in vivo throughout the vascular system can be estimated by measuring levels of the thrombin activation markers prothrombin fragment F1.2 or thrombin-antithrombin complex (TAT).3–6 The rate of thrombin production is not the same as the average level of thrombin activity in blood. The average amount of thrombin activity in vivo can be estimated by measuring fibrinopeptide A (FPA) levels, a measure of fibrinogen activation to fibrin by thrombin (Fig. 2). To interpret activation markers, it is important to understand how changes in production of the marker affect marker levels. If the marker has a short half-life and rapid clearance such as FPA ($t_{1/2}$ 4 minutes) or TAT ($t_{1/2}$ 10

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The concentration of the marker in blood will change in parallel with the formation rate and is essentially a direct measure of the formation rate of the marker. If the marker has a longer half-life and slower clearance such as prothrombin activation peptide F1.2 (t1/2 90 minutes) or d-dimer (t1/2 8 hours), the concentration of the marker during CPB is cumulative, thus the change or slope of the concentration versus time curve is proportional to the formation rate, not the concentration itself. Most activation markers are proteins or protein fragments that are cleared by the liver. The clearance rate remains the same even when marker production is increased. In most patients, liver blood flow is well maintained during CPB and marker clearance seems to be similar to preoperative values.

The surgical wound produces increased hemostatic thrombin and fibrin at the wound site, but has little systemic effect. Immediately after going on CPB, hemodilution by the priming fluid in the bypass circuit reduces all factors in blood including coagulation factors, inhibitors, and activation markers, by approximately 30% to 40% (Fig. 3). Changes during CPB in stable factor levels with long half-lives, such as albumin, coagulation proteins, and antithrombin (AT), primarily reflect hemodilution, blood loss, and transfusion with consumption having only a minor role. Hemodilution tends to obscure the underlying changes occurring in the hemostatic system during CPB. Because all proteins in the blood are diluted equally at the start of CPB, any factor that does not decrease must be undergoing a rapid increase in formation to maintain its concentration at preoperative levels. Most studies present activation data as marker level versus sample number with no reference to time or hemodilution effects. With this kind of data, it is difficult to gauge what the underlying rate of activation is. One approach is correction for hemodilution, that is, dividing results by the average percent change in stable factor levels to give an indication of what the marker level would be if hemodilution had not occurred. If hemodilution-corrected results are plotted versus sample time, it is possible to get a sense of the magnitude and rate of change in the system. The problem with correction for hemodilution is that it produces a set of values that are not the actual measured values from the patient, but adjusted values based on a simple dilution model.

Another approach to the analysis of hemostatic data is to use a computer to account for changes in marker levels caused by alternations of patient blood volume, hemodilution, blood loss, blood transfusion, timing of samples, and clearance of proteins. In most studies, none of these factors is accounted for when presenting raw measurements of marker levels in blood, yet conclusions are drawn from changes in the marker levels as if these effects were known. Computer analysis or modeling allows the reader to know the specific assumptions made in analyzing the data, what was accounted for, and what was not. As new information is developed, the model can be updated to improve the analysis. When all of the factors affecting marker levels are accounted for, it is possible to estimate the formation rate in vivo of thrombin or other factors. It is further possible to validate the estimate of formation rate by comparing rates based on different markers that measure the same process but have different clearance rates and thus marker patterns.
for raw data. Figure 4 shows the estimated in vivo thrombin formation rate. The overall best estimate can be determined based on the average or best fit data using both markers. Computer modeling is not the same as de novo simulation; modeling is essentially a more complete method for correcting hemodilution and other processes that affect marker levels.

Conventional CPB leads to substantial increases in thrombin activation markers, unrelated to the surgical wound itself. Figure 5 shows the estimated rate of thrombin generation, total fibrin generation, and soluble fibrin generation using computer analysis of data from one study of conventional CPB. After thoracotomy, there was only a small increase in the total amount of thrombin and fibrin generated. However, within 5 minutes of starting CPB, thrombin generation and soluble fibrin formation both increased approximately 20-fold, but because the patient was heparinized, thrombin activity and total fibrin generation actually decreased. Normally, fibrin does not circulate in blood; it is present only at the site of the wound. Soluble fibrin is nonhemostatic fibrin formed in circulating blood due to dysregulation of hemostasis in some way. Under normal circumstances, only approximately 1% of the fibrin formed circulates as soluble fibrin, and the remainder stays in the wound. Soon after CPB is started, total fibrin formation is reduced because of heparinization whereas soluble fibrin formation is increased to approximately 35% of the total. This indicates that much of the thrombin being formed during CPB is nonhemostatic thrombin, in turn producing soluble fibrin. Non–wound-related thrombin generation and soluble fibrin formation continue to be 5- to 10-fold increased throughout the remainder of CPB. Soluble and circuit-bound fibrin provide binding sites for non–wound-related thrombin that protects this thrombin from inhibition by AT, necessitating high-dose heparin as an anticoagulant.

Another burst of nonhemostatic thrombin and soluble fibrin generation occurs after reperfusion of the heart and lungs. Thrombin generation after reperfusion may be involved in myocardial ischemia-reperfusion injury and impaired hemodynamic recovery, but the increase in thrombin generation after reperfusion is reduced or eliminated if shed blood is not reinfused. After protamine reversal, there is another peak in thrombin generation as more thrombin and fibrin are produced at the site of the wound. The increase in postoperative thrombin generation lasts hours to days and then begins to decrease toward baseline levels.

An in vitro thrombin generation test, also called calibrated automated thrombography, measures the ability of plasma to generate thrombin when stimulated, termed the “endogenous thrombin potential” (ETP). Briefly, the method adds TF and phospholipids to the patient’s platelet-poor plasma and monitors the cleavage of a fluorogenic substrate, producing a curve, the area under which represents ETP. Low ETP, such as can occur after CPB, may indicate a hypocoagulable state and bleeding risk, whereas high ETP may predict possible thrombotic risk. Two limitations of the ETP are
Figure 4. Computer model of in vivo thrombin production. This figure shows 2 approaches used to analyze in vivo thrombin production during cardiopulmonary bypass (CPB). The top row of graphs shows the original measured levels of thrombin activation markers. The second row shows hemodilution corrected marker levels versus sampling time, a better indicator of the magnitude and rate of marker changes. Using both F1.2 and thrombin-antithrombin complex data, the bottom graph shows the estimated in vivo thrombin generation rate in the patient based on analysis of the data using a computer model of the patient’s vascular system that accounted for hemodilution, blood loss, transfusion, and marker clearance. The 2 peaks correlate with commencement of CPB and release of the aortic cross-clamp. (This research was originally published in Blood. Chandler WL, Velan T. Estimating the rate of thrombin and fibrin generation in vivo during cardiopulmonary bypass. Blood 2003;101:4355–4362. © the American Society of Hematology.)
that it measures the ability of plasma to produce thrombin in vitro, which is not the same as thrombin generation in vivo, hence the term thrombin “potential,” and that the test cannot be run in the presence of heparin or direct thrombin inhibitors (DTIs).

MECHANISMS OF ACTIVATION
Hemostatic system activation occurs via several mechanisms including the contact system, fibrinolysis, inflammation, and platelets. This is summarized in Figure 6 and detailed in the sections below.

The Contact System
Kininss are a diverse set of proteins involved in vascular tone, patency, and tissue repair. The best studied member of this family is bradykinin, which may have a role in attenuating cardiac ischemia and hypertension. Kinins are synthesized as kininogens, of either high molecular weight (HMWK) or low molecular weight, and are inactive until cleaved by proteins known as kallikreins. In plasma, kallikrein circulates in an inactive form known as prekallikrein, or Fletcher factor, until activated by factor XIIa, also known as Hageman factor. The “contact system” refers to factor XII, factor XI, HMWK, and prekallikrein, which are associated proteins that travel together in the plasma. There is normally a low level of kallikrein activity on endothelial cell surfaces producing kinins, including bradykinin, that are rapidly degraded by kininases, which are enzymes found in plasma and in high concentrations in kidney and lung tissue.

Once CPB is initiated, there is a dramatic increase in contact system activity as blood touches the artificial material comprising the CPB circuit. Factor XII auto-cleaves itself upon contact with a variety of anionic surfaces including glass, polyethylene, and silicone rubber, and produces FXIIa, which converts prekallikrein to active kallikrein. Plasma kallikrein creates a positive feedback loop by cleaving more FXII, as well as producing bradykinin from HMWK. Prekallikrein and HMWK levels decrease not only because of hemodilution, but also because

Figure 5. Estimated thrombin, total fibrin, and soluble fibrin generation rates during conventional cardiopulmonary bypass (CPB). Error bars indicate the standard error. White squares indicate a significant difference (P < 0.05) from baseline. Values based on computer modeling. (Adapted from Chandler and Velan and Eisses et al.)

Figure 6. Summary of hemostatic activation mechanisms on cardiopulmonary bypass (CPB). BK = bradykinin; FXIIa = activated factor XII; TF = tissue factor; TPA = tissue plasminogen activator; Plt = platelets; Fib = fibrin degradation products; Endo = endothelium. Details provided in text.
of consumption and binding to the CPB circuit.47 Bradykinin levels increase 10-fold due to increased HMWK cleavage as well as reduced lung clearance because pulmonary blood flow is minimal.36,48 This has important implications for fibrinolysis because elevated bradykinin levels induce secretion of tissue plasminogen activator (tPA) (see below).49,50

The role of FXIIa in activation of the hemostatic system remains unclear.51 Besides producing kallikrein, FXIIa has been shown to convert FXI to FXIa in vitro, thus initiating the intrinsic pathway of coagulation. However, FXII-deficient patients do not have hemostatic defects, indicating that FXIIa does not normally have a role in hemostasis.52 Indeed, FXII deficiency does not stop the increase in thrombin generation during CPB.53,54 However, FXIIa has been shown to activate plasminogen to plasmin in vitro, suggesting its possible role in inducing fibrinolysis during CPB.55,56 Additionally, FXIIa and other fragments of FXII activate the classic complement cascade, accounting for some of the “crosstalk” between coagulation and inflammation.

The Fibrinolytic System

Endothelial cell release of tPA is a major activator of plasminogen, turning it into fibrin-degrading plasmin. On average, CPB stimulates a 5-fold increase in tPA secretion and active tPA levels,68,71 although there is some variability and approximately one-third of patients may show no change.59 Although active thrombin has been shown to release tPA in vitro,60 human in vivo studies are lacking and it is more likely that bradykinin is the main stimulus. Indeed, tPA release has been shown to be reduced by blocking bradykinin receptors or reducing its production by inhibiting kallikrein.61,62

Increased tPA alone does not increase fibrinolytic activity if no fibrin is present. D-dimer levels, an indicator of fibrin degradation, do not change under normal conditions, even when tPA levels are transiently increased 10-fold.59 In the setting of CPB, however, soluble and circuit-bound fibrin provide a huge surface for plasminogen activation to occur.66,64,65 There is a 10- to 100-fold increase in plasminogen generation shortly after the commencement of CPB, and plasmin generation, along with fibrin degradation, remain increased 10- to 20-fold throughout the duration of CPB.66 Normally only 1% of fibrin is degraded by the fibrinolytic system, with the remainder being removed by cells during wound healing. During CPB, however, fibrin formation and degradation rates are nearly equal, indicating that much of the fibrin degradation is not at the sites of vascular injury. This hyperfibrinolytic state consumes fibrinogen, leaving less available for coagulation postoperatively. Additionally, large amounts of plasmin can damage platelets through cleavage of their glycoprotein (GP)IIb receptor,67,68 and partially activate them (see below), making them less responsive to further activation with agonists such as adenosine diphosphate and arachidonic acid.69–71

It is important to recognize that a hypofibrinolytic state can also occur postoperatively. Plasminogen activator inhibitor 1 (PAI-1) prevents the formation of plasmin. Although levels on CPB are initially much less than tPA, PAI-1 is an acute phase reactant and, by 2 hours after surgery, its secretion is increased 15-fold.56,72–74 This increase may continue into the first postoperative day, which is associated with an increased risk of coronary graft occlusion.75 Similar to tPA levels, there is some variability with approximately one-third of patients showing no postoperative PAI-1 increase.59 This individual variability is one of the reasons it is difficult to predict which patients are at risk for bleeding versus thrombosis.

Inflammation

The coagulation and immune responses are linked; a break in the vasculature not only must be fixed, but also any foreign invaders neutralized. Inflammation has multiple mediators that can create profound amplification, sometimes resulting in an out-of-proportion response to the stimulating event and causing pathologic conditions in the host. A sepsis-like clinical picture that often results from CPB, termed the systemic inflammatory response syndrome, can be linked to “crosstalk” with the coagulation system and has been extensively reviewed elsewhere.76–80 A few key points will be emphasized here.

Leukocytes, including neutrophils and monocytes, bind to and are activated by the surface of the bypass circuit.64,81–88 which leads to an increase in TF expression, procoagulant activation, and thrombin generation on these cells.83–85,89 Shed blood contains increased numbers of activated leukocytes and levels of TF bound to cells and microparticles, as well as soluble TF.81,82,90–92 CPB also alters the protein C system. Protein C is activated by the binding of thrombin to thrombomodulin expressed on endothelial cells. This normally functions to suppress further thrombin formation away from the wound by destroying FVIIIa and FVa. Activated protein C also binds with endothelial protein C receptors to downregulate cytokine production and decrease vascular permeability.93,94 In addition to hemodilution, CPB further decreases protein C levels by downregulating thrombomodulin and endothelial protein C receptor expression of the endothelium. Overall, systemic inflammatory response syndrome caused by CPB increases TF expression while simultaneously depressing protein C activation, thereby favoring the production of thrombin.

Platelets

Fibrinogen bound to the CPB circuit provides a large binding site for platelets through their GPIb/IIa receptors. Once platelets bind to either the vascular system or to the circuit are activated, they spread pseudopods, express receptors, release granules and microparticles, and support thrombin formation.64,95–101 Additionally, there is some evidence that leukocytes may stimulate TF release directly from platelets.102 CPB increases platelet activation markers including β-thromboglobulin, platelet factor 4, soluble and platelet P-selectin, and platelet GMP140 (granule membrane protein 140).14,30,32,49,69,103–108 Shed blood shows evidence of platelet activation including reduced platelet levels, increased platelet activation markers, increased microparticles, and decreased platelet responsiveness.32,108–110 When shed blood is reinfused, part, but not all, of the increase in systemic platelet activation markers can be accounted for by markers in the shed blood. However,
platelet activation still occurs during CPB even when shed blood is not reinfused.32,34,111–113

During CPB, platelets are activated, platelet thrombin receptor responsiveness is reduced, and platelet protease-activated receptor 1 (PAR1) cleavage is increased. This suggests that thrombin generated during CPB is activating platelets through PAR1.114,115 Plasmin formed by activation of the fibrinolytic system can damage and directly activate platelets through PAR4, causing them to aggregate and release α and dense granule contents.116–119 Use of tranexamic acid (TXA) during CPB preserves platelet adenosine diphosphate levels, and use of aprotinin during CPB reduces platelet activation, preserves PAR1 function, and reduces platelet GPIb cleavage.67,104,115,120–122

**REDUCING ACTIVATION**

Ideally, hemostatic activation should be minimized during CPB and then quickly maximized after its termination. Placing the system in a sort of “hibernation” until needed would not only maintain required fluidity and reduce thrombotic risk, but also prevent the unproductive consumption of coagulation factors, fibrinogen, and platelets. Efforts to achieve this goal have focused both on modifying the conduct of CPB and its circuit, as well as pharmacologic methods to reduce the patient’s response to these insults.

**Limiting Use of Cardiotomy Suction**

During conventional CPB, blood in the surgical field is typically removed using cardiotomy suction (“pump suckers”) and returned to the venous reservoir where it can be oxygenated and reinfused into the patient via arterial inflow. Advantages include returning red cells and coagulation factors back to the patient. However, shed blood that has been exposed to wounded tissue surfaces has already started to activate hemostatic proteins, albeit appropriately. Pericardial blood in particular shows increased levels of F1.2, TAT, fibrin degradation products, and elevated levels of TF.81,82,92,123–125 From a purely research perspective, reinfusing the already activated blood complicates data analysis by increasing the measured level of activation markers in the patient, although it may not represent “new” formation of the markers.26,32 From a clinical standpoint, shed blood contains fibrin and fibrin degradation products that can stimulate increased activity of tPA and contribute to platelet dysfunction.35,117 Thus, use of the cardiotomy suction may contribute to both “true” and “false” increases in nonhemostatic thrombin formation.

Small observational studies showed a reduction in hemostatic activation if shed blood was not reinfused, or if the cells were washed (i.e., “cell saver” was used in lieu of cardiotomy suction). Four recent studies ranging from 29 to 75 on-CPB coronary artery bypass graft (CABG) patients have shown lower markers of inflammation and platelet activation in patients in whom cardiomyectomy suction blood was not retransfused.112,126–128 de Haan et al.,33 who conducted a study with 40 on-CPB CABG patients, demonstrated decreased blood loss and lower blood product consumption in patients who were not retransfused cardiomyectomy suctioned blood. Likewise, in the latest meta-analysis of cell-saver use during cardiac surgery from 1982 to 2008, the authors concluded that cell-saver use, versus retransfusion of cardiomyectomy suction blood, reduces exposure to allogeneic blood products when used throughout the entire surgical procedure.129 The results of all of these studies must be interpreted with the caveat that study populations were almost exclusively first-time CABG patients with CPB runs in the 2-hour range and blood volumes of approximately 1000 mL being processed through the cell saver. More-complex operations result in higher hemostatic activation,113 and longer CPB exposure resulting in higher cell-saver use would likely result in more coagulation factors and platelets being washed out.

**Increasing Circuit Biocompatibility**

As mentioned above, the large foreign surface of the CPB circuit provides ample space for the deposition of fibrin and other proteins that activate platelets and leukocytes. Efforts to increase the biocompatibility of these circuits have focused on either incorporating heparin into the tubing or modifying the surface polymers to decrease protein adsorption.130 Heparin-bonded circuits have been around the longest and are the best studied. One randomized trial with high-risk patients, including those with preexisting lung or kidney impairment, showed a decreased incidence of postoperative renal dysfunction and fewer days of mechanical ventilation.131 In a meta-analysis of heparin-bonded circuits versus conventional tubing, the authors showed a modest decrease in bleeding and red cell transfusion with heparin circuits.132 Other than heparin, circuits have been coated with polymethoxethylacrylate, phosphorylcholine, and siloxane in an attempt to make the tubing less favorable for cell binding.133–136 None of the coatings, however, has demonstrated in vivo reductions in hemostatic activation.137 A more recent systematic review of biocompatible CPB circuits concluded that although they may offer some benefit in reducing red cell transfusions, a decreased incidence of atrial fibrillation, and shorter intensive care unit (ICU) stays, high-quality studies are limited and the surfaces alone do little to contain hemostatic activation without implementing additional measures.138

**Decreasing CPB Circuit Size**

So-called “miniaturized” CPB has been developed with the idea of reducing blood contact with foreign material and air by using low prime-volume tubing and eliminating the venous reservoir and cardiotomy suction. In general, priming volume for miniaturized CPB systems is on the order of 500 mL versus the 1500 to 2000 mL in conventional circuits, and virtually all systems use some type of heparin-bonded tubing. Lower levels of thrombin activation have been reported with the use of miniaturized CPB.139,140 Two recent meta-analyses of randomized trials confirmed a reduced need for blood-product transfusions using the smaller circuits.141,142 However, this would be expected given the significant reduction in hemodilution using lower prime volumes. Additionally, because reinfusion of shed blood alone has been shown to increase hemostatic activation, it is not clear whether miniaturized CPB systems offer any benefit regarding hemostatic activation other than simply eliminating the cardiotomy suction. It is likely that any combined approach using heparin-bonded circuits,
adequate antifibrinolytic therapy, and removal of cardiomyotomy suction will reduce hemostatic activation.\(^{35}\)

**Off-Pump Coronary Artery Bypass**

Of course, the ultimate reduction in CPB circuit size is to eliminate CPB entirely. Although not practical for many cardiac operations, off-pump coronary artery bypass (OPCAB) currently comprises about 20% of coronary bypass graft procedures, and has been shown to be a viable technique with regard to graft patency.\(^{143}\) Although the patient still undergoes thoracotomy, heparinization, and grafting, there is no blood contact with foreign material and blood in the surgical field is generally cleared using a cell-saver device because there is no cardiomyotomy suction. The time course for hemostatic activation is somewhat different for OPCAB. In general, there is no early peak of thrombin generation, presumably because of the lack of contact activation, and activation of the fibrinolytic system is less.\(^{106}\) However, there is equal activation of the TF pathway, and thrombin generation and fibrinolytic activity are actually equal to CPB patients within 24 hours postoperatively.\(^{144}\) In general, studies have shown less platelet activation and dysfunction with OPCAB, leading to the potential concern of a greater prothrombotic state in the early postoperative period.\(^{145,146}\) Increased prothrombotic states may last as long as 1 month after surgery for both OPCAB and standard CABG on CPB, and there does not seem to be a greater risk of graft thrombosis at experienced OPCAB centers.\(^{147}\)

**Heparin Versus DTIs**

Unfractionated heparin (UFH) has been, and continues to be, the mainstay anticoagulant used for CPB, primarily because of its rapid effect and availability of a neutralizing agent (protamine). It is not a direct inhibitor of thrombin, but instead enhances the effects of AT. It is this dependency on AT that partially accounts for the drug’s variable anticoagulation efficacy in individual patients and in various situations.\(^{23}\) However, AT levels alone cannot predict UFH’s ability to achieve a desired activated clotting time (ACT) value.\(^{148}\) Other factors, such as the heterogeneity of UFH’s chain lengths and its variable binding to endothelial cells, macrophages, and plasma proteins, affect its bioavailability.\(^{149}\) It is this variability that makes frequent monitoring necessary while on CPB, most commonly using the ACT. Yet, the ACT itself has significant limitations, beginning with a lack of consensus as to what ACT value reflects adequate anticoagulation for CPB.\(^{150}\) ACT values do not correlate well with actual heparin plasma concentrations,\(^{151}\) and thrombin is still activated despite values \(>480\).\(^{5,152}\) Efforts to dose UFH more effectively have centered on measuring heparin plasma levels and maintaining a constant concentration. Although some studies have shown decreased hemostatic activation using this strategy,\(^{153,154}\) others have shown no difference than ACT-based dosing.\(^{155}\)

Aside from dosing problems, there are other issues that prevent UFH from being an ideal anticoagulant. Heparin itself is known to cause platelet activation and stimulate fibrinolysis.\(^{156}\) Heparin-induced release of TF pathway inhibitor occurs as well, potentially exhausting TF pathway inhibitor stores from the endothelium.\(^{157,158}\) Heparin-induced thrombocytopenia (HIT), which has been extensively reviewed elsewhere,\(^{159-162}\) is a result of antibodies formed to the complex of heparin and platelet factor 4. Approximately 25% to 50% of patients will develop the antibodies 5 to 10 days after surgery, which can lead to thrombotic complications if heparin therapy is continued in the postoperative period.\(^{163}\)

The above limitations of heparin have helped drive the development of DTIs. A major advantage of DTIs is that AT is not required and their smaller molecular size enables greater inhibition of thrombin bound to fibrin (i.e., clot-bound versus free thrombin).\(^{164}\) More effective thrombin inhibition with less platelet activation would obviously be desirable for decreasing hemostatic activation. Bivalirudin, a DTI with a half-life of 25 minutes, has been shown to adequately suppress hemostatic activation on CPB when cardiomyotomy suction is not used.\(^{165}\) Interestingly, when cardiomyotomy was used, markers of activation such as d-dimer, TAT, and FPA levels were significantly increased. This is likely attributable to the fact that stagnant blood causes a tremendous amount of thrombin generation, which may locally overwhelm the reversible inhibition of the DTI. Multicenter trials using bivalirudin for CABG patients both on and off CPB have demonstrated the same safety and procedural efficacy as heparin anticoagulation, although in the United States it is currently only approved for patients with HIT undergoing percutaneous coronary interventions.\(^{166,167}\) Argatroban is another DTI that has been used in the setting of HIT, although the development of intraoperative thrombi has been reported when used for CPB anticoagulation.\(^{168-170}\) Use of DTIs in the setting of CPB is also currently limited by lack of a neutralizing agent. Oral DTIs, such as dabigatran etexilate, have been developed as potential replacements for coumadin therapy, and may pose a bleeding risk when patients present to surgery. It is recommended that dabigatran therapy be discontinued 2 to 4 days before cardiac surgery, and longer in patients with impaired renal function.\(^{171}\)

**AT Supplementation**

AT levels show a 30% to 50% decrease from baseline after initiation of CPB, a consequence of both acute hemodilution and typical heparin administration, then recover, although not fully, several hours postoperatively.\(^{172,173}\) However, after prolonged CPB use, especially that associated with deep hypothermic circulatory arrest, AT levels can decrease even further and can take days to return to baseline levels.\(^{174}\) This can contribute to inadequate thrombin suppression with heparin, as well as potential thrombotic complications.\(^{175,176}\) Indeed, studies have shown that post-CPB patients with AT levels <60% of normal have a greater risk of adverse neurologic and cardiac events in the ICU.\(^{177,178}\) Most studies of low-dose AT supplementation during CPB have failed to show a decrease in thrombin generation, plasmin generation, or platelet activation.\(^{179-182}\) Although clinical trials have shown that AT supplementation corrects heparin resistance in patients with low AT activity and reduces the need for fresh frozen plasma, outcomes have been similar to patients simply receiving additional heparin.\(^{183-185}\)
Antifibrinolytics
As previously noted, tPA and plasmin production are increased during CPB. The lysine analogs, e-aminocaproic acid (EACA) and TXA, are frequently used to mitigate this potentially hyperfibrinolytic state. Both agents competitively inhibit the fibrin binding site on plasminogen, thus reducing the rate of fibrinolysis, although plasmin production is unaffected.12,186 TXA is more potent than EACA, has a longer elimination half-life, and is the better studied agent in cardiac surgery.187 Its prophylactic use has been the subject of 2 large meta-analyses, with one demonstrating a reduced need for blood transfusions,188 and the other showing no benefit compared with placebo.189 Additionally, TXA may increase the risk of seizures during open heart procedures.190 By decreasing fibrinolysis without reducing thrombin generation, there is the potential for thrombotic complications. Although studies have not demonstrated increased risk of myocardial infarction, stroke, deep vein thrombosis, or pulmonary embolism from TXA or EACA use in cardiac surgery, there are case reports of retinal artery and glomerular capillary thrombosis, and the agents should probably be used with caution in patients with other risk factors for hypercoagulability.191

Aprotinin is a nonspecific serine protease inhibitor that also inhibits plasmin. Aprotinin therapy has been shown to increase the rate of plasmin inhibition 10-fold during CPB, which in turn reduced the rate of fibrin degradation a similar amount.192 Unlike the lysine analogs, however, aprotinin inhibits a broad spectrum of other proteins involved in coagulation including kallikrein, activated protein C, and thrombin.193 Platelet activation is also reduced with aprotinin therapy, possibly by protecting PAR4 receptors and by blocking thrombin activation of platelet PAR1 receptors.67,115 As such, it has both pro- and anticoagulant effects as well as antiinflammatory effects. Multiple studies have shown its efficacy at decreasing markers of hemostatic activation and preserving platelet function post-CPB.29,30,62,67,194–196 Additionally, multiple clinical trials have demonstrated its efficacy at reducing transfusion of blood products during cardiac surgery.186,197 However, marketing of the drugs was suspended in November 2007 after preliminary results of the BART trial, which showed an increased mortality trend relative to the lysine analogues.198 The underlying cause of the increased mortality is unclear, but it has been suggested that aprotinin’s risk-benefit profile is more suited to patients undergoing cardiac surgical procedures at high risk for massive blood loss.199

Genomics and Future Directions


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