Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) are at increased risk for excessive perioperative blood loss requiring transfusion of blood products. Strategies to optimize administration of heparin and protamine and the assessment of their effects on coagulation are evolving in cardiac surgical patients. Two recent evaluations have focused on the use of multiple point-of-care (POC) coagulation assays for patient-specific adjustment of heparin and protamine dosage. These studies indicate that blood loss and transfusion requirements in cardiac surgical patients may be reduced with more accurate control of heparin anticoagulation and its reversal. Blood component administration in patients with excessive post-CBP bleeding is generally empiric in part, related to turnaround times of laboratory-based tests. Methods are now available for rapid, POC assessment of coagulation to allow appropriate, targeted therapy for acquired hemostatic abnormalities. Recent studies indicate that a rapid evaluation of thrombocytopenia and coagulation factor deficiencies with POC tests can facilitate the optimal administration of pharmacologic and transfusion-based therapy in patients who exhibit excessive bleeding after CPB. POC tests that assess platelet function have been developed, and their use may facilitate identification of which patients at risk for excessive blood loss may respond to pharmacologic interventions such as desmopressin acetate or antifibrinolytic agents.

**Pathophysiology of Hemostasis Abnormalities with Cardiac Surgery**

Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) are at increased risk for excessive perioperative blood loss requiring transfusion of blood products. This risk is dependent on the type of procedure [1, 2] and the duration of CPB [3, 4]. Although excessive perioperative bleeding with CPB may occasionally be related to preexisting hemostatic abnormalities, CPB may cause numerous hemostatic alterations that predispose patients to excessive bleeding [2, 3, 5]. First, administration of crystalloid solution, which is used to prime the CPB circuit and as a component of cardioplegia, can result in substantial hemodilution and may, in part, account for the decreases of coagulation factors and platelets that have been demonstrated with CPB [2, 6]. Second, excessive activation of the hemostatic system that occurs with CPB may lead to consumption of platelets and labile coagulation factors. Excessive hemostatic activation may be related to the interaction of the contact factors XII and XI, high-molecular-mass kininogen, and prekallikrein with the extensive CPB surfaces [7], and activation of the extrinsic pathway [8] secondary to surgical trauma or retransfusion of pericardial blood [9]. Third, excessive fibrinolysis may be triggered via CPB-mediated contact system activation of factor XII [10] and thrombin, hypothermia [11], and retransfusion of tissue plasminogen activator from the pericardial cavity [12], subsequent to release from injured endothelial cells during surgery [13]. Fourth, heparin may inhibit coagulation [14] and platelet function [15, 16]; similarly, excess protamine may inhibit coagulation [17] and affect platelet function [18]. Fifth,

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2 Nonstandard abbreviations: CPB, cardiopulmonary bypass; POC, point-of-care; DDAVP, 1-deamino-8-D-arginine vasopressin (desmopressin acetate); ACT, activated clotting time; PT, prothrombin time; aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; MVB, microvascular bleeding; TEG, thromboelastograph; PAF, platelet-activating factor; MA, maximum amplitude (of TEG).
release of elastase from polymorphonuclear leukocytes may affect the hemostatic system [19].

Thrombin and plasmin activities are important because they mediate several important reactions (Fig. 1). In addition to generation of fibrin monomer, thrombin activates factors V, VIII, XIII, and platelets. At the same time, thrombin down-regulates hemostasis via release of tissue plasminogen activator, release of tissue factor pathway inhibitor, and activation of protein C, which in conjunction with thrombomodulin clears activated factors V and VIII. Despite relatively high doses of heparin, thrombin is generated during CPB [8, 20], and its activity increases with time on CPB as demonstrated by increasing concentrations of F1.2, thrombin–antithrombin complexes, and fibrin monomers [21]. Although decreases in fibrinogen concentrations during CPB are generally clinically insignificant [2, 22–24], excessive plasmin activity may lead to hypofibrinogenemia, fibrinogen/fibrin degrad product-mediated platelet dysfunction [15], and degradation of factors V, VIII, and XIII [25]. Plasmin may cause proteolytic removal of platelet membrane glycoproteins (glycoprotein Ib), impair the in vitro response of platelets to various agonists [26], and enhance the platelet response to thrombin at lower temperatures [27]. Although proteolysis of glycoprotein Ib receptors by plasmin was considered to be an important mechanism for reduced von Willebrand factor binding [28], more recent evidence indicates that plasmin induces changes in platelet structure, centralization of platelet granules, and translocation of glycoprotein Ib from the plasma membrane into the canalicular system [27, 29]. Therefore, excessive activation of coagulation and fibrinolysis with consumption of platelets and labile coagulation factors may occur even with routine high-dose heparin-induced anticoagulation [2, 3, 5].

Numerous hemostatic abnormalities have been reported in patients with CPB such as decreases in plasma coagulation factors [2, 6, 10, 30, 31], disseminated intravascular coagulation [22, 32, 33], or isolated primary fibrinolysis [34], thrombocytopenia, or transient platelet dysfunction (Fig. 2). The latter two are considered to be the most important abnormalities in the early postoperative period after CPB [3, 5, 35–38]. Platelet dysfunction may be induced by adherence of platelets to the CPB surfaces [39] resulting in platelet activation/degranulation/desensitization [3, 37, 38, 40–42], as well as heparin and hypothermia [3]. Numerous platelet abnormalities have been described, including prolonged bleeding time [3, 30, 31, 43], thrombocytopenia [2, 44, 45], and a variety of platelet or platelet activation-related abnormalities. Impaired platelet reactivity has been demonstrated both in vivo [3, 37] and in vitro [3, 31, 45]. The loss of platelet receptors for fibrinogen [39, 40, 46, 47] von Willebrand factor binding [39, 40, 47], loss from platelets of α- and dense granules into plasma [3, 37, 38], and increased expression of α-granule (GMP-140) and liposomal proteins on the plate...

Fig. 1. Mechanisms and effects of excessive hemostatic activation with cardiac surgery.

_Dashed line designates release of protein cleavage by-products. The following coagulation factors, hemostatic mediators, and by-products are abbreviated as follows (activated factors are designated by a lowercase a): XII, factor XII; VII, factor VII; X, factor X; VIII, factor VIII; IX, factor IX; V, factor V; XIII, factor XIII; PT, prothrombin; FPA, fibrinopeptide A; Fibrin (m), fibrin monomer; Fibrin (p), fibrin polymer; PAI1, plasminogen activator inhibitor; tPA, tissue plasminogen activator; FSP, fibrinogen/fibrin degradation products; D-dimers, polymerized fibrin degradation products._


Monitoring of Heparin Anticoagulation and Protamine Reversal: Impact on Blood Loss and Blood Component Transfusion

The activated clotting time (ACT) is the most commonly used method for monitoring heparin anticoagulation during CPB, based on ease of use and a few early studies that demonstrated a reduction in postoperative bleeding when ACT was used to monitor heparin and protamine therapy. The impact of heparin/protamine dosing guided by ACT-based [48–59] and heparin concentration [50, 60–65] protocols on bleeding and blood conservation has been variable. This variability in outcome may be related to different patient demographics (e.g., more or less complex and reoperation procedures, age), variability of utilization of pharmacologic (e.g., antifibrinolytic agents, DDAVP, prostaglandin I2, direct thrombin inhibitors) or nonpharmacologic blood conservation strategies (e.g., normovolemic hemodilution with blood pooling, platelet-plasmapheresis, cell salvage/hemofiltration techniques, retransfusion of shed mediastinal blood), changes in extracorporeal circuit technology (e.g., bubble vs membrane oxygenators, centrifugal vs roller pumps, hemofiltration, heparin-bonded CPB circuits, variability in priming solutions/volumes), and variability in study designs (retrospective vs prospective), source of heparin, heparin and protamine dosing protocols involving in vitro assays (ACT or heparin concentration methods), and patient-specific criteria vs time-dependent fixed dosage protocols, heparin-rebound monitoring, definition of patients at risk for bleeding, and lack of transfusion protocols.

Two recent evaluations have focused on the use of point-of-care (POC) coagulation assays for patient-specific adjustment of heparin and protamine dosage. The impact of a new POC hemostasis system (RXDX System; International Technidyne) on blood loss and transfusion requirements was recently examined [65]. This system allows estimation of patient-specific anticoagulant response to heparin, determination of Celite ACT values, and calculation of protamine dose by ACT-based approximations of heparin concentration (protamine response test). Forty-eight adult patients undergoing primary, cardiac surgical procedures were prospectively randomized into test and control groups. For control patients, anticoagulation consisted of an initial heparin dose of 300 IU/kg and additional 5000 IU heparin doses administered with Celite ACT <400 s. Heparin was neutralized with an initial fixed dose of protamine (1 mg of protamine/100 IU of total heparin including the 5000 IU CPB prime dose). For test patients, the anticoagulation protocol consisted of an initial dose of heparin based on a heparin dose Celite ACT response assay. Additional heparin doses were administered with a Celite ACT <400 s. The protamine dose was based on the protamine response test. Treatment of excessive bleeding after CPB was at the discretion of the anesthesia and surgical staff. In this study, test patients were found to have received slightly more heparin and a markedly lower dose of protamine than the control patients. Supplemental protamine was given twice as often to control patients and frequently when no heparin was detectable. Test patients exhibited less chest tube drainage in the first 24 postoperative hours; additionally, fewer test patients were transfused when compared with control patients. In addition to facilitating accurate prediction of heparin dose requirements, use of this POC hemostasis system resulted in the administration of a more appropriate protamine dose. This study confirmed previously published data indicating that reduced doses of protamine are associated with lower perioperative blood loss [48, 49], possibly secondary to lesser increases in complement activation [66, 67] or reduced protamine-induced platelet dysfunction [68].

Data from one prospective study indicated that maintaining adequate heparin concentration during CPB may result in reduced blood product utilization [62]. However, other studies failed to demonstrate a difference [61, 63, 64]. Previous studies suggested that excessive bleeding may be related to the use of greater doses of bovine heparin during CPB guided by dosing protocols.
based on body weight and ACT values [69] or based on maintenance of a defined heparin concentration [64]. However, more recent studies found no differences in blood loss when either bovine [63] or porcine heparin was used [4,65,70]. The discrepant results between these studies may be related to differences between studies in one or more of the previously described demographic, operative, or procedure-related issues. Table 1 summarizes important factors related to anticoagulation, which may in part explain the discrepancies in outcome between studies that examined the effect of higher heparin doses on blood loss and transfusion outcomes by several monitoring protocols. We performed a study to determine whether heparin dose was related to either blood loss or transfusion requirements in a large series of patients [4]. Patients who received lower initial and total heparin dosage had increased blood loss and transfusion requirements. In view of the previously observed inverse relationship between heparin concentration and thrombin activity as reflected by fibrinopeptide A concentrations [64], a formal comparison between various POC measurements and anti-Xa heparin concentration measurements was performed [71]. This trial demonstrated a good correlation between whole-blood heparin concentration values compared with an anti-Xa assay [71], a finding substantiated by a subsequent study [72]. In the same study [71], ACT values correlated poorly with anti-Xa heparin concentrations, in part related to the effects of hypothermia and hemodilution on these assays (Fig. 3). However, others have reported that heparin measurements derived with an automated protamine titration method can vary appreciably from anti-Xa measurements [73].

In a prospective trial we evaluated the impact of heparin and protamine administration based on a POC, whole-blood hemostasis system (Hepcon; Medtronic Blood Management) on bleeding and blood transfusion when compared with an ACT-based protocol [70]. This system allows estimation of patient-specific anticoagulant response to heparin, assay of kaolin ACT values, and whole-blood heparin concentration via a previously validated, automated protamine titration method [71]. Patients (n = 254) requiring CPB for primary, reoperation, and complex/multiple cardiac surgical procedures were enrolled in this recent study [70]. Patients were randomly assigned to either a control or intervention group. For

![Cardiopulmonary Bypass Time](image)

**Table 1. Studies that examined the effect of higher heparin doses directly or indirectly by using different anticoagulation monitoring protocols on perioperative blood loss and transfusion outcomes.**

<table>
<thead>
<tr>
<th>Trial year (n)</th>
<th>Heparin concn. vs fixed dose</th>
<th>Heparin dose, IU/kg</th>
<th>Heparin source</th>
<th>Patient-specific monitoring</th>
<th>Heparin rebound monitoring</th>
<th>CPB time, min</th>
<th>Transfusion requirements</th>
<th>Blood loss, mL CTD in 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowie et al., 1985 (150)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>No</td>
<td>?</td>
<td>↓</td>
<td>400 vs 850a</td>
<td></td>
</tr>
<tr>
<td>Boldt et al., 1994 (60)</td>
<td>640 vs 354</td>
<td>Bovine</td>
<td>NA</td>
<td>No</td>
<td>107</td>
<td>↑</td>
<td>1150 vs 700a</td>
<td></td>
</tr>
<tr>
<td>Heparin concn. vs ACT</td>
<td>Gravlee et al., 1990 (21)</td>
<td>564 vs 442</td>
<td>Bovine</td>
<td>No/yes</td>
<td>No</td>
<td>105</td>
<td>NE</td>
<td>1104 vs 699a</td>
</tr>
<tr>
<td>Urban et al., 1991 (38)</td>
<td>601 vs 497</td>
<td>?</td>
<td>Yes/yes</td>
<td>?</td>
<td>?</td>
<td>ND</td>
<td>317 vs 362a</td>
<td></td>
</tr>
<tr>
<td>Gravlee et al., 1992 (63)</td>
<td>740 vs 354</td>
<td>Bovine</td>
<td>No/yes</td>
<td>Yes</td>
<td>115</td>
<td>ND</td>
<td>1035 vs 901</td>
<td></td>
</tr>
<tr>
<td>Despotis et al., 1995 (254)</td>
<td>612 vs 462</td>
<td>Porcine</td>
<td>Yes/yes</td>
<td>Yes</td>
<td>145</td>
<td>↓</td>
<td>840 vs 924a</td>
<td></td>
</tr>
</tbody>
</table>

*P = .05.

**Factors related to anticoagulation that may in part, explain the discrepant results between studies are included. Patient-specific monitoring for ACT values (anticoagulant response) or heparin concentration are also included. Numeric values represent the mean values for each group. Bovine, bovine lung; porcine, porcine mucosal. ?, not described in manuscript; NA, not applicable; NE, not examined; ND, no difference; CTD, chest tube drainage. The arrows indicate transfusion requirements in the high-heparin cohort; for CPB time, data from both cohorts were combined.**

**Fig. 3. Limitations of ACT in heparin monitoring with CPB.**

Comparison of ACT values obtained with two different contact activating agents and heparin concentration measurements by a laboratory-based and POC method obtained in 32 patients during CPB. Mean values of ACT are expressed as seconds/100 for both Celite (Hemochron) HC ACT and kaolin (Hemotec) HT ACT assays. Plasma equivalent heparin concentration (WB HC) and anti-Xa plasma heparin concentration (anti-Xa HC) are expressed as IU/mL. Hematocrit (Hct) values are expressed as percent divided by 10 (%/10) and core body temperature (Temp) is expressed as °C/10. Blood specimens were obtained before heparin administration and 10 min after heparin administration (A), initiation of CPB (B), achievement of hypothermia (C), and rewarming (D) as well as immediately before discontinuation of CPB (E). From Despotis GJ, Summerfield AL, Joist JH, et al. Comparison of activated coagulation time and whole blood heparin concentrations, in part related to the effects of hypothermia and hemodilution on these assays (Fig. 3). However, others have reported that heparin measurements derived with an automated protamine titration method can vary appreciably from anti-Xa measurements [73].

In a prospective trial we evaluated the impact of heparin and protamine administration based on a POC, whole-blood hemostasis system (Hepcon; Medtronic Blood Management) on bleeding and blood transfusion when compared with an ACT-based protocol [70]. This system allows estimation of patient-specific anticoagulant response to heparin, assay of kaolin ACT values, and whole-blood heparin concentration via a previously validated, automated protamine titration method [71]. Patients (n = 254) requiring CPB for primary, reoperation, and complex/multiple cardiac surgical procedures were enrolled in this recent study [70]. Patients were randomly assigned to either a control or intervention group. For
control patients, the anticoagulation protocol consisted of an initial fixed dose of 250 IU/kg heparin, and additional 5000 IU heparin doses were administered with Celite ACT <480 s. Heparin was neutralized with an initial fixed dose of protamine (0.8 mg of protamine/mg of total heparin). For intervention patients, the anticoagulation protocol consisted of an initial dose of heparin based on a kaolin ACT heparin dose–response assay, with additional heparin doses administered with heparin concentrations less than the reference concentration or for a kaolin ACT <480 s. The protamine dose was based on the measured, residual heparin concentration. Treatment of excessive bleeding after CPB was based on a previously validated algorithm utilizing POC testing with whole-blood prothrombin time (PT), activated partial thromboplastin time (aPTT) (Biotrack 512), heparinase ACT, and platelet count (Coulter T540; Coulter Electronics) [2]. No differences between the two treatment groups were identified in regard to demographic, preoperative anticoagulant medications, preoperative hemostatic data, number of reoperations or combined procedures, and duration of CPB. Patients in the intervention cohort received greater doses of heparin and had lower protamine to heparin ratios when compared with control patients. We found indirect evidence for consumption of coagulation factors and platelets in the control patients who had more prolonged whole-blood PT and aPTT values after CPB. Furthermore, patients in the control cohort received substantially more platelets, fresh frozen plasma (FFP), and cryoprecipitate. Twice as many control patients required transfusion of these blood components during the perioperative interval. Control patients also had longer operative times after CPB for closure and had greater mediastinal chest tube drainage in the first 4 h after surgery. Thus, higher heparin doses in the intervention group were not associated with excessive postoperative bleeding and in fact may have contributed to preservation of hemostasis. In contrast to the study by Jobes et al. [65], our protocol not only allowed more accurate estimation of initial heparin and protamine doses but also facilitated maintenance of appropriate, patient-specific heparin concentrations during CPB. ACT-based anticoagulation protocols may contribute to a hemostatic consumptive state, particularly in patients requiring prolonged use of CPB because the ACT may be prolonged by factors other than heparin such as hemodilution or hypothermia leading to inappropriately low heparin concentrations during CPB (Fig. 3) [71].

Because generation of fibrinopeptide A [64, 74] and inhibition of clot-bound thrombin [75] have been shown to be inversely related to heparin concentration, maintenance of therapeutic heparin concentrations may more effectively preserve hemostasis through antithrombin III or possibly heparin cofactor II-mediated inactivation of thrombin [76]. This hypothesis was recently tested in a trial involving 31 patients requiring repeat or combined cardiac procedures (i.e., coronary revascularization plus valve repair/replacement) and thus at particularly high risk for excessive bleeding [77]. We found more effective suppression of excessive hemostatic system activation (as reflected by decreased concentrations of fibrinopeptide A) and fibrinolysis (D-dimer). More importantly, maintenance of higher heparin concentrations resulted in better preservation of consumable antithrombin III and factors I, V, and VIII in the intervention patients. Higher, stable heparin concentrations during CPB may also preserve platelet function because bleeding times were more prolonged and a trend towards higher β-thromboglobulin concentrations was observed in the control group. In addition, a significant correlation between fibrinopeptide A and β-thromboglobulin concentrations suggested that higher heparin concentrations more effectively preserved platelet function via better suppression of thrombin-mediated activation of platelets. Evaluations have demonstrated a dose-related inhibition of collagen-mediated platelet aggregation by heparin [63, 78]. Inhibition of platelet function by heparin [16] may be mediated through suppression of factor VIII-mediated platelet aggregation [79] or von Willebrand factor-related mechanisms [80].

Impact of POC Assays on Management of Excessive Microvascular Bleeding (MVB) after CPB

In the past, blood component administration in patients with excessive MVB after CPB and heparin neutralization has been generally empiric and not based on direct assessment of hemostasis because turnaround times of laboratory-based tests are too long [34]. Thus, transfusion of erythrocytes, platelets, and FFP to cardiac surgical patients requiring CPB varies considerably among institutions, in part because of prophylactic administration of FFP and platelets [81], despite evidence that this practice is unwarranted [24, 82]. Furthermore, FFP and platelets are frequently administered in an attempt to distinguish between MVB related to hemostatic system impairment vs surgical bleeding [83, 84]. Neither approach appears to be efficient and safe and therefore both are inappropriate. Methods are now available for rapid POC assessment of coagulation to allow appropriate, targeted therapy for post-CPB hemostatic defects.

Detection of Residual Heparin or Heparin Rebound

Persistent concentrations of circulating heparin, resulting from inadequate neutralization [85, 86] or heparin rebound [86, 87], can contribute to MVB after CPB. In fact, one study demonstrated that blood loss can be reduced if heparin rebound is detected with ACT values and treated with additional protamine. However, the ACT may not be the most appropriate method for assessment of postoperative heparin rebound because it has been shown to have a relatively high detection limit for heparin concentrations, e.g., 600 1U/L [88, 89]. Thus, whole-blood POC heparin concentration measurements are more suitable for detecting heparin rebound than the ACT [90]. Hepa-
rinase (IBEX), an enzyme that degrades heparin to smaller, inactive fragments, also has been used to improve the detection of residual low concentrations of heparin by the ACT [91]. Laboratory-based [92] and POC whole-blood [93] PT and aPTT assays (Boehringer Mannheim Diagnostics) with and without heparinase may also be useful in detecting low heparin concentrations. In addition, a whole-blood thrombin time with protamine neutralization (HNTT; International Technidyne) is available to assess residual heparin or heparin rebound in the post-CPB period [65, 94, 95].

ROLE OF CLINICAL ALGORITHMS AND POC TESTING

Because of the complex and often serious nature of bleeding disorders after CPB, several treatment paradigms with laboratory-based tests have been suggested for management of patients with post-CPB MVB. A step-wise approach using laboratory-based tests (PT, aPTT, platelet count, and possibly fibrinogen or fibrinogen/ fibrin degradation product) for intraoperative treatment of the actively bleeding cardiac surgical patient has been suggested by Traber and Jobes [96]. Similarly, Horrow [97] recommended a strategy for diagnosis and treatment of postoperative bleeding with PT/aPTT, fibrinogen/ fibrin degradation product, fibrinogen, platelet count, and bleeding time. The clinical usefulness of these approaches has not been formally evaluated in randomized, prospective, controlled trials. In a recent, prospective trial, empiric treatment of MVB in CPB patients was compared with therapy that was administered according to a transfusion algorithm dependent on rapid POC measurements of whole-blood PT, aPTT (Coaguchek instrument), and platelets (Coulter T540) [2]. A transfusion algorithm was used according to previously published guidelines for transfusion on the basis of coagulation assays [98–101]. Use of POC assays for platelet count, whole-blood PT, and aPTT improved the management of MVB [2]. The algorithm-treated patients received fewer blood products, had shorter operative times, and had less blood loss after identification of MVB. Reduced transfusion requirements and blood loss may have been a consequence of optimal management of bleeding [2], identification of patients with a surgical source of bleeding, a change in the transfusion trigger, or some combination of these [102].

The usefulness of preset criteria for transfusion was confirmed in two other recent studies that demonstrated that preset transfusion triggers can dramatically affect transfusion requirements of patients undergoing cardiac surgery with either laboratory-based [103] or POC methods [104]. In the first study, the efficacy of strict transfusion criteria as a sole blood conservation strategy was evaluated by comparing homologous blood product use in 314 consecutive patients undergoing coronary artery bypass grafting procedures (treatment group) with that in a retrospective series of 947 patients (control group) who were transfused without preset, defined criteria. The preset criteria utilized for the treatment group were as follows: hematocrit <18 for transfusion of erythrocytes during CPB, hematocrit <20 for transfusion of erythrocytes after discontinuation of CPB, excessive bleeding + PT >1.6 × control for transfusion of FFP, and excessive bleeding + platelet count <100 000/μL for transfusion of platelets. The two groups had similar demographic, operative, and laboratory profiles. A substantial decrease in the percentage of patients receiving erythrocytes (26% vs 41%) and FFP (13% vs 24%) was observed in the treatment group when compared with control patients. In addition, the percentage of patients not receiving homologous blood products was substantially greater in the treatment group (69%) when compared with historical controls (48%). The authors concluded that adherence to defined transfusion criteria can be a simple, safe, and effective strategy for decreasing blood product utilization. Another algorithm that combines laboratory-based platelet counts and fibrinogen concentrations with thromboelastogram-based measurements was utilized by Spiess [105]. A retrospective analysis revealed that use of this approach can reduce transfusion requirements [104].

These studies [102–104] confirm that adherence to transfusion triggers for erythrocytes, FFP, and platelets can have a dramatic impact on blood product usage in perioperative cardiac surgical patients’ setting, which may be quite variable between institutions [81]. Furthermore, POC testing may be justified from an economic perspective. For example, by reducing transfusion requirements and operative time, use of platelet count, whole-blood PT, and aPTT to manage post-CPB bleeding can substantially reduce expenditures related to these outcome variables. At our institution this equates to a yearly savings of $267 658 as previously outlined [106].

Newer POC technologies have become available that provide rapid hemostasis results with whole blood. The accuracy and reliability of the POC PT/aPTT and platelet assays previously utilized in prospective, randomized trials in determining thromboctopenia and coagulation factor deficiencies have been documented [106, 107]. The whole-blood PT was shown to correlate well with laboratory PT in two previous studies [106, 108]. In addition, both Coaguchek and laboratory PT methods responded similarly to factors V, VII, and X as assessed by the comparison of the slopes between respective regression relationships [106]. In an initial evaluation, the whole-blood aPTT correlated well with the laboratory aPTT, with correlation coefficients ranging from 0.79 to 0.83, depending on the comparison reagent and instrumentation used [109]. This correlation coefficient was in the same range as that obtained for laboratory aPTTs with different reagents (r = 0.79). In contrast, other studies with either linear regression or bias analysis have demonstrated discrepant results between whole-blood and laboratory aPTT methods [106, 110, 111]. This is not surprising given the known variability of PT/aPTT measurements because of differences in reagents and clot timers [112]. In one study [106], variability between whole-blood
(Coaguchek Plus) and laboratory aPTT was found to be most likely related to differences in normal reference ranges and responsiveness to coagulation factor concentrations between the two assay systems. Both laboratory and whole-blood aPTT assays were shown to have a similar correlation to factor X concentrations, whereas whole-blood aPTT correlated better with factors V, VII, and XII than did laboratory aPTT [106]. In this same study, the disease state was defined as detection of at least one coagulation factor less than a defined concentration (e.g., 0.2, 0.3, or 0.4 IU/mL) whereas PT or aPTT measurements were positive when equal to or greater than a defined cutoff value (e.g., 1.5 x control, 1.8 x control). Use of Bayes’ theorem, a frequently used statistical method that can be useful in evaluating the accuracy of assay systems, revealed that the diagnostic performance of whole-blood aPTT with respect to identification of patients with a factor deficiency was similar to laboratory aPTT [106]. Finally, POC whole-blood fibrinogen assays have recently been evaluated that may help identify occasional patients with post-CPB MVB who might benefit from administration of fibrinogen-rich cryoprecipitate in addition to FFP [113–115].

Identification of Patients at Risk for Excessive Postoperative Blood Loss and Who May Benefit from Pharmacologic Interventions

Tests for evaluation of platelet function. It has been suggested that routine preoperative coagulation tests can predict blood loss after cardiac surgery [116]. However, other studies have not confirmed this with coagulation tests performed either pre- or postoperatively [117–121]. In particular, transient platelet dysfunction, considered to be the most common and important hemostatic defect in the early postoperative period after CPB [3, 5, 36–38], cannot be readily determined with routine laboratory-based or POC tests. Laboratory-based tests such as aggregometry, adhesion tests, viscometry, flow cytometry, electron microscopy, secretion assays, and measurements of platelet activation markers such as β-thromboglobulin, platelet factor 4, or thromboxane A2, can provide useful information. However, they are time-consuming, involve long turnaround times, and require considerable technical expertise in both performance and interpretation, which limits their clinical utility. POC tests for evaluation of qualitative platelet function such as in vitro bleeding time [122, 123], clot retraction [124, 125], other tests of clot viscoelastic properties [126–128], agglutination of fibrinogen-coated beads [129], or clot formation [120, 130] have been evaluated or are currently being studied. Development of the dual-channel Thrombostat 4000 (VDG-von der Goltz, Seeon, Germany) instrument now allows automated measurement of in vitro bleeding time with either citrate-anticoagulated platelet-rich plasma, or whole blood [123]. A significant (P = 0.04) but weak (r² = 0.07) relationship between in vitro bleeding volume measured at the end of surgery and blood loss in the first 24 postoperative hours was demonstrated in 54 patients undergoing cardiac surgery [131]. Methods that assess viscoelastic properties of blood clots include the thromboelastograph (TEG), the Sonoclot®, and the Hemodyne® instrument. The Hemodyne instrument is a POC method that can detect qualitative platelet abnormalities by measuring clot retraction [125, 132]. Measurements of platelet force derived from this instrument have been shown recently to correlate with blood loss after cardiac surgery in a small series of patients [124]. Data from an early study [128] indicate that Sonoclot measurements may identify patients with MVB when compared with either a non-bleeding control group or patients with a surgical source of bleeding. Another POC assay is based on the ability of platelets in whole blood to rapidly agglutinate fibrinogen-coated beads when stimulated with a peptide (iso-S) FLLRN that activates a platelet thrombin receptor but resists inactivation by plasma aminopeptidase M [129]. Measurements obtained with this instrument were shown to correlate with increased glycoprotein IIb/IIIa receptor blockade with c7E3 Fab and may therefore be useful in identifying patients with qualitative platelet abnormalities.

We evaluated another recently developed POC test for assessment of platelet function based on whole-blood ACT measurements. The hemoSTATUS® (Medtronic Blood Management) test is designed to assess the effects of platelet-activating factor (PAF) in shortening the kaolin ACT in whole blood [120, 130]. PAF-accelerated coagulation (clot ratio values) was assessed at four different time points in a series of 150 patients: before institution of CPB, before discontinuation of CPB, after protamine administration, and after arrival in the ICU [120]. When compared with baseline clot ratios before anesthetic induction, a marked reduction in clot ratios was observed after protamine administration in both channels 5 and 6 despite average platelet counts >100 000/μL. There was a high degree of correlation between channel 5 clot ratio values (r = −0.85) and postoperative blood loss (cumulative chest tube drainage in the first 4 postoperative hours). The significant (P <0.01) improvement in clot ratios observed after arrival in the ICU in both channels 5 and 6 in patients receiving DDAVP or platelets supports the concept that the shortening of the ACT by PAF is largely due to direct or indirect effects of PAF on the availability of procoagulant activity on platelets.

In a subsequent study [133], the effects of various concentrations of platelets, leukocytes, and Fab fragments of a monoclonal antibody (c7E3, Reopro™) directed at the platelet glycoprotein IIb/IIIa receptor complex on ACT-based clot ratio values (hemoSTATUS) were evaluated in healthy volunteers. ACT-based clot ratio values obtained in heparinized whole blood, presumably reflecting PAF-inducible platelet procoagulant activity, were affected by decreasing platelet concentrations (<50 000/μL). Unexpectedly, test results were also affected by leukocyte concentrations; clot ratio values decreased when leuko-
cyte concentrations were <4000/µL or >9000/µL. A dose-dependent reduction in clot ratios by c7E3 was also demonstrated in this study [133], which supports the notion that this relatively simple and robust POC test may detect platelet dysfunction induced by certain drugs. Because ACT-based clot ratio values correlated strongly with postoperative blood loss and detected amelioration of depressed PAF-accelerated coagulation subsequent to DDAVP or platelet therapy [120], the hemoSTATUS assay may be useful in the identification of patients at risk for excessive blood loss and who may benefit from administration of DDAVP or platelets.

Thromboelastography has been shown by some to predict the risk of postoperative bleeding [126, 127], but others have failed to confirm its ability to predict either intraoperative [116] or postoperative bleeding [134]. DDAVP has been shown to be efficacious in patients with von Willebrand disease and mild hemophilia A [135], as well as in those with uremia [136] or cirrhosis [137], in certain cardiac surgical patients such as those requiring prolonged use of CPB [138], and in patients on platelet-inhibiting drugs [139]. Although, in general, prophylactic administration of DDAVP to cardiac surgical patients has not been shown to be clinically beneficial [140], certain patients identifiable by the TEG may benefit [127]. In a recent randomized, prospective trial, assessment of hemostasis with the TEG allowed identification of patients at risk for excessive postoperative MVB and who might respond to DDAVP therapy [127]. Patients with an abnormal (<50 mm) TEG maximum amplitude (MA) had substantially greater mediastinal chest tube drainage than matched patients that received DDAVP or those with a normal TEG-derived MA value. In a follow-up trial at the same institution, use of the TEG to direct DDAVP therapy in cardiac surgical patients at high-risk for MVB also resulted in reduced blood product utilization in the intervention cohort [141]. Although the effects of DDAVP on in vitro platelet function have been variable [142–144], the effects of DDAVP on expression of glycoprotein Ib receptors [145], generation of platelet microparticles [146], and release of platelet von Willebrand factor [147] may be important. Major limitations of the TEG method are the

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**Fig. 4.** Treatment algorithm for patients with excessive post-CPB MVB.

TT/HNTT, whole-blood thrombin time/heparin-neutralized thrombin time test (Hemochron instrument). Heparinase ACT, heparinase kaolin ACT test (ACT instrument). Heparinase APTT, heparinase-activated partial thromboplastin time test (Coaguchek Plus). WB HC, whole-blood heparin concentration cartridge (Hepcon instrument). D-dimers, whole-blood D-dimer assay (SimpleRED test). MA/A60 ratio, maximum amplitude/amplitude at 60 min (TEG). CR, clot ratio values (hemoSTATUS cartridge, Hepcon instrument). PF, platelet force measurements (Hemodyne Instrument). R2/R3, R2 and R3 slope values (Sonoclot instrument). WB FIB, whole-blood fibrinogen test (Hemochron instrument). Platelets, platelet transfusion (6 units of random donor or apheresis unit equivalent). Antifibrinolytic Rx, antifibrinolytic therapy (e.g., e-aminocaproic acid, tranexamic acid, aprotinin). FFP, plasma therapy (2 units of FFP); [+] MVB, continued MVB; PT:APTT, prothrombin time and activated partial thromboplastin time control values (values/mean values from a normal reference population); PLAT Count, platelet count (1000/µL). (See text for detailed description.)
relatively long measurement time (30–45 min) and the requirement for considerable technical expertise.

**Tests for evaluation of excessive fibrinolysis.** TEG measurements have been shown to be useful during liver transplantation when used to detect and treat hyperfibrinolysis [148]. The TEG may also potentially help in identifying patients who have excessive post-CPB fibrinolysis and who may respond to aminopropanoic acid administration [149]. With the TEG, a whole-blood clot lysis index [maximum amplitude/amplitude 60 ratio (MA/A60)] can be determined and may be useful in detecting hyperfibrinolysis. Others, however, have not been able to demonstrate substantial correlations between TEG measurements and D-dimer [150]. The thrombolytic assessment system (TAS, Cardiovascular Diagnostics) is a portable, lightweight instrument that utilizes a dry reagent system and can be used to measure whole-blood PT and aPTT and detect the onset of clot lysis in samples of citrated whole blood or plasma. This instrument is currently being evaluated clinically. The SimpleRED test (Agen Diagnostics, Queensland, Australia) allows assessment of D-dimer concentrations within 5 min with whole blood obtained by fingerstick or venipuncture. A bispecific antibody binds with high affinity on a site on the γ chain on D-dimer (3B6/22) and an erythrocyte binding antibody (RAT-IC3/86), thereby causing erythrocyte agglutination [151]. Data from two recent studies indicate that this assay may be useful in ruling out deep vein thrombosis when used in combination with bilateral impedance plethysmography [152, 153].

With new technological developments, it may become possible not only to identify patients at risk for excessive blood loss but also to determine specific hemostatic defects in a timely fashion that can then be corrected by specifically targeted treatment (Fig. 4). For example, assays may be used to determine whether patients may benefit from the following pharmacologic interventions before administration of hemostatic blood products: additional protamine (heparin-neutralized thrombin time, heparinase ACT, PT/aPTT, whole-blood heparin concentration), antifibrinolytic agents (whole-blood D-dimer, TEG MA/A60 ratio, thrombolytic assessment system clot lysis), or DDAVP (TEG MA, hemoSTATUS CR values, Hemodyne platelet force measurements, Sonoclot R2/R3 slope values, Thrombastat clot time and bleeding volume, platelet function estimates from the latex bead assay). In addition, whole-blood fibrinogen measurements could be utilized in the setting of abnormal PT and aPTT values (>1.8 × control) to identify patients with substantial hypofibrinogenemia who may benefit from transfusion of cryoprecipitate. Finally, further intraoperative inspection or exploration may be considered postoperatively when relatively normal POC hemostasis test results are obtained in patients with diffuse pericardial bleeding (MVB) intraoperatively or excessive mediastinal chest tube drainage postoperatively.

POC tests of hemostasis are beneficial in monitoring heparin therapy during and its reversal after extracorporeal circulation. In addition, the usefulness of POC tests for evaluation of platelet number and function, coagulation factors, and fibrinogen may facilitate optimal, targeted administration of pharmacologic agents and blood components in patients with excessive bleeding after CPB.

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**References**


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