

**Original Article**

## ***Do Heparinase Thrombelastographs Predict Postoperative Bleeding?***

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### **ABSTRACT**

Postoperative hemorrhage is a major cause of morbidity and mortality in patients who undergo cardiopulmonary bypass (CPB). The thrombelastograph (TEG) is a viscoelastic whole blood test that measures clot dynamics from clot formation through clot lysis. Previous studies have shown that post-bypass TEGs are accurate predictors of postoperative bleeding.

TEGs from heparinized blood reversed with heparinase may be employed during CPB to evaluate coagulation. CPB heparinase TEGs may allow for earlier recognition of patients who may bleed after bypass. Earlier TEG analysis would allow targeting of specific therapies to begin before the patient bleeds excessively. Fifty-four heparinase TEGs during warming and fifty-four native TEGs post-protamine administration were collected. Parameters evaluated were R, K, alpha angle, MA, MA<sub>60</sub>, coagulation index, activated clotting time, hematocrit, prothrombin time, partial thromboplastin time, thrombin time, fibrinogen concentration, platelet count, blood loss during and after CPB, and blood and blood product administration. Coagulation indexes for CPB heparinase TEGs that were less than -2 or heparinase TEGs that were fibrinolytic were 87% accurate in predicting patients with excessive intraoperative blood loss, but were not predictive of blood product administration. The sensitivity was 12.5% and the specificity was 100% in predicting excessive intraoperative bleeding. Post-protamine coagulation index inversely correlated with intraoperative red blood cell administration ( $r=-0.403$ ,  $p<0.05$ ), but was not predictive. Patients with fibrinolytic TEGs required blood products to compensate for expected blood loss associated with the fibrinolytic state. Simultaneous routine coagulation tests did not correlate significantly with blood loss or blood product administration, nor were they predictive. The findings of this study suggest that the presence of fibrinolysis in either a heparinase TEG on bypass or a post-protamine TEG is the most important predictor of blood and blood product administration. But, since only 20% of the patients in the study exhibited fibrinolytic TEGs, a study that included a much larger sample of patients would need to be done to confirm this finding.

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## INTRODUCTION

Postoperative hemorrhage occurs in 5-18% of all patients who undergo cardiopulmonary bypass (CPB) surgery (1,2). Of these patients, about 3% require reoperation (3). There are many causes of postoperative hemorrhage, some of which include: thrombocytopenia, decreased coagulation factor levels, accelerated fibrinolysis, inadequate heparin reversal, excessive protamine, inadequate surgical hemostasis, defective clot retraction, abnormal platelet function, and increased plasminogen activator. Accurate and immediate determination of abnormal coagulation status intraoperatively is necessary for the diagnosis and treatment of a patient with possible postoperative hemorrhage (3).

The routine coagulation tests (RCT) used to assess coagulation before and after CPB include: prothrombin time (PT) which measures the extrinsic pathway, partial thromboplastin time (PTT) which measures the intrinsic pathway, platelet count which quantifies the amount of platelets but does not express platelet function, fibrinogen concentration which quantifies the amount of fibrinogen, and the activated clotting time (ACT). Each of these tests only looks at isolated portions of the overall coagulation cascade. None of these tests evaluate platelet function. This is relevant in that 56% of patient who bleed do so because of platelet dysfunction (3).

The thrombelastograph or TEG, as described by Hartert in 1948, is a device that measures clot formation *in vitro* and aids in the analysis of whole blood coagulation (4). The TEG provides a graphic representation of whole blood clot dynamics from clot formation through clot lysis. Five qualitative variables from the TEG tracing are used to analyze clot formation. The reaction time (R) represents the initiation of clot formation. The K value represents the speed of fibrin buildup and crosslinking. The alpha angle represents the speed of clot formation and fibrin crosslinking. The maximum amplitude (MA) represents clot strength. The maximum amplitude at 60 minutes ( $MA_{60}$ ) represents the rate of clot lysis. A 10% decrease in the  $MA_{60}$  is indicative of fibrinolysis (5). A TEG is fibrinolytic if the clot forms normally and is immediately broken down. The TEG has been shown to be a useful monitor of hemostasis management during liver transplantation and cardiac surgery (6,7).

Systemic heparinization that extends the ACT 5 to 6 times normal is necessary for bypass to prevent clot formation and thrombosis (8). This amount of heparin precludes TEG measurements until after heparin reversal with protamine. The average time for the post-protamine TEG tracing to run, in order to determine whether or not the patient is coagulopathic, is 60-90 minutes. The average time for thawing and delivery of blood products into the operating room, is about 40 minutes. By the time that an abnormal TEG was seen and blood products ordered, the patient would have been bleeding for 1/2 to 2 hours before treatment can be made available. Earlier recognition of patient coagulation status allows for targeting of specific therapies to

begin including drugs, blood and blood products such as fresh frozen plasma, platelets, and cryoprecipitate.

Heparin distorts clot formation (6). Heparinase is an enzyme isolated from *Flavobacterium heparinum* that neutralizes heparin *in vitro* (6). Heparinase allows for an on bypass determination of coagulation using the TEG. We hypothesize that heparinase TEGs run during bypass should be predictive of post-bypass post-protamine TEGs. The purpose of this study is to ascertain whether heparinase TEG parameters on bypass and post-protamine TEG parameters equally predict excessive post-operative bleeding and blood product administration.

## MATERIALS AND METHODS

Fifty-four adult patients undergoing first time coronary artery bypass grafting (CABG), valve repair or replacement, or combination CABG and valve procedure were studied prospectively. The comparison of coagulation parameters was done on a thrombelastograph<sup>a</sup>. TEGs were compared for their ability to predict postoperative bleeding and blood product administration. The coagulation index is a linear combination of the measured variables from the TEG tracing that provides information about patient whole blood coagulation status. The equation for the coagulation index (CI) is:

$$CI = -(0.1227 \cdot R) + (0.0092 \cdot K) + (0.1655 \cdot MA) - (0.0241 \cdot \alpha \text{ angle}) - 5.022$$

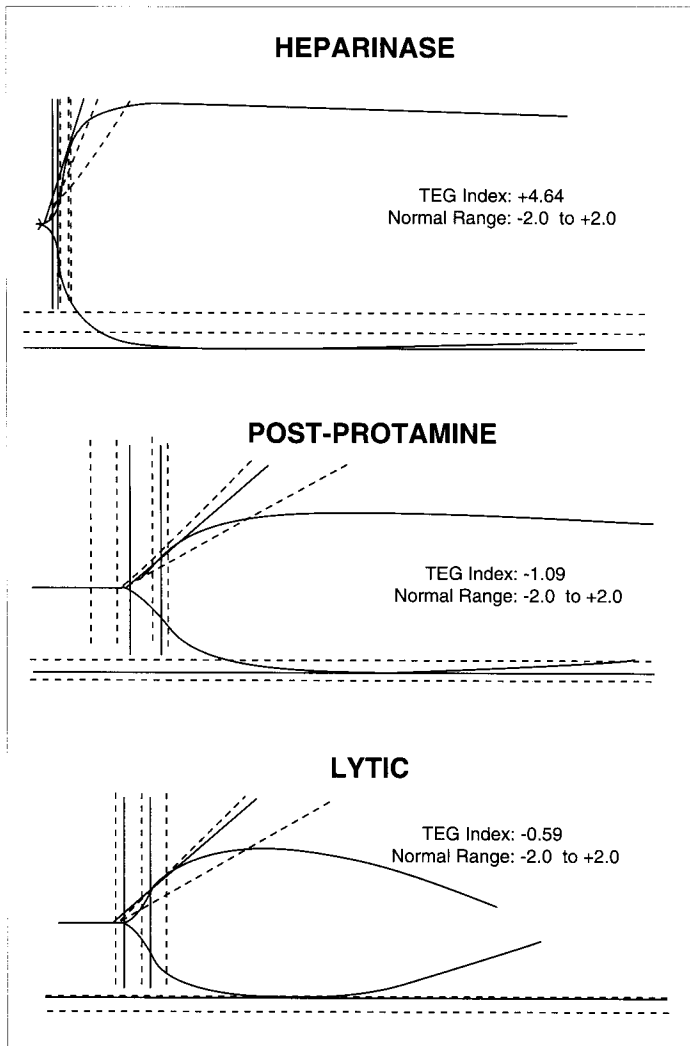
The normal values of the coagulation index are between -2 and +2. Values less than -2 indicate a hypocoagulable state and values greater than +2 indicate a hypercoagulable state (Haemoscope TEG Operations Manual; 1991). The CIs were calculated for each TEG and were used as a measure of coagulability. Since the equation for CI does not include the  $MA_{60}$ , and TEGs that are fibrinolytic are not normal, a fibrinolytic TEG may have a normal CI. Therefore, we defined an abnormal TEG as one that had a  $CI < -2$  or a TEG that exhibited fibrinolysis. A TEG was considered to be fibrinolytic if the clot formed normally and was immediately broken down (Figure 1).

Four TEGs were performed on each patient: one native TEG was run pre-heparinization, one heparinase TEG was run on bypass five minutes after rewarming had begun, one native TEG was run 20 minutes after protamine administration, and one native TEG was run as the patient was leaving the operating room. Where there was a question of heparin contamination, indicated by a prolonged R time over 40 minutes, the TEG was excluded from the analysis.

In addition to the TEGs, the following information was collected preoperatively on each patient: height, weight, age, gender, and routine coagulation test results. Intraoperative infor-

a Hellige Thrombelastograph, Haemoscope Corporation, Morton Grove, IL 60053

**Figure 1: Examples of thrombelastograph tracings. From top: Heparinase reversed TEG obtained on bypass; TEG obtained after protamine administration; Fibrinolytic TEG. TEG index refers to the coagulation index; see text for discussion.**



mation included: surgeon, type of operation, volume of blood loss, and blood and blood product administration. At the termination of CPB, the protamine dose was calculated using a heparin dose response curve and was administered to neutralize the heparin. Fifteen minutes after protamine administration, an ACT and a heparin concentration were performed in order to determine the adequacy of heparin reversal. Heparin concentrations of 0.0 u/ml and ACTs within 10% of baseline were required before the post-protamine TEG was performed. If the ACT was extended or the heparin concentration was > 0.0 u/ml, the surgeon was informed, the dose of additional protamine calculated and administered, and the post-protamine ACT and TEG repeated. The final TEG was performed immediately before the patient was transported to the intensive care unit. Blood loss in

the operating room was determined by weighing the used laps and sponges and subtracting their dry weight. Volume in the waste canisters was also recorded. The scrub nurses estimated the volume of saline used for irrigation during the case and this volume was subtracted from the total volume in the waste canister. For the last 25 patients, a hematocrit was done on the volume in the waste canister and the following ratio was used to more accurately estimate the amount of blood volume that was collected in the suction canister:

$$\text{(Patient HCT prior to CPB termination [\%])} \times \text{(X)} = \text{(Canister volume HCT [\%])} \times \text{(Canister volume [ml])}$$

Excessive blood loss in the operating room was defined as blood loss greater than 19.2 ml/kg, which was one standard deviation above the mean estimated intraoperative blood loss for the last 25 patients. Blood loss outside the operating room was determined through chest tube drainage 6, 12, and 24 hours postoperatively. The threshold for red blood cell transfusion was a HCT < 20% (25% for one surgeon).

Accuracy was calculated using the formula:

$$\frac{\text{[(number of correctly predicted bleeders + number of correctly predicted non-bleeders)]}}{\text{(total number of patients)}}$$

Correlation and analysis of variance were performed to determine the level of significance between all measured parameters. The Bonferonni procedure was used to determine differences when the ANOVA rejected the null hypothesis. A p-value less than 0.05 was considered significant. The null hypothesis is that there is no difference in the accuracy of on-bypass heparinase TEGs and post-protamine TEGs to predict postoperative bleeding and blood product administration.

## RESULTS

Heparinase TEGs that were fibrinolytic or that had a coagulation index less than -2 were found to be 87% accurate in predicting intraoperative bleeding. (Figure 2) The sensitivity was 12.5% and the specificity was 100%. Only one of eight bleeding patients expressed an abnormal heparinase TEG, and that TEG was fibrinolytic. All of the 47 non-bleeders had normal heparinase TEG CIs and none were fibrinolytic.

The post-protamine CI significantly correlated inversely with intraoperative red blood cell administration ( $r = -0.403$ ,  $p < 0.05$ ); however, this correlation was not clinically significant since abnormal post-protamine TEGs were only 70% accurate in predicting intraoperative bleeding and 56% accurate in predicting 6 hour chest tube output. The transport TEG was 72%

accurate in predicting 6 hour chest tube output.

Eleven patients exhibited fibrinolytic TEGs: six were on bypass heparinase TEGs and five were post-protamine TEGs. Of those eleven patients, ten patients received blood or blood products intraoperatively (91%). All five of the patients with fibrinolytic TEGs post-protamine administration received blood and blood products in the operating room (100%). Six of the seven patients with fibrinolytic heparinase TEGs received blood

or blood products in the operating room (86%).

The CIs at each of the four time periods were compared for each patient. The baseline and heparinase CIs were significantly more coagulable than both the post-protamine and transport CIs ( $p < 0.05$ ). (Figure 3) None of the routine coagulation tests correlated significantly with bleeding in the operating room or blood and blood product administration.

Eight of the patients in the study received an antifibrinolytic drug as part of an ongoing randomized trial (4 aminocaproic acid, 4 tranexamic acid). None of these patient exhibited fibrinolytic TEGs at any time period. Two of these patients had excessive blood loss in the operating room (25%). Only one (12.5%) of these patients received blood products in the operating room. Four (50%) received blood either on bypass or immediately post-CPB because their HCT dropped below the threshold. Two of these were due to excessive hemodilution (body weight 50 and 54kg). Removal of these patients from the accuracy of the heparinase TEG in predicting excessive intraoperative bleeding calculation increased the accuracy to 90% (47/52). These two patients had normal heparinase TEGs but bled excessively.

**Figure 2: Cross-tabulation of excessive postoperative bleeding and normality of the heparinase TEG. CI = coagulation index**

| Heparinase TEG abnormal? | Excessive intraoperative bleeding? |                |    |
|--------------------------|------------------------------------|----------------|----|
|                          | YES >19.2 ml/kg                    | NO <19.2 ml/kg |    |
| YES<br>CI < -2 or lytic  | 1                                  | 0              | 1  |
| NO<br>CI > -2            | 7                                  | 46             | 53 |
|                          | 8                                  | 46             | 54 |

$$\text{Accuracy} = \frac{1 + 46}{54} = 0.87$$

$$\text{Sensitivity} = \frac{1}{8} = 0.125$$

$$\text{Specificity} = \frac{46}{46} = 1.00$$

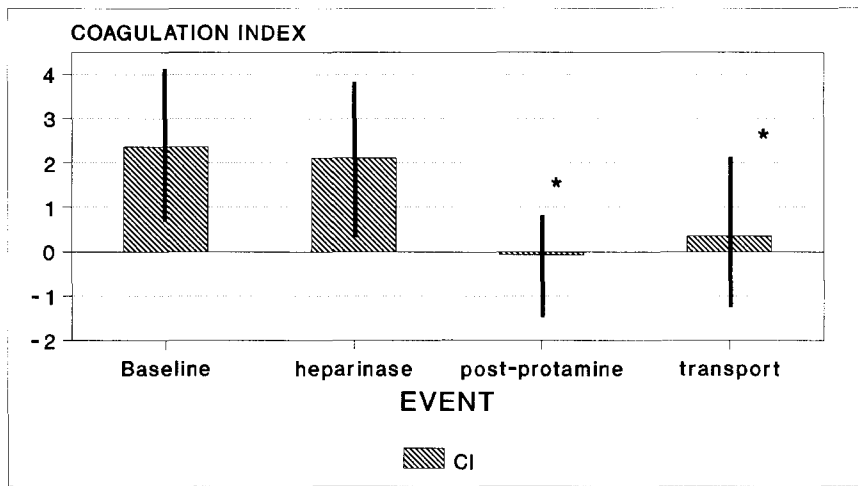
## DISCUSSION

CPB may cause hemostatic abnormalities by reductions in coagulation factors, inadequate heparin reversal, excessive protamine administration, increased fibrinolytic activity, thrombocytopenia, and defective platelet function. (3) The assessment of platelet function is necessary in order to determine which patients will bleed in the operating room. Knowledge of the patient's coagulation status will then allow the OR staff to adequately treat the

bleeding. Methods for determining patients at risk for bleeding before CPB such as routine coagulation tests and TEGs have been compared for accuracy. Dorman, et al. found that baseline TEGs show a poor correlation to the routine coagulation tests as well as to operative blood loss. (9)

Post-bypass TEGs that are hypocoagulable may indicate that a patient will bleed. Tuman, et al. compared the TEG to the RCTs before and after CPB to assess their accuracy in predicting clinical hemostasis. (3) Post-protamine, post-bypass TEGs were found to be 88% accurate in predicting bleeding and RCTs were only 33% accurate in predicting bleeding. The RCTs provide less information about the quality of the clot and the way it forms, and therefore, would not be able to identify causes of clot dys-

**Figure 3: Bar graph of the average coagulation index for the TEGs obtained baseline, on bypass (with heparinase), post-protamine, and prior to transport to the intensive care unit. The post-protamine and transport coagulation indices are significantly different from the baseline and heparinase coagulation indices. CI = coagulation index.**



\* =  $p < 0.05$  from baseline and heparinase

function. (3) Patients who bled excessively had abnormal preoperative parameters reflecting platelet-fibrin interaction (alpha angle, MA, MA<sub>60</sub>) that was significantly different postoperatively. Martin, et al. found post-protamine TEGs to be 100% accurate in predicting postoperative bleeding in pediatric patients. (10) Our study differed in that the CIs were evaluated rather than each individual TEG parameter, and we found that post-protamine TEGs correctly predicted bleeding 70% of the time.

Earlier recognition of poor patient coagulation status would allow for the administration of blood and blood products to begin before the patient bleeds excessively. Adding heparinase to a blood sample on bypass would allow for a TEG tracing. The heparinase TEGs that are hypocoagulable may indicate which patients will bleed after CPB, but our data indicated that the CIs of the hypocoagulable heparinase TEGs did not accurately predict or correlate with excessive bleeding. Assessment of blood loss is important in determining which patients bleed intraoperatively. Without accurate blood loss calculations, the predictive ability of the TEGs to determine bleeding is diminished. In this study, blood loss measurement was probably overestimated because the volume in the suction canisters included crystalloid volume that was not consistently accounted for. This could contribute to the reason that many patients who were not in the excessive blood loss group received blood and blood products intraoperatively. This may also help explain the low sensitivity of the heparinase TEGs. To correct for this problem, the hematocrit of the waste volume was run and the volume of actual blood loss calculated using a ratio formula. Excessive blood loss index only decreased from 19.2 ml/kg to 18.5 ml/kg, indicating that either the first estimate of blood loss may not have been excessive or that this method of estimating blood loss is not accurate either. Since excessive bleeding occurs in only a small number of patients (nine patients (17%) in this study), a study that included a larger sample size may show improved correlations and predictive parameters.

The baseline CI and the on-bypass heparinase CI were not significantly different from each other. The post-protamine CI and transport TEG CI were also not statistically different. We predicted that heparinase TEGs would be qualitatively similar to post-protamine TEGs; however, the heparinase TEGs were generally hypercoagulable compared to the post-protamine TEGs. Based on our findings, the heparinase and post-protamine TEGs are not the same, which corresponds with their differences in predictive abilities.

The accuracy of the heparinase fibrinolytic TEGs in predicting blood product administration is 86%. Six of seven patients with heparinase fibrinolytic TEGs received blood or blood products intraoperatively. Fibrinolytic CPB heparinase TEGs accurately predict intraoperative blood product administration, but they do not predict intraoperative bleeding. Only one of the seven patients had excessive intraoperative bleeding (14%). This may have been because these patients looked hypocoagulable early enough that the surgeons ordered blood products to be ad-

ministered as soon as bypass was discontinued, but this qualitative variable was not studied. Earlier administration of these products would have decreased the amount of bleeding that occurred in the operating room.

The findings of this study seem to suggest that the presence of fibrinolysis in either a heparinase TEG on bypass or a post-protamine TEG is the most important predictor of blood and blood product administration. However, since only 20% of the patients in the study exhibited fibrinolytic TEGs, a study that included a much larger sample of patients would need to be done to confirm this finding.

## CONCLUSIONS

- 1 The coagulation indexes of heparinase TEGs run on bypass during rewarming are 88% accurate in predicting excessive intraoperative bleeding.
- 2 Post-protamine TEG CIs statistically significantly correlate inversely with red blood cell administration, but they are not predictive of red blood cell administration.
- 3 Fibrinolytic post-protamine TEGs are 100% predictive of red blood cell administration in the operating room.
- 4 CPB warming heparinase TEGs that were fibrinolytic are 86% accurate in predicting blood product administration intraoperatively.
- 5 Routine coagulation tests did not significantly correlate with blood product administration or blood loss intraoperatively, nor were they predictive.

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