Does incorporation of thromboelastography improve bleeding prediction following adult cardiac surgery?

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Cardiopulmonary bypass (CPB) coagulopathy increases utilization of allogenic blood/blood products, which can negatively affect patient outcomes. Thromboelastography (TEG) is a point-of-care measurement of clot formation and fibrinolysis. We investigated whether the addition of TEG parameters to a clinically based bleeding model would improve the predictability of postoperative bleeding. A total of 439 patients' charts were retrospectively investigated for 8-h chest tube output (CTO) postoperatively. For model 1, the variables recorded were patient age, gender, body surface area, clopidogrel use, CPB time, first post-CPB fibrinogen serum level, first post-CPB platelet count, first post-CPB international normalized ratio, the total amount of intraoperative cell saver blood transfused, and postoperative first ICU hematocrit level. Model 2 had the model 1 variables, TEG angle, and maximum amplitude. The outcome was defined as 0–8-h CTO. The predictor variables were placed into a forward stepwise regression model for continuous outcomes. Analysis of variance with adjusted \( R^2 \) was used to assess the goodness-of-fit of both predictive models. The predictive accuracy of the model was examined using CTO as a dichotomous variable (75th percentile, 480 ml) and receiver operating characteristic curves for both models. Advanced age, male gender, preoperative clopidogrel use for 5 days or less, greater cell saver blood utilization, and lower postoperative hematocrit levels were associated with increased 8-h CTO (\( P < 0.05 \)). Adding TEG angle and maximum amplitude to model 1 did not improve CTO predictability. When TEG angle and maximum amplitude were added as predictor factors, the predictability of the bleeding model did not improve. Blood Coagul Fibrinolysis 25:561–570 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction
Cardiac surgery consumes 10–20% of the national blood supply [1]. A minority of patients consume 80% of the allogenic blood transfused during cardiac surgery [1]. Approximately, 50% of platelet, 30% of fresh frozen plasma (FFP), and 15% of red blood cell (RBC) transfusions are inappropriate [2]. Transfusion of blood, FFP, and platelets is associated with increased patient morbidity and mortality [3]. The cause of coagulopathy is multifactorial. Cardiopulmonary bypass (CPB) induces systemic inflammatory syndrome, which activates the coagulation cascade and results in coagulation factor and platelet activation/consumption. Other causes include hypothermia, acidosis, residual heparin anticoagulation, and hyperfibrinolysis [4]. Despite the Society of Thoracic Surgeons (STS) transfusion guidelines, studies have demonstrated great variability in institution transfusion practices (RBC transfusions from 27 to 92% and coagulation factor transfusions from 0 to 36%), with a marked lack of consensus regarding transfusion triggers [5,6]. The incorporation of reliable, rapid, and predictive point-of-care (POC) coagulation testing algorithms for transfusion guidelines is needed to guide perioperative blood/blood product transfusions better.

In contrast to standard coagulation tests (SCT), thromboelastography (TEG) measures the mechanical properties of the developing clot, maximum clot strength, and clot lysis [7]. TEG-guided transfusion algorithms during cardiac surgery have resulted in a reduced administration of blood products [8–10]. The addition of TEG parameters to cardiac surgery bleeding models to help predict bleeding more accurately has been controversial [11,12].

Over a 5-year period, we investigated, based on type of adult cardiac surgery performed, patient blood/blood product, intraoperative cell saver blood (CSB) utilization, and postoperative blood loss by measuring 8-h CTO. We hypothesized that the addition of TEG to our clinical bleeding model would help predict bleeding more effectively, thus paving the way for early detection and treatment of CPB coagulopathies, which would eventually result in rational and possibly reduced utilization of blood products.
Materials and methods

After obtaining institutional research ethics board approval, the data were retrospectively collected from cardiac surgery/transfusion/TEG/perfusion and nursing records from 2007 to 2012. All the adult patients (>18 years) who underwent cardiac surgery with CPB and TEG coagulation monitoring were included. The exclusion criteria were patients who had off-CPB coronary artery bypass graft (CABG), coagulation disorders requiring prophylactic blood products, preexisting hepatic disease (transaminase levels > two times normal), and renal disease requiring dialysis. Patients who underwent chest re-exploration and who had surgical causes for bleeding were also excluded.

We examined the association of variables for two models [model 1 or the clinical bleeding model; and model 2, or the clinical bleeding model + TEG parameters (maximum amplitude and angle)] and postoperative bleeding, as measured by chest tube output (CTO) for the first 8 h. The model 1 variables were patient age, gender, body surface area (BSA), preoperative clopidogrel use for 5 days or less, CPB time, first post-CPB fibrinogen serum level, first post-CPB platelet count, first post-CPB international normalized ratio (INR), total amount of intraoperative CSB transfused, and postoperative first ICU hematocrit level.

The patient records were investigated for preoperative hematocrit levels and SCT, which included platelet count, partial thromboplastin time (PTT), and INR. Serum fibrinogen levels were not ordered as part of the preoperative SCT, but were included in the post-CPB SCT. The TEG studies were performed using a TEG 5000 Thrombelastograph Hemostasis Analyzer. The first (pre-CPB) sample (baseline) was drawn after the arterial line placement. The second (post-CPB) sample was drawn just before the CPB was terminated or after the heparin protamine reversal, but before chest closure. The pre-CPB samples were collected in citrated tubes and analyzed within 30 min of collection after re-calcification and activation with kaolin. The post-CPB samples were collected in a noncitrated manner, and analyzed after kaolin activation in cups with heparinase to reverse 6 IU of heparin. The TEG parameters recorded were R (reaction time; time of latency from the time that the blood was placed in the analyzer until initial fibrin formation), angle (α; the rapidity of the fibrin build-up and cross linking clot strength), and maximum amplitude (the maximum dynamic properties of platelet and fibrin bonding representing the final clot strength; Fig. 1).

Heparin anticoagulation dosage was determined utilizing Hepcon HMS Plus (Medtronic Inc., Minneapolis, Minnesota, USA). Additional heparin was administered to maintain an activated clotting time (ACT) above 480 s. The CPB machine was primed with 1.5 l Normosol R pH 7.4, 50 mEq NaHCO₃, 12.5 g mannitol, 10 000 units heparin, and 250 ml Voluven (Hospira Inc., Lake Forest, Illinois, USA). The CPB management included a normothermic systemic temperature maintained at 37°C, α-stat pH management, targeted mean perfusion pressure between 50 and 70 mmHg, and pump flow rates of 2.0–2.5 l/min per m². Myocardial protection was achieved with intermittent antegrade and occasionally, retrograde blood cardioplegia. During CPB, pericardial shed blood was salvaged into the cardiotomy suction reservoir and re-infused via the CPB circuit as long as the patient was anticoagulated. Heparin was neutralized with protamine sulfate to a target ACT within 10% of baseline. Shed blood after heparin neutralization was not re-infused to the CPB circuit. All the patients received e-aminocaproic acid (Hospira Inc.), with 10 g as the initial loading dose, followed by 2 g/h by continuous infusion. Post-CPB blood salvage and reinfusion was achieved by utilizing a continuous autotransfusion system (C.A.T.S.; Fresenius Kabi AG, Bad Homburg, Germany). When hemodynamically tolerated by patients, retrograde autologous priming (RAP) and modified ultrafiltration were utilized by the perfusion team.

During this time period, no transfusion protocol was followed. The administration of blood products was at the discretion of the clinical/surgical team who were made aware of the SCT/TEG results that may or may not have influenced their decision to transfuse blood/blood products.

Statistical analysis

The statistical analyses were performed using JMP 10.0 (SAS Institute, Cary, North Carolina, USA). We defined an outcome for this study as 0–8-h CTO. Linear
regression models were used to examine the clinical variables and TEG parameters as predictor variables of outcomes. The predictor variables (categorical and continuous) were placed into a forward stepwise regression model for the continuous outcome. The stepwise function utilized a \( P \) value threshold of 0.25 for entering the model and 0.1 for leaving the model. Stepwise analysis was applied to two different linear models, with model 1 including clinical and laboratory factors and model 2 containing the same variables as model 1 along with the TEG parameters angle and maximum amplitude. Analysis of variance with the adjusted coefficient of determination values (adjusted \( R^2 \)) was used to assess the goodness-of-fit of both predictive models.

The predictive accuracy of the models was examined using two methodologies. First, we used CTO as a dichotomous variable (stratified at the 75th percentile, 480 ml) and receiver operating characteristic (ROC) curves for both models were developed. As the data were paired (i.e. values were obtained from the two models on the same patients), the null hypothesis of the test was that values of ROC curves were identical for both models. We used a paired \( t \)-test to evaluate the average difference between the ROC curves against the null hypothesis that the difference is zero. The second approach was based on the calculation of the bias and precision of the predicted value minus the actual value. (The mean difference is the bias; twice the standard deviation of the differences is the precision). \( P < 0.05 \) was considered significant.

**Results**

From 2007 to 2012, 28 patients were excluded, and 439 patients who underwent cardiac surgery with TEG were retrospectively investigated after meeting the inclusion criteria. The patient demographic/clinical/surgical characteristics are listed in Table 1/Fig. 2. Table 2 provides patient laboratory and TEG values. All of the parameters differed between these time points \( (P < 0.05) \), except for the TEG \( R \) values. Figures 3–6 demonstrate 8-h CTO postoperatively, total intraoperative CSB utilization, and blood/blood component utilization based on type of cardiac surgery performed. Refer to Table 3 for abbreviations for clinical terminology used, and type of cardiac surgery performed.

All 439 patients studied had preoperative and first ICU hematocrit level, preoperative platelet count, and SCT results. Thirty patients did not have first post-CPB hematocrit level results, and 39 patients were lacking first post-CPB platelet count, INR, and PTT results. All patients had preoperative TEG parameters recorded; 38 patients were lacking warming/postprotamine TEG results.

Of the variables, model 1 showed that age, gender, preoperative clopidogrel use for 5 days or less, the total intraoperative CSB given during surgery, and the

**Table 1 Patient demographic/outcome characteristics**

| Characteristics                        | Median (IQR) or n (%) |
|----------------------------------------|-----------------------|
| (A) Patient demographics               |                       |
| Age (years)                            | 68 (59–75)            |
| Sex                                     |                       |
| Male                                    | 67%                   |
| Female                                  | 33%                   |
| BSA (m²)                                | 2.01 (1.84–2.15)      |
| Diabetic                                | 30%                   |
| Preoperative ejection fraction (EF) %   | 80% (50–65%)          |
| New York Heart Association (NYHA)       | 2.9, 9.3, 37.1, 49.5% |
| (B) Patient percentage preoperative     |                       |
| medication utilization                  |                       |
| ASA                                     | 78%                   |
| Angiotensin-converting enzyme (ACE)     | 43%                   |
| inhibitors                              |                       |
| \( \beta \)-Blockers                    | 81%                   |
| Amiodarone                              | 16%                   |
| Statins                                 | 82%                   |
| Clopidogrel                             | 10%                   |
| Clopidogrel (less than 5 days)          | 6%                    |
| (C) Intraoperative data                 |                       |
| Cardiac pulmonary bypass time (min)     | 116.4 (88.3–157.2)    |
| Aortic cross-clamp time (min)           | 88.2 (65.3–126.3)     |
| Intraoperative intraaortic balloon      |                       |
| utilization                             | 4.40%                 |
| (D) Short-term/long-term patient        |                       |
| outcome data                            |                       |
| Time to tracheal extubation (h)         | 5.1 (3.5–9.2)         |
| Total hospital length of stay (LOS) in days | 7.6 (6–9)            |
| % Patients alive 30 days postsurgery    | 97.5%                 |

Data are reported as median and 25–75th interquartile range (IQR) or percentage of patients meeting condition. ASA, acetyl salicylic acid; BSA, body surface area.

**Fig. 2**

Patient percentage distribution based on the type of cardiac surgery performed. AVR, aortic valve replacement; CABG, coronary artery bypass graft; CEA, carotid endarterectomy; MVR, mitral valve repair/replacement.
postoperative first ICU hematocrit level contributed significantly to the predictability of the clinical bleeding model (Table 4). The higher CTO at 8 h was associated with advanced age, men, patients who received preoperative clopidogrel for 5 days or less, and patients who were transfused with larger amounts of intraoperative CSB. Lower patient postoperative first ICU hematocrit level was associated with increased CTO at 8 h.

Table 2 Patient coagulation/thromboelastography profile

(A) Preoperative vs. first post-CPB

| Clinical variable | Preoperative | First post-CPB | SE; t-ratio; n; P value* |
|-------------------|--------------|---------------|--------------------------|
| Hematocrit (%)   | 39.5         | 26.3          | 0.35288; -37.8934; 408; <0.0001 |
| Platelet count (10^9) | 235         | 128           | 4.15237; -25.831; 400; <0.0001 |
| INR               | 1.1          | 1.9           | 0.03641; 23.43046; 400; <0.0001 |
| aPTT (s)          | 28.1         | 33.6          | 0.84633; 6.114938; 400; <0.0001 |

(B) Preoperative vs. postoperative first ICU (hematocrit only)

| Clinical variable | Preoperative | First ICU | SE; t-ratio; n; P value* |
|-------------------|--------------|-----------|--------------------------|
| Hematocrit (%)   | 39.5         | 32.2      | 0.39457; 18.6072; 439; <0.0001 |

(C) Baseline TEG vs. warming/postprotamine

| TEG                          | Baseline | Warming/postprotamine | SE; t-ratio; n; P value* |
|------------------------------|----------|-----------------------|--------------------------|
| R (min)                      | 7.2      | 7.1                   | 0.1188; -0.57193; 401; 0.5877 |
| K (min)                      | 1.8      | 2.0                   | 0.03476; 7.805933; 401; <0.0001 |
| Angle (°)                    | 65.5     | 64.3                  | 0.41075; -2.91603; 401; 0.0037 |
| Maximum amplitude (mm)       | 64.4     | 58.5                  | 0.35416; -16.7863; 401; <0.0001 |

aPTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; TEG, thromboelastography.  * Based on unpaired t test.

Fig. 3

Eight-hour chest tube output (CTO) in milliliters based on the type of cardiac surgery performed, where A = median CTO (ml), B = average CTO (ml), C = CTO (ml) [25–75th interquartile range (IQR)], x = standard deviation (SD), and n = number of patients. AVR, aortic valve replacement; CABG, coronary artery bypass graft; CEA, carotid endarterectomy; MVR, mitral valve repair/replacement.
Because of strong colinearity with other model variables, post-CPB prothrombin time and PTT were not included.

Based on the sorted estimate analysis, in which the effects are sorted based on the absolute value of the $t$-ratio, the most important factor that influenced postoperative blood loss at 8 h for both models was the total amount of intraoperative CSB that was transfused. There was a significant difference between the male and female patients with regard to intraoperative transfused CSB. Male patients received, on average 774.2/±388.7 ml ($n = 296$), whereas female patients received 667.4/±441.0 ml ($n = 142$; $P = 0.01$). However, if one would consider BSA as a covariate, this difference disappears ($P = 0.31$).

Collectively, the hematological and clinical parameters significantly explained 23% of the variability observed in CTO. When the TEG angle and maximum amplitude parameters were added to model 1 as the predictor factors (model 2), no added significant contribution to the predictability of the model was observed (Table 4). This finding was further assessed and confirmed by ROC analysis (Fig. 7); model 1 was as predictive with respect to CTO as model 2 ($P = 0.37$).

Bias and precision values for model 1 were (259.4; 846.3) and model 2 were (1125.5; 849.7). Model 1 has less bias than model 2. However, both models were equally precise (Fig. 8).

Model 1 can be presented as follows: blood loss (8h) = 917.04 + 4.298 [age (years)] – 86.70 [sex (+1 for women; –1 for men)] – 193.14 [BSA] – 0.239 [first post-CPB fibrinogen level] – 12.75 [ICU hematocrit level] – 99.93 [received clopidogrel ≤5 days preoperatively (+1 for no; –1 for yes)] + 0.238 [total intraoperative CSB given].

Model 2 can be presented as follows: blood loss (8h) = 545.26 + 5.03 [age (years)] – 81.16 [sex (+1 for women; –1 for men)] – 205.86 [BSA] – 0.218 [first post-CPB fibrinogen level] – 12.64 [ICU hematocrit level] – 99.93 [received clopidogrel ≤5 days preoperatively (+1 for no; –1 for yes)] + 0.238 [total intraoperative CSB given].
level] – 104.13 [received clopidogrel ≤5 days preoperatively (+1 for no; −1 for yes)] +0.233 [total intraoperative CSB given] +6.029 [maximum amplitude TEG (mm)].

**Discussion**

Three million patients receive 11 million RBC units annually in the United States, of which 20% are transfused during cardiac surgery [13]. Despite a 5%/year increase in the demand for blood, fewer people are donating blood (of the 60% eligible donors, only 5% donate). The majority of patients have minimal postoperative blood loss, but a subset has life-threatening postoperative bleeding requiring multiple transfusions. Blood/blood product transfusions are associated with increased patient morbidity and mortality [14–16]. Patients receiving blood transfusions were twice as likely to die, compared with those who received no blood transfusions [17]. Per unit RBC transfused, the incidence of infection increased by 29% [16].

In contrast to SCT, TEG measures the viscoelastic properties of blood clot formation and fibrinolysis, thus
better defining the influence of the qualitative defects on coagulation factors and platelets [7]. In cardiac surgery, implementation of POC coagulation testing resulted in a 50% reduction of blood/blood product transfusions [18]. As the blood supply in USA declines and as the donor and patient population age, better prediction models for postoperative cardiac surgery bleeding are vitally important for blood banks to prepare, stock, and deliver blood [19]. The use of TEG to predict bleeding following cardiac surgery is controversial. Ereth et al. [20] and Welsby et al. [11] demonstrated that TEG maximum amplitude was more predictive for postoperative bleeding than SCT. Shore-Lesserson et al. [9] demonstrated that although TEG POC coagulation monitoring reduced total and postoperative transfusions, postoperative CTO up to 24 h was not statistically different between the TEG-guided
transfusion group and the control transfusion group. Lee et al. [12] recently demonstrated that the addition of rotational thromboelastometry to their clinical bleeding model did not improve the bleeding predictability.

The aim of our study was to investigate the incremental value of the TEG parameters when added to our clinical bleeding model for cardiac surgery patients. The variables that were associated with postoperative bleeding were advanced age, male gender, preoperative clopidogrel use for 5 days or less, increased CSB during surgery, and lower postoperative first ICU hematocrit levels. Advanced age has been a validated transfusion risk factor in two recent scoring systems [21,22]. Platelet receptor inhibitor use of clopidogrel 5 days or less before surgery is also an established risk factor for bleeding [23].

We demonstrated that intraoperative CSB use is associated with increased postoperative bleeding. Studies have demonstrated that CSB may reduce exposure to allogenic RBC transfusions [24]. While salvaging the RBCs, CSB removes platelets and coagulation factors that are concentrated in the cell washing supernatant, which can promote bleeding postoperatively. Our results validate recent studies by Rubens et al. [25] and Djaiani et al. [26], which demonstrated an association of CSB use with increased postoperative bleeding and increased use of FFP and platelet transfusions.

The study limitations included the following. First, we used a single center, retrospective observational study design, and thus, the results may not be generalized because of a homogenous sample population. Second, patients who were transfused with blood products intraoperatively and postoperatively were included in our study, which could have influenced the amount of postoperative CTO output. Third, only two intraoperative TEG samples were drawn on a consistent basis (baseline and warming/postprotamine), although CTO was recorded for 8 h after the completion of surgery. TEG-derived data could have contributed significantly to the model if the TEG sampling were more frequent, especially after chest closure (before leaving the operating room) or early in the postoperative period, because dynamic thrombin generation, platelet response, clot formation, and lysis may change dramatically over time with marked interpatient and intrapatient variability. Fourth, TEG platelet mapping was not available to us to evaluate platelet receptor inhibition in the patients on platelet inhibitors, which could have resulted in prophylactic platelet transfusions and thus influenced postoperative CTO. Fifth, in contrast to SCT, TEG also has its limitations, which include meticulous and frequent instrument calibration, validation, and quality control issues. Motion artifacts can render TEG readings difficult to interpret. Von Willebrand factor deficiency and hypothermia-induced coagulopathy can also go undetected [7]. Although TEG maximum amplitude is one of the most widely used parameters, it is an imposed 0–100 scale based upon a complex formula of conversion of clot strength force in dynes/cm² to the 0–100 scale, and is not linear.

Table 3 Abbreviations for clinical terminology and type of cardiac surgery performed

| (A) Clinical terminology | TEG, thromboelastography |
|--------------------------|--------------------------|
| SCT, standard coagulation test | CTO, chest tube output |
| CSB, cell saver blood |

| (B) Type of cardiac surgery performed | CABG, coronary artery bypass graft |
|--------------------------------------|--------------------------|
| AVR, aortic valve replacement |
| MVR, mitral valve repair/replacement |
| AVR plus, AVR + re-sternotomy, or AVR + proximal aorta repair/replacement |
| CEA, carotid endarterectomy |
| CABG + AVR, coronary artery bypass graft + aortic valve replacement |
| CABG + MVR, coronary artery bypass graft + mitral valve repair/replacement |

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Hundred is infinite clot strength (never happens) and 0 is water (no clotting and happens with heparin). Between 50 and 60 mm, the changes are essentially logarithmic, but above that range they become exponential, and similarly they fall exponentially below 40–50.

The statistical models predicting the cumulative blood loss at 8 h postoperatively are limited by the input variables shown in Table 4. These input variables were chosen by the investigators because of variables’ valuable contributions during the clinical assessment of patients. Thus, the statistical models presented herein reflect this dependency on the accuracy of the clinical decision made in their selection. The use of ROC suffers from limitations (it ignores the predicted probability values and the goodness-of-fit of models [27], summates test performance over ROC spatial regions in which one rarely operates [27], and weights omission and commission errors equally, and the rate of the well predicted absences and the AUC scores depend on the total extent to which the models are carried out) [27]. Despite limitations, ROC analysis has been widely accepted and utilized in clinical investigations, and our decision to use it as a tool in this investigation was to facilitate comparison with historical and future investigations in this field.

The prediction of postoperative bleeding following adult cardiac surgery is difficult. Bleeding involves the interplay of various patient factors, surgical techniques, perfusion strategies, and intensive care management issues that should be studied and better defined in multicenter, blinded, prospective, randomized studies. The most important patient factors that cardiac surgery clinical bleeding models, including ours, do not take into account are genetic factors. Various genetic polymorphisms of inflammatory mediators and adhesion molecules (98T E-selectin) could play key roles in bleeding after cardiac surgery [28]. Adding genetic factors to clinical factors doubled the ability to predict bleeding after cardiac surgery [29]. Currently, such genetic testing is not commercially available for patients.

**Conclusion**
Consistent with other trials [12], our clinical bleeding model variables accounted for 23% of the variance in postoperative bleeding (expressed as CTO output at 8 h),
but more than 70% remains unexplained. In contrast to other studies, we demonstrated the strong association between CSB use during surgery and CTO. Although TEG-guided transfusion algorithms could help to reduce significantly the transfusion of blood/blood products [8–10], we were unable to demonstrate that the addition of TEG parameters to our clinical bleeding model improved the predictability of postoperative bleeding.

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Conflicts of interest

There are no conflicts of interest.

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