Anesthesiology 2002; 96:1115–22

Utility of Whole Blood Hemostatometry Using the Clot Signature Analyzer® for Assessment of Hemostasis in Cardiac Surgery

Nauder Faraday, M.D., Eliseo Guallar, M.D., Dr.P.H.,† Valerie A. Sera, M.D.,‡ Everlie D. Bolton, B.S.,§ Robert B. Scharpf, M.S.,§ Ann M. Cartarius, R.N.,‖ Kathryn Emery, R.N.,‖ Julia Concord, R.N.,‖ Thomas S. Kickler, M.D.#*

Background: **A hemostatic monitor capable of rapid, accurate detection of clinical coagulopathy within the operating room could improve management of bleeding after cardiopulmonary bypass (CPB). The Clot Signature Analyzer® is a hemostatometer that measures global hemostasis in whole blood. The authors hypothesized that point-of-care hemostatometry could detect a clinical coagulopathic state in cardiac surgical patients.**

Methods: **Fifty-seven adult patients scheduled for a variety of elective cardiac surgical procedures were studied. Anesthesia, CPB, heparin anticoagulation, protamine reversal, and transfusion for post-CPB bleeding were all managed by standardized protocol. Clinical coagulopathy was defined by the need for platelet or fresh frozen plasma transfusion. The Clot Signature Analyzer® collagen-induced thrombus formation (CITF) assay measured platelet-mediated hemostasis *in vitro*. The activated clotting time, platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen concentration were also measured.**

Results: **The postprotamine CITF was greater in patients who required hemostatic transfusion than in those who did not (17.6 ± 8.0 min *vs.* 10.5 ± 5.7 min, respectively; $P < 0.01$). Postprotamine CITF values were highly correlated with platelet and fresh frozen plasma transfusion (Spearman r = 0.50, $P < 0.001$ and r = 0.40, $P < 0.005$, respectively). Receiver operator characteristic curves showed a highly significant relation between the postprotamine CITF and intraoperative platelet and fresh frozen plasma transfusion (area under the curve, 0.78–0.81, $P < 0.005$) with 60–80% sensitivity, specificity, positive and negative predictive values at cutoffs of 12–14 min. Logistic regression demonstrated that the CITF was independently predictive of post-CPB hemostatic transfusion, but standard hemostatic assays were not.**

Conclusions: **The Clot Signature Analyzer® CITF detects a clinical coagulopathic state after CPB and is independently predictive of the need for hemostatic transfusion. Hemostatometry has potential utility for monitoring hemostasis in cardiac surgery.**

BLEEDING after cardiopulmonary bypass (CPB) is a common complication of cardiac surgical procedures. Both the severity and etiology of bleeding are often difficult to objectively assess, and the time available for diagnosis is limited. Management is complicated by the wide differential diagnosis of post-CPB bleeding, which includes inadequate surgical hemostasis, dilution of platelets and coagulation factors,[1] platelet dysfunction,[2,3] excessive fibrinolysis,[4,5] residual heparin,[1,6] and hypothermia.[7] A number of standard assays (*e.g.*, platelet count, prothrombin time [PT], activated partial thromboplastin time [aPTT], thromboelastography) and newer methodologies (*e.g.*, automated protamine titration tests, platelet activated clotting time, sonoclot) are available to help guide hemostatic management in cardiac surgical patients. However, these tests have limited utility for diagnosis of post-CPB coagulopathy because their results are only weakly associated with parameters of clinical bleeding, because they are not rapidly available, or both.[8–12] As a result, patients judged to have intraoperative bleeding are frequently treated empirically (*e.g.*, with platelet or fresh frozen plasma [FFP] transfusion) or diagnosis and therapy are delayed until the patient reaches the intensive care unit (ICU). Reduction in both unnecessary transfusions and undesirable treatment delays requires a hemostatic monitor capable of rapid, accurate diagnosis of clinical coagulopathy within the operating room (OR).

Hemostatometry is a methodology that allows *ex vivo* assessment of multiple aspects of hemostasis in whole blood.[13] The technique uses shear stress and collagen to initiate hemostasis in blood that is perfused through a small tube.[14,15] Hemostatic plug formation within the tube causes a characteristic pattern of pressure changes that can be detected and quantified by the hemostatometer. The Clot Signature Analyzer (CSA®; Xylum Corporation, Scarsdale, NY) is a novel hemostatometer modified for point-of-care use. The device measures *ex vivo* hemostasis using three separate assays: (1) the time to collagen-induced thrombus formation (CITF); (2) the platelet-mediated hemostasis time (PHT); and (3) the clotting time (CT). The CITF and PHT may be measures of platelet function because they detect defects caused by platelet inhibitors such as aspirin, prostacyclin,[14] and antibodies to platelet glycoproteins IIb-IIIa (fibrinogen receptor) and Ib-IX (von Willebrand receptor).[16] The CT appears to assess fibrin stability because inhibitors of fibrin formation and fibrinolytics (*e.g.*, heparin, warfarin, and streptokinase) prolong this measurement.[15,16] Normal values for the CSA® CITF, PHT, and CT assays were

* Associate Professor, ‡ Assistant Professor, § Research Assistant, ‖ Research Nurse, Department of Anesthesiology and Critical Care Medicine, † Assistant Professor, Department of Epidemiology and Welch Center for Prevention, Epidemiology, and Clinical Research, # Professor, Department of Pathology.

Received from the Departments of Anesthesiology and Critical Care Medicine, Epidemiology, and Pathology, and the Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, Maryland. Submitted for publication August 2, 2001. Accepted for publication Janaury 2, 2002. Supported by a grant from the Xylum Coporation, Scarsdale, New York. Presented in part at the annual meeting of the Society of Cardiovascular Anesthesiologists, Vancouver, British Columbia, Canada, May 6–10, 2001.

Address reprint requests to Dr. Faraday: Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Hospital, Meyer 298, 600 N. Wolfe Street, Baltimore, Maryland 21287. Address electronic mail to: nfaraday@jhmi.edu.

established after extensive field testing on normal volunteers.[16]

Some investigators have advocated the clinical use of hemostatometry for general coagulation screening[15] and platelet function monitoring[17]; indeed, some investigators demonstrated a weak association between preoperative hemostatometry results and postoperative bleeding in cardiac surgical patients.[18] However, no study has evaluated hemostatometry for point-of-care hemostatic monitoring in cardiac surgery. Because the CSA® is a point-of-care hemostatometer capable of detecting multiple coagulation abnormalities simultaneously, we hypothesized that it could detect a clinically relevant coagulopathic state after CPB. Specifically, we hypothesized that: (1) patients who required platelet or FFP transfusion would have higher CSA® values than those who did not; and (2) CSA® values would correlate with perioperative hemostatic transfusion and chest tube drainage. Furthermore, we hypothesized that the association between CSA® measurements and post-CPB coagulopathy would be stronger than that observed for standard hemostatic assays.

Methods

Patient Population

After we obtained approval from the Johns Hopkins Joint Committee on Clinical Investigation and informed consent, patients older than 18 yr who were scheduled for elective cardiac surgical procedures involving the use of CPB were evaluated. The following surgical procedures were included: primary coronary artery bypass grafting, repeat coronary artery bypass grafting, aortic valve replacement, mitral valve replacement, ascending aortic aneurysm repair, and complex procedures involving combined valve–coronary artery bypass grafting and multiple valve procedures. Patients undergoing repair of congenital heart disease were excluded.

Clinical Protocol

Anesthesia, CPB, heparin anticoagulation, protamine reversal, and transfusion therapy were all managed by standardized protocol. Patients were anesthetized with fentanyl (15–20 μg/kg) and midazolam (0.1–0.2 mg/kg) supplemented with isoflurane and pancuronium. CPB was performed using moderate hypothermia (28–32°C) at flows of 2.2–2.4 $l \cdot min^{-1} \cdot m^{-2}$ and with the use of a membrane oxygenator. All patients were anticoagulated with 300 U/kg bovine heparin to achieve a celite-activated clotting time (ACT) of greater than 480 s before institution of CPB, and additional heparin was administered during CPB to keep the ACT greater than 480 s. After rewarming (core temperature $>$ 36.5°C) and separation from bypass, anticoagulation was reversed with protamine up to a maximum fixed dose of 1 mg/100 U of total heparin administered before and during CPB. Initial protamine was generally administered at a submaximal dose that was determined from *in vitro* protamine titration testing (Protamine Response Test; Hemochron, Edison, NJ). A celite-activated clotting time (Hemochron) was obtained 5 min after protamine to determine the adequacy of heparin neutralization. An ACT of 130 s or less was deemed adequate. In the presence of excessive bleeding, additional protamine was administered (50–100-mg increments) up to the maximum fixed dose until the ACT was 130 s or less or excessive bleeding abated.

Hemostatic Management Algorithm

Hemostatic management was protocolized in the OR and ICU. In both locations, the protocol began with the clinical assessment of hemostasis, and the hemostatic algorithm was activated by the presence of excessive bleeding. After the initial dose of protamine was administered, excessive intraoperative bleeding was assessed and defined by the surgical team as the presence of diffuse microvascular bleeding without an identifiable surgical source. In the ICU, excessive bleeding was defined by the presence of high chest tube drainage as follows: (1) greater than 100 ml/h for three consecutive hours, (2) greater than 150 ml/h for two consecutive hours, or (3) greater than 200 ml/h for any 1-h interval. In the presence of excessive bleeding, patients received the following staged treatments until adequate hemostasis was achieved: (1) additional protamine to a maximum of 1 mg/100 U heparin used for CPB (if maximum dose had not already been administered); (2) empiric platelet transfusion (5–8 units); (3) additional platelet transfusion or FFP transfusion according to coagulation testing (*i.e.*, platelet count $<$ 100,000 or PT/aPTT $>$ 1.5 $\times$ control value, respectively). Packed erythrocyte transfusion was permitted for a hemoglobin less than 8 g/dl during CPB and less than 9 g/dl after CPB.

Hemostatic Measurements and Clinical Variables

Clot Signature Analyzer® assays were performed at four time points perioperatively: (1) before the induction of anesthesia; (2) 5 min after protamine administration; (3) on arrival in the ICU; and (4) 4 h after arrival in the ICU. At each time point, blood was drawn from a radial arterial catheter, and each draw was preceded by withdrawal of 10 ml into a waste syringe. Two 3-ml syringes were filled at each draw and immediately (within 2 min) inserted into the CSA® test cassette for determination of CITF, PHT, and CT. A detailed description of the CSA® device and its test cassettes is provided elsewhere.[16] In brief, the CSA® is an automated tabletop device that uses prepackaged test cassettes for its hemostatic assays. Each cassette is composed of two channels: one that performs the CITF test and one that performs the PHT and CT tests. Once the test cassette is inserted

into the CSA® device, blood samples are processed automatically, and test results for all three assays are displayed within 30 min. In addition to CSA® assays, the following standard hemostatic measurements were performed on blood obtained 5 min after protamine administration: (1) celite-activated clotting time (Hemochron), platelet count (Coulter Counter, Hialeah, FL), PT, aPTT, and fibrinogen concentration. The PT, aPTT, and fibrinogen concentration assays were performed by the Johns Hopkins Hospital Coagulation Laboratory using photooptical clot detection methodology (Dade-Behring, Glasgow, DE).

The surgical, anesthesia, and ICU teams were blinded to all hemostatic test results obtained as part of the study protocol, and no clinical decisions were based on protocol data. Clinical decisions were based solely on clinical judgment in conjunction with any tests ordered by the clinical care team. Transfusion of platelets, FFP, and packed erythrocytes, and hourly chest tube drainage were recorded intraoperatively and for the first 24 h postoperatively. In addition to hemostatic variables, demographics, medical histories, and operative variables were recorded.

Statistical Analysis

The protocol was constructed using a prospective, blinded, observational design to determine the relation between CSA® measurements (CITF, PHT, and CT) and clinical measures of coagulopathy in cardiac surgical patients. Clinical coagulopathy was defined by the need for platelet or FFP transfusion intraoperatively and during the 24-h perioperative period (OR + ICU). Hemostatic transfusion was only permitted in the presence of excessive bleeding after heparin neutralization as defined by the aforementioned criteria. To determine if CSA® measurements were associated with clinical coagulopathy, data were analyzed by two-way analysis of variance, with patients grouped by their need (or lack thereof) for hemostatic transfusion. Main effects were noted, and differences between individual means assessed by Bonferroni-corrected *post hoc* test. To determine the strength of the association between hemostatic assays and transfusion or chest tube drainage, data were analyzed by nonparametric Spearman correlation. The ability of CSA® measures to diagnose clinical coagulopathy was determined from receiver operator characteristic curves with area under the curve (AUC) quantification. Logistic regression was used to determine the independent predictive value of coagulation assays for post-CPB hemostatic transfusion. We estimated that a sample size of 29 was needed to establish a correlation of $r = 0.5$ between CSA measures and hemostatic transfusion, with 80% power and two-tailed α of 0.05. An $r = 0.5$ was selected because we believed that a correlation of this magnitude was required for results to be clinically meaningful. To allow analysis of subgroups of surgical patients, we planned to study 60 patients. Unless otherwise specified, data are presented as mean ± SD, and $P < 0.05$ was considered significant.

Table 1. Demographic, Historical, and Operative Characteristics of the Study Population

Age (yr)	62.2 ± 12.2
Gender (% M/% F)	56/44
Height (m)	1.71 ± 9.9
Weight (kg)	81.9 ± 15.0
Body surface area (m^2)	1.95 ± 0.24
Medical history (%)	
Hypertension	63
Diabetes mellitus	32
Myocardial infarction	49
Preoperative antithrombotic medications (%)	
Aspirin	58
Clopidogrel	18
Intravenous heparin	28
Low-molecular-weight heparin	4
Coumadin	4
Procedure (%)	
Primary CABG	53
Repeat CABG	4
Aortic or mitral valve replacement	17
Ascending aortic aneurysm repair	2
Combined procedures	24
Prophylactic antifibrinolytics (%)	61
ϵ-Aminocaproic acid	54
Aprotinin	7
Heparin dose (U)	42,600 ± 17,700
Protamine dose (mg)	374 ± 94
Protamine to heparin ratio (mg/100 U)	0.95 ± 0.26
CPB time (min)	140 ± 55

CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass.

Results

A total of 61 patients were studied. Three patients were excluded for breach of the hemostatic protocol (*i.e.*, platelets or FFP were transfused in the absence of defined criteria for excessive bleeding), and one was excluded for surgical hemorrhage (reexploration with identification of a surgical source of bleeding). The demographic, historical, and operative variables describing the 57 patients included in the analysis are summarized in table 1. Hemostatic transfusion and chest tube drainage data are summarized in table 2. Nineteen patients (33%) were transfused for intraoperative coagulopathy. All 19 received platelet transfusion, and 11 (19%) received FFP. Only six patients (10%) were transfused for coagulopathy in the ICU (two received platelets and five received FFP), and, on average, postoperative chest tube drainage was modest (table 2). A total of 20 patients (35%) received at least one hemostatic transfusion for excessive bleeding during the perioperative period (OR + ICU), all of whom received platelets. Of these, nine patients received platelet concentrates only, and 19 of the 20 patients who received platelets were treated empirically.

Table 2. Hemostatic Transfusion and Chest Tube Drainage after Cardiopulmonary Bypass

Transfusion	Intraoperative	24 h ICU	OR + 24 h ICU
Platelets	33%	4%	35%
	0 (0–1)/0–2	0 (0–0)/0–2	0 (0–1)/0–4
FFP	19%	9%	19%
	0 (0–0)/0–6	0 (0–0)/0–4	0 (0–0)/0–10
Cumulative Chest Tube Drainage	4 h	12 h	24 h
Mean ± SD (ml)	174 ± 119	354 ± 205	496 ± 294
Range (ml)	20–570	80–1,360	130–1,480

Transfusion data are reported as percent of patients who underwent transfusion and median (25–75 percentile)/range of the number of transfusions administered during the indicated interval. Platelet transfusion data are reported for packs transfused with each pack equaling 5–8 platelet units, depending on patient size and blood bank availability. Fresh frozen plasma data are reported for units transfused.

24 h = first 24 postoperative hours; ICU = intensive care unit; OR = operating room; FFP = fresh frozen plasma.

To determine if CSA® CITF, PHT, and CT assays could detect abnormal hemostasis intraoperatively, we monitored CSA® measurements throughout the perioperative period. The CITF was prolonged 5 min after protamine administration and returned to baseline in the ICU (8.5 ± 4.0, 13.0* ± 7.4, 9.6 ± 5.0, and 8.5 ± 5.1 min for postprotamine *vs.* preinduction, ICU arrival, and 4-h post ICU arrival, respectively; $^{*}P < 0.01$). PHT and CT did not change significantly during the perioperative period (data not shown). To determine if the *in vitro* alteration of CITF was associated with a clinical coagulopathic state, we compared mean CITF values between groups of patients who did and did not require hemostatic transfusion. In patients who received intraoperative platelets or FFP, the postprotamine CITF was markedly elevated and was prolonged compared with those who did not require hemostatic transfusion (fig. 1A). By contrast, patients who did not require intraoperative hemostatic transfusion demonstrated only a modest increase in postprotamine CITF (fig. 1A). Box plot analysis of CITF data obtained after protamine administration confirmed the ability of the CITF to discriminate between patients who did and did not receive transfusion (fig. 1B). Inclusion of all 61 patients in data analysis yielded similar results (postprotamine CITF, 18 ± 8 *vs.* 10 ± 5 min for hemostatic *vs.* no hemostatic transfusion, respectively; $P < 0.01$). Similar analyses for PHT and CT data did not demonstrate a significant difference between patients by transfusion status (data not shown).

To determine the strength of the association between intraoperative CSA measurements and clinical bleeding in the OR, we correlated CITF, PHT, and CT values obtained at the postprotamine time point with the number of platelet or FFP transfusions administered intraoperatively (table 3). CITF was highly correlated with the amount of platelets or FFP transfused in the OR; however, PHT and CT were not. Because intraoperative coagulopathy may extend into the ICU, particularly if left untreated in the OR, we repeated our correlative analysis using perioperative (OR + ICU) hemostatic transfusion as the clinical metric of post-CPB coagulopathy. Data in table 3 show that the postprotamine CITF remained

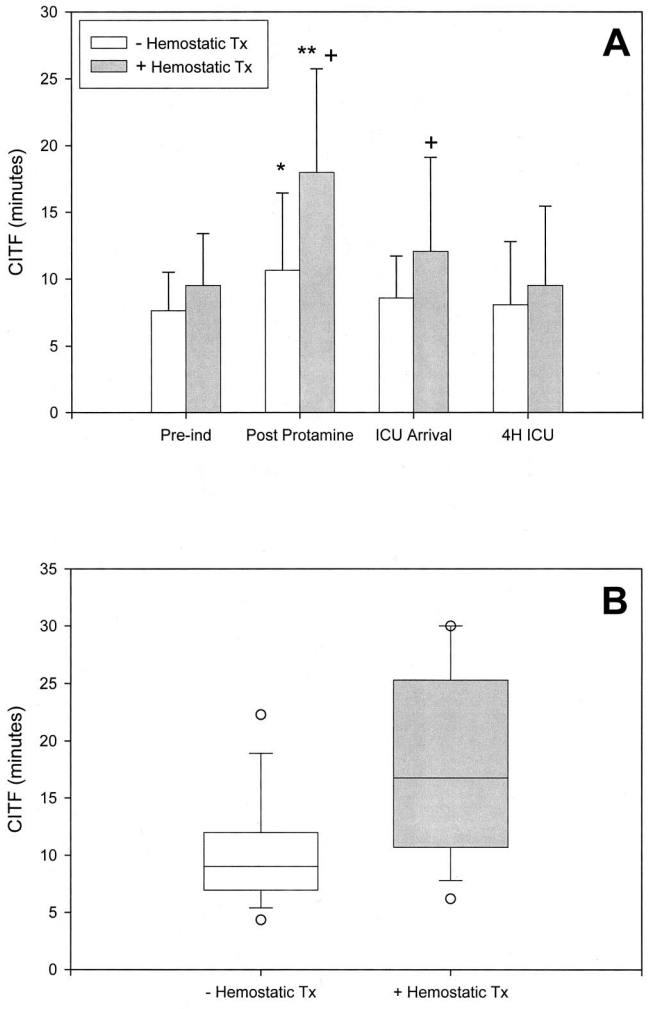

Fig. 1. Collagen-induced thrombus formation (CITF) is prolonged in patients who require hemostatic transfusion for post-cardiopulmonary bypass coagulopathy. (*A*) Blood was drawn at the indicated time points for CITF. Data were analyzed by two-way analysis of variance grouped according to hemostatic transfusion. Data were significantly different for main effects of group ($P < 0.001$), time ($P < 0.001$), and group–time interaction ($P < 0.005$). $^{*}P < 0.01$ *versus* before induction of anesthesia; $^{**}P < 0.005$ *versus* before induction of anesthesia, intensive care unit arrival, and 4 h after intensive care unit arrival; $^{+}P < 0.01$ for hemostatic transfusion *versus* no hemostatic transfusion by Bonferroni-corrected *post hoc* test. (*B*) Box plot analysis of CITF values after protamine administration grouped by hemostatic transfusion. Plots indicate median, 25–75 percentiles, and 95% confidence intervals. Open circles indicate individual values outside the 95% confidence interval. Hemostatic tx = intraoperative platelet or fresh frozen platelet transfusion; Preind = before induction of anesthesia; Post Protamine = 5 min after protamine administration; ICU arrival = on arrival to the intensive care unit; 4H ICU = 4 h after arrival in the intensive care unit.

Table 3. Correlation between Intraoperative Hemostatic Assays and Measures of Clinical Coagulopathy after Cardiopulmonary Bypass

	Platelet Transfusion		FFP Transfusion		Chest Tube Drainage (h)		
Assay	OR	OR + ICU	OR	OR + ICU	4	12	24
CITF	0.50* ($P < 0.001$)	0.45* ($P < 0.001$)	0.40* ($P < 0.005$)	0.41* ($P < 0.005$)	−0.04 ($P = 0.95$)	0.04 ($P = 0.76$)	0.02 ($P = 0.89$)
PHT	0.24 ($P = 0.07$)	0.24 ($P = 0.07$)	0.09 ($P = 0.49$)	−0.03 ($P = 0.85$)	−0.12 ($P = 0.39$)	−0.09 ($P = 0.51$)	−0.09 ($P = 0.52$)
CT	0.22 ($P = 0.14$)	0.23 ($P = 0.12$)	0.01 ($P = 0.96$)	0.01 ($P = 0.92$)	0.21 ($P = 0.15$)	0.25 ($P = 0.10$)	0.27 ($P = 0.06$)
ACT	0.06 ($P = 0.64$)	0.10 ($P = 0.45$)	0.16 ($P = 0.23$)	0.16 ($P = 0.24$)	−0.07 ($P = 0.62$)	−0.04 ($P = 0.76$)	−0.08 ($P = 0.55$)
PLT	−0.34* ($P = 0.009$)	−0.32* ($P = 0.02$)	0.02 ($P = 0.88$)	0.02 ($P = 0.90$)	−0.18 ($P = 0.18$)	−0.19 ($P = 0.17$)	−0.22 ($P = 0.11$)
PT	0.29* ($P = 0.03$)	0.28* ($P = 0.04$)	0.22 ($P = 0.10$)	0.23 ($P = 0.08$)	0.25 ($P = 0.06$)	0.27 ($P = 0.05$)	0.21 ($P = 0.13$)
aPTT	0.50* ($P < 0.001$)	0.46* ($P < 0.001$)	0.44* ($P = 0.001$)	0.45* ($P = 0.001$)	0.09 ($P = 0.51$)	0.16 ($P = 0.25$)	0.16 ($P = 0.23$)
FGN	0.08 ($P = 0.59$)	0.09 ($P = 0.56$)	−0.02 ($P = 0.88$)	−0.01 ($P = 0.94$)	−0.07 ($P = 0.62$)	−0.22 ($P = 0.14$)	−0.08 ($P = 0.56$)

Nonparametric Spearman correlation was used to determine the strength of the relations between hemostatic assays (obtained 5 min after protamine administration) and the number of platelet (packs) and fresh frozen plasma (FFP; units) transfusions. Similar analysis was used to determine the relation between hemostatic assays and postoperative chest tube drainage at the indicated time points. In each case, data are presented as Spearman ρ followed by P value in parentheses.

* Statistically significant results.

OR = operating room; ICU = intensive care unit; CITF = collagen-induced thrombus formation; PHT = platelet hemostasis time; CT = clotting time; ACT = activated clotting time; PLT = platelet count; PT = prothrombin time; aPTT = activated partial thromboplastin time; FGN = fibrinogen concentration.

highly correlated with the total amount of platelets and FFP transfused. Correlations between postprotamine CITF and intraoperative hemostatic transfusion were similar when all 61 patients were included in the data analysis (Spearman r = 0.46, $P < 0.001$ and r = 0.36, $P < 0.005$ for platelet and FFP transfusion, respectively). However, none of the CSA® measurements obtained intraoperatively correlated with postoperative chest tube drainage (table 3). We also correlated standard hemostatic assays (5 min postprotamine) to clinical measures of coagulopathy. Only the aPTT demonstrated a correlation with hemostatic transfusion similar to that observed with the CITF (table 3). All other hemostatic assays were less well correlated (platelet count and PT) or were not correlated at all (ACT and fibrinogen concentration) to perioperative hemostatic transfusion. In addition, none of the standard assays correlated with postoperative chest tube drainage (table 3).

The strength of the associations between postprotamine CITF and intraoperative hemostatic transfusion were similar for patients undergoing primary coronary artery bypass grafting (n = 30) and those undergoing repeat, valve, and combined procedures (n = 27; Spearman r = 0.51 for platelet transfusion and 0.39 for FFP transfusion, $P < 0.01$ for both procedure groups). However, correlations between CITF and intraoperative transfusion were significant only in the subgroup of patients receiving prophylactic antifibrinolytic therapy (n = 35; Spearman r = 0.59 for platelet transfusion and 0.40 for FFP transfusion, $P < 0.01$). There was also a correlative trend in patients who did not receive antifibrinolytics (n = 22; Spearman r = 0.36, $P = 0.10$ and r = 0.34, $P = 0.12$ for platelet and FFP transfusion, respectively); however, with only 22 patients in this subgroup, this analysis had limited power.

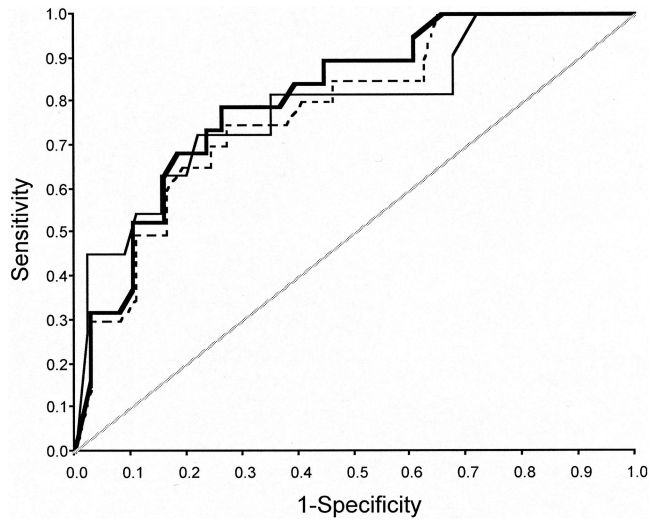

Fig. 2. Receiver operating characteristic curves demonstrate the ability of intraoperative collagen-induced thrombus formation to detect post-CPB coagulopathy. Receiver operating characteristic curves were generated to relate the postprotamine collagen-induced thrombus formation to the intraoperative transfusion of platelets (bold solid line, area under the curve [AUC] = 0.81, $P < 0.005$), fresh frozen plasma (thin solid line, AUC = 0.79, $P < 0.005$), and platelets or plasma (dashed line, AUC = 0.78, $P < 0.005$). The diagonal line in gray indicates the line of identity (AUC = 0.50).

Table 4. Among Hemostatic Assays, only CITF and aPTT Show Significant Capacity for Diagnosis of Post-CPB Coagulopathy

Assay	Area under the ROC Curve	95% Confidence Interval
CITF	0.78*	0.66–0.91
ACT	0.57	0.42–0.73
PLT	0.65	0.48–0.92
PT	0.63	0.47–0.79
aPTT	0.77†	0.62–0.92
FGN	0.56	0.40–0.73

The diagnostic capabilities of each hemostatic assay for detecting the need for intraoperative platelet transfusion, fresh frozen plasma transfusion, or both were determined by receiver operating characteristic (ROC) analysis. The area under each curve and 95% confidence intervals were quantified.

* $P < 0.005$ and † $P < 0.01$ *versus* line of identity (area under the curve = 0.50).

CITF = collagen-induced thrombus formation; aPTT = activated partial thromboplastin time; CPB = cardiopulmonary bypass; ACT = activated clotting time; PLT = platelet count; PT = prothrombin time; FGN = fibrinogen concentration.

Receiver operator characteristic curves were generated to determine the ability of intraoperative hemostatic measurements to diagnose post-CPB coagulopathy. Receiver operator characteristic analyses (fig. 2) demonstrated a highly significant relation between postprotamine CITF and intraoperative transfusion of platelets (AUC = 0.81, $P < 0.005$), FFP (AUC = 0.79, $P < 0.005$), or any hemostatic transfusion (AUC = 0.78, $P < 0.005$). Receiver operator characteristic analyses were similar when transfusion during the entire perioperative period (OR + ICU) was considered (data not shown). Among standard hemostatic assays, only the aPTT was significantly related to the need for hemostatic transfusion (AUC = 0.77, $P < 0.01$), but other hemostatic assays were not (table 4).

The sensitivity, specificity, and predictive values of the CITF for any intraoperative hemostatic transfusion (platelets or FFP) were determined through a range of cutoff values (table 5). For values between 12 and 14 min, diagnostic indices ranged between 60 and 80%. Values were similar when analysis was performed on the relation between CITF values and total hemostatic transfusion (OR + ICU, data not shown). Logistic regression demonstrated that of all the hemostatic measurements, only CITF and aPTT had the ability to predict the need for post-CPB hemostatic transfusion (table 6). Furthermore, of the two assays, only the CITF was independently predictive of transfusion (table 6).

Table 6. Intraoperative CITF, but Not Standard Hemostatic Assays, Is Independently Predictive of Hemostatic Transfusion after CPB

Assay	Univariate *P* Value	Multivariate *P* Value
CITF	<0.01	0.02
ACT	0.49	—
PLT	0.36	—
PT	0.11	—
aPTT	0.02	0.29
FGN	0.25	—

Univariate logistic regression was performed to determine the relation between postprotamine hemostatic assays and the need for intraoperative hemostatic transfusion (platelets, fresh frozen plasma, or both). Assays significantly associated with transfusion in univariate analysis were included in multivariate analysis.

CITF = collagen-induced thrombus formation; CPB = cardiopulmonary bypass; ACT = activated clotting time; PLT = platelet count; PT = prothrombin time; aPTT = activated partial thromboplastin time; FGN = fibrinogen concentration.

Discussion

We sought to determine the utility of whole blood hemostatometry for assessing hemostasis in cardiac surgery. We hypothesized that the CSA®, a novel point-of care hemostatometer, could detect a clinical coagulopathic state after CPB and that the association between CSA® assays and clinical measures of coagulopathy would be stronger than that observed with standard hemostatic assays. Results of this study demonstrate that the CSA® CITF detects a hemostatic abnormality *in vitro* associated with the clinical transfusion of platelets and FFP, and the association between the CITF and clinical coagulopathy was equivalent or greater than that observed for standard hemostatic assays. Furthermore, the CITF was independently predictive of hemostatic transfusion after CPB, but standard hemostatic assays were not. In addition, diagnostic indices of the CITF for detection of coagulopathy were in a clinically useful range (60–80%), and test results could be rapidly obtained (*i.e.*, within 15 min using cutoff values of 12–14 min). In sum, the data suggest that point-of-care hemostatometry

Table 5. Diagnostic Indices of CITF for Hemostatic Transfusion after CPB

CITF Cutoff (min)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
10	80	60	52	85
12	70	74	61	82
14	65	78	65	81
16	50	84	62	76

Indices were determined for the ability of the postprotamine CITF to detect the need for any intraoperative hemostatic transfusion (platelets, fresh frozen plasma, or both).

CITF = collagen-induced thrombus formation; CPB = cardiopulmonary bypass.

as performed by the CSA® CITF has potential utility for monitoring hemostasis in cardiac surgery.

The CITF (but not the PHT or CT) was prolonged in patients who required hemostatic transfusion and was highly correlated with the amount of platelets and FFP transfused. In contrast, most routine hemostatic assays showed only modest or no significant relation to post-CPB bleeding or transfusion, a finding that is consistent with previous reports.[8,11] None of the hemostatic assays correlated with postoperative chest tube drainage. The aggressive treatment of intraoperative bleeding with platelets and FFP (33% of patients received intraoperative hemostatic transfusion) may have led to early correction of hemostatic abnormalities and rendered postoperative chest tube drainage less sensitive than transfusion as a measure of post-CPB coagulopathy. Low rates of postoperative chest tube drainage (< 500 ml/24 h), ICU transfusion (10% of patients), and reexploration (1 of 61 patients) support the position that post-CPB hemostatic abnormalities were corrected by the clinical team intraoperatively.

The postprotamine CITF detected a clinically relevant coagulopathic state after CPB. However, the specific hemostatic abnormality or abnormalities detected by the CSA® remain unknown. The observation that CITF increased after CPB and was associated with hemostatic transfusion suggests that altered platelet responsiveness to collagen contributes to post-CPB coagulopathy. This finding is consistent with other reports that have demonstrated an association between post-CPB bleeding and reduced platelet responsiveness to agonist stimulation *in vitro*.[9,19,20] The CITF was also the only hemostatic assay that was independently predictive of postoperative transfusion, whereas measures of residual heparinization (ACT and aPTT) and coagulation factor concentration/activity (PT, aPTT, and fibrinogen concentration) were not. However, this study was not designed to determine the etiology of post-CPB coagulopathy but, rather, to determine if point-of-care hemostatometry could detect a clinically relevant coagulopathic state. Additional studies that concurrently analyze CITF and standard platelet function assays are necessary to confirm if the coagulopathy detected by the CSA® is caused by post-CPB platelet dysfunction.

The importance of intraoperative hemostatic monitoring is well recognized; however, no single hemostatic monitor has proven effective for this purpose. For example, monitors of heparin anticoagulation, such as automated heparin and protamine titration tests, have not consistently been shown to reduce post-CPB blood loss or transfusion.[12,21,22] The utility of standard hemostatic tests (*e.g.*, platelet count, PT, and aPTT), thromboelastography, and the platelet activated clotting time have also been evaluated. These tests have demonstrated only modest correlations (r = 0.05–0.39) and positive predictive values (10–60%) for post-CPB bleeding, although negative predictive values for some of these tests have been high (> 90%).[8,10,11,23] The sensitivity, specificity, and predictive values of the CITF for post-CPB coagulopathy ranged between 60 and 80%, which compares favorably with the best of the hemostatic assays previously studied.[11]

A combination of hemostatic assays may provide more effective diagnostic information than the use of any single test. Indeed, the use of multiple monitors as part of a hemostatic management algorithm has been shown to reduce post-CPB transfusion.[24–26] Interestingly, this benefit was evident despite the fact that the assays incorporated into the hemostatic management algorithms are only modestly related (or not related at all) to bleeding after CPB. The effectiveness of hemostatometry alone or in combination with other assays for hemostatic management after CPB is unknown but appears to warrant further investigation.

Bleeding is common after CPB. Intraoperative diagnosis of the presence and cause of post-CPB coagulopathy would enable more effective hemostatic management because accurate assessment of intraoperative bleeding could prevent both unnecessary transfusions and undesirable treatment delays. A point-of-care monitor capable of rapid, accurate detection of clinical coagulopathy would provide objective data to guide intraoperative management. The CSA® is a point-of-care hemostatometer capable of rapid detection of a clinical coagulopathic state after CPB. The ability of hemostatometry to improve hemostatic management in cardiac surgical patients requires further study.

Study Limitations

Many of the hemostatic therapies used as part of this study were empiric instead of guided by laboratory testing. This was particularly the case for intraoperative administration of additional protamine and platelet transfusion. It is impossible to know if clinical judgment was accurate in detecting and treating excessive post-CPB bleeding and if the hemostatic therapies used were truly warranted. The overall rate of hemostatic transfusion (35%) in this study was somewhat higher than previously reported (13–31%[11,23,25,27,28]); however, chest tube drainage (< 500 m/24 h) and reexploration (1.6%) were lower than in other studies (> 900 ml/24 h and 1.9–8.0%, respectively.[11,23,25,27,28]) It is unclear if the relation we observed between the CITF and clinical measures of coagulopathy would have been the same if diagnosis of bleeding required more coagulation testing or if a different therapeutic strategy had been used to treat bleeding. Another limitation of this study is that we did not identify the mechanism of post-CPB bleeding, and as such, we were unable to define the best therapy for excessive bleeding in response to an abnormal CITF. Finally, it is important to note that the US Food and Drug Administration has not approved the CSA® device, and the de-

vice manufacturer (Xylum Corporation) is no longer supplying the device or test cassettes. As such, further research and development are necessary before hemostatometry becomes available for clinical use.

References

1. Woodman RC, Harker LA: Bleeding complications associated with cardiopulmonary bypass. Blood 1990; 76:1680–97
2. Harker LA, Malpass TW, Branson HE, Hessel ED, Slichter SJ: Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: Acquired transient platelet dysfunction associated with selective alpha-granule release. Blood 1980; 56:824–34
3. Rinder CS, Bohnert J, Rinder HM, Mitchell J, Ault K, Hillman R: Platelet activation and aggregation during cardiopulmonary bypass. ANESTHESIOLOGY 1991; 75:388–93
4. Stibbe J, Kluft C, Brommer EJP, Gomes M, De Jong DS, Nauta J: Enhanced fibrinolytic activity during cardiopulmonary bypass in open-heart surgery in man is caused by extrinsic (tissue-type) plasminogen activator. Eur J Clin Invest 1984; 14:375–82
5. Gram J, Janetzko T, Jespersen J, Bruhn HD: Enhanced effective fibrinolysis following the neutralization of heparin in open heart surgery increases the risk of post-surgical bleeding. Thromb Haemost 1990; 63:241–5
6. Kestin AS, Valeri CR, Khuri SF, Loscalzo J, Ellis PA, MacGregor H, Birjiniuk V, Ouimet H, Pasche B, Nelson MJ, Benoit SE, Rodino LJ, Barnard MR, Michelson AD: The platelet function defect of cardiopulmonary bypass. Blood 1993; 82: 107–17
7. Valeri CR, Khabbaz K, Khuri SF, Marquardt C, Ragno G, Feingold H, Gray AD, Axford T: Effect of skin temperature on platelet function in patients undergoing extracorporeal bypass. J Thorac Cardiovasc Surg 1992; 104:108–16
8. Gravlee GP, Arora S, Lavender SW, Mills SA, Hudspeth AS, Cordell AR, James RL, Brockschmidt JK, Stuart JJ: Predictive value of blood clotting tests in cardiac surgical patients. Ann Thorac Surg 1994; 58:216–21
9. Ray MJ, Hawson GAT, Just SJE, McLachlan G, O'Brien M: Relationship of platelet aggregation to bleeding after cardiopulmonary bypass. Ann Thorac Surg 1994; 57:981–6
10. Ereth MH, Nuttall GA, Klindworth JT, MacVeigh I, Santrach PJ, Orszulak TA, Harmsen WS, Oliver W Jr: Does the platelet-activated clotting test (Hemo-STATUS) predict blood loss and platelet dysfunction associated with cardiopulmonary bypass? Anesth Analg 1997; 85:259–64
11. Nuttall GA, Oliver WC, Ereth MH, Santrach PJ: Coagulation tests predict bleeding after cardiopulmonary bypass. J Cardiothrorac Vasc Anesth 1997; 11: 815–23
12. Shore-Lesserson L, Reich DL, DePerio M: Heparin and protamine titration do not improve haemostasis in cardiac surgical patients. Can J Anaesth 1998; 45:10–8
13. Gorog P, Ahmed A: Haemostatometer: A new in vitro technique for assessing haemostatic activity in blood. Thromb Res 1984; 34:341–57
14. Gorog P, Path MRC, Kakkar VV: Transient effect of aspirin on collagen-induced platelet accumulation. Am J Clin Pathol 1986; 86:311–6
15. Gorog P, Kovacs I B: Coagulation of flowing native blood: Advantages over stagnant (tube) clotting tests. Thromb Res 1991; 64:611–9
16. Li CKN, Hoffmann TJ, Hsieh P-Y, Malik S, Watson WC: The Xylum Clot Signature Analyzer: A dynamic flow system that simulates vascular injury. Thromb Res 1998; 92(Suppl):S67–77
17. Kovacs IB, Hutton RA, Kernoff PBA: Hemostatic evaluation of bleeding disorders from native blood: Clinical experience with the Hemostatometer. Am J Clin Pathol 1989; 91:271–9
18. Ratnatunga CP, Rees GM, Kovacs IB: Preoperative hemostatic activity and excessive bleeding after cardiopulmonary bypass. Ann Thorac Surg 1991; 52: 250–7
19. Halloway DS, Summaria L, Sandesara J, Vagher JP, Alexander JC, Caprini JA: Decreased platelet number and function and increased fibrinolysis contribute to postoperative bleeding in cardiopulmonary bypass patients. Thromb Haemost 1988; 59:62–7
20. Ferraris VA, Ferraris SP, Singh A, Fuhr W, Koppel D, McKenna D, Rodriguez E, Reich H: The platelet thrombin receptor and postoperative bleeding. Ann Thorac Surg 1998; 65:352–8
21. Jobes DR, Schwartz AJ, Ellison N, Andrews R, Ruffini RA, Ruffini JJ: Monitoring heparin anticoagulation and its neutralization. Ann Thorac Surg 1981; 31:161–6
22. Beholz S, Grubitzsch H, Bergmann B, Wollert HG, Eckel L: Hemostasis management by use of Hepcon/HMS: Increased bleeding without increased need for blood transfusion. Thorac Cardiovasc Surg 1999; 47:322–7
23. Nuttall GA, Oliver WC, Beynen FM, Santrach PJ, Strickland RA, Murray MJ: Determination of normal versus abnormal activated partial thromboplastin time and prothrombin time after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1995; 9:355–61
24. Despotis GJ, Grishaber JE, Goodnough LT: The effect of an intraoperative treatment algorithm on physicians' transfusion practice in cardiac surgery. Transfusion 1994; 34:290–6
25. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA: Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg 1999; 88:312–9
26. Nuttall GA, Oliver WC, Santrach PJ, Bryant S, Dearani JA, Schaff HV, Ereth MH: Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after cardiopulmonary bypass. ANESTHESIOLOGY 2001; 94: 773–81
27. Despotis GJ, Levine V, Filos KS, Santoro SA, Joist JH, Spitznagel E, Goodnough LT: Evaluation of a new point-of-care test that measures PAF-mediated acceleration of coagulation in cardiac surgical patients. ANESTHESIOLOGY 1996; 85:1311–23
28. Despotis GJ, Filos KS, Zoys TN, Hogue CW, Spitznagel E, Lappas DG: Factors associated with excessive postoperative blood loss and hemostatic transfusion requirements: A multivariate analysis in cardiac surgical patients. Anesth Analg 1996; 82:13–21