

## Original Article

# *Evaluation of the Thrombelastograph Targeted Coagulation Assessment*

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### ABSTRACT

Extracorporeal circulation predisposes patients to hemorrhagic risk which may increase both homologous transfusion requirements and the need for pharmacological intervention. The aim of this study was to evaluate the efficacy of a new diagnostic coagulation assay utilizing the thrombelastograph (TEG).

Following Institutional Review Board approval, blood was drawn from healthy, non-medicated volunteers and four *in vitro* coagulopathic conditions were created, which included: hyperfibrinolysis (100% lysis), hypofibrinogenemia (<50 mg/dl), and both qualitative (1000 ug/ml nitroglycerin) and quantitative (<50 K/mm<sup>3</sup>) platelet abnormalities. Each of these four blood samples was then divided among four vials that contained known quantities of either: aminocaproic acid, fresh frozen plasma (FFP), platelet concentrate, or heparinase, and TEG profiles were completed.

Twenty-one samples were evaluated and the following results were obtained. Hyperfibrinolysis- 100% correction of fibrinolytic potential in the aminocaproic acid vial, but none in the other vials. Qualitative platelet dysfunction- significantly improved time to coagulation in the platelet vial but not in the FFP, heparinase or aminocaproic acid vials. Quantitative platelet dysfunction- no significant difference observed between any vials. Hypofibrinogenemia- significant improvement in the TEG index in the FFP vial ( $-2.7 \pm 0.5$ ) when compared to the aminocaproic acid ( $-8.6 \pm 2.5$ ,  $p < .001$ ), platelet ( $-6.5 \pm 0.5$ ,  $p < .01$ ) and heparinase ( $-8.8 \pm 2.5$ ,  $p < .001$ ) vials.

We conclude that this coagulation assessment assay may help in identifying the specific source of bleeding during surgeries where hyperfibrinolysis, hypofibrinogenemia, or qualitative platelet dysfunctions are present.

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## INTRODUCTION

During cardiopulmonary bypass (CPB) blood is exposed to various synthetic surfaces in the extracorporeal circuit. As blood comes in contact with the foreign surfaces, many changes take place which include alterations to formed elements (red blood cells, white blood cells and platelets) and non-formed elements (proteins) of blood (1,2). Many of these alterations have been shown to increase hemorrhagic risk (3-5). Excessive bleeding during open heart surgery can be life threatening, and treatment must be directed appropriately and rapidly implemented. If the source is determined to be anatomical, then re-operation or re-exploration may be necessary. If the source cannot be identified, blood products such as fresh frozen plasma (FFP), packed red blood cells, platelets and/or cryoprecipitate may be given. When blood products are given, the risk of disease transmission and transfusion reactions increases (4,6,7), but perhaps more significant is the increase in morbidity and length of hospital stay that is associated with the use of transfused blood products (6,7).

Platelets are the primary blood components affected by CPB (8-10), with both the quantity and the quality being affected. Circulating platelet numbers decrease 40-60% due to the hemodilution and endogenous sequestration that occur during CPB. Platelet dysfunction is caused primarily by alterations in the platelet membranes (7,9), which include changes in the surface receptors glycoprotein IIb/IIIa and glycoprotein Ib. Hypothermia during CPB also causes impairment of thromboxane A2 synthesis (1,9). Platelet aggregation has also been shown to be induced by the shear stresses created at various places in the extracorporeal circuit, such as cannulae and sucker tips (2). Finally it has been shown that CPB increases platelet aggregation by increasing platelet activators such as platelet factor 4 (PF4), beta-thromboglobulin and thromboxane B2 (9).

Another effect of CPB on patients' blood is an increased fibrinolytic potential, via activation of various substances including kallikrein and Factor XII (2). An increase in kallikrein activity directly induces activation of plasminogen and Factor XII (2). The fibrinolytic pathway is also activated by tissue-type plasminogen activator (t-PA), and its release has been shown to be accelerated during CPB (11-13). This extensive activation of fibrinolysis can impair or even prevent the formation of clot in the patient resulting in increased bleeding and possible transfusion of blood products. Epsilon aminocaproic acid, a lysine analogue, has been shown to inhibit plasminogen activators which leads to decreased fibrinolysis (3,14). Tranexamic acid is another synthetic antifibrinolytic that is six to ten times more potent than aminocaproic acid.

Cardiopulmonary bypass can also have an adverse effect by decreasing a patient's fibrinogen level. Hemodilution and the consumption of fibrinogen by surgically damaged tissue are the main causes of the decrease in postoperative fibrinogen levels.

The intent of this study was to examine a coagulation assay which could identify specific defects in coagulation leading to hemorrhage and thrombosis. This assay has the potential to provide a method of determining the underlying cause of excessive bleeding and may help the clinician to make the proper decision when selecting blood products for hemotherapy, which could possibly lead to a decrease in the number of blood products transfused to patients.

## MATERIALS AND METHODS

With the approval of the Institutional Review Board, ten ml samples of blood were drawn from healthy volunteers greater than nineteen years old who had not been taking any medication for seven days prior to the draws. These samples were used as controls and to create various coagulopathies which included: hyperfibrinolysis, hypofibrinogenemia, quantitative, and qualitative platelet abnormalities. The samples were collected in buffered 0.105 M sodium citrate tubes in a ratio of 9 parts blood to 1 part sodium citrate. All samples were recalcified with 0.2M CaCl<sub>2</sub> prior to performing the coagulation assay<sup>a</sup> and thrombelastograph (TEG)<sup>a</sup>. A TEG was used to assess the various clotting abnormalities that were created.

**Coagulation Assay.** The Targeted Coagulation Assessment (TCA)<sup>a</sup>, a commercially available coagulation assay kit, contains quantities of blood constituents or drugs to mimic clinical interventions. Each kit included one vial of each of the following: platelets (100,000 per vial), FFP (0.1 ml of FFP), aminocaproic acid (30 ul of 12 mg/ml) and heparinase (4 IU).

**Hyperfibrinolysis.** A hyperfibrinolytic state was created by adding 0.4 units (17.2 ul) of urokinase<sup>b</sup> to the sample. The

a Haemoscope Corporation, Skokie, IL 60077

b Sigma Chemical #U 8627, St. Louis, MO 63178

**Table 1: Targeted Coagulation Assessment: Hyperfibrinolysis (n=4).**

	Control	Heparinase	Platelets	FFP	Aminocaproic Acid
R time	22.4 ± 8.7 <sup>a,b,d</sup>	23.8 ± 0.35 <sup>a,b,d</sup>	8.3 ± 3.6	6.5 ± 2.8	9.1 ± 4.7
K time	7.5 ± 1.7	*	*	*	8.9 ± 2.9
MA	56.6 ± 4.0 <sup>a,b,c,d</sup>	4.0 ± 1.4 <sup>d</sup>	10.7 ± 4.7 <sup>d</sup>	14.8 ± 7.4 <sup>d</sup>	43.9 ± 10.4
Alpha angle	47.5 ± 6.8 <sup>c</sup>	15.3 ± 7.4 <sup>a,b,d</sup>	46.5 ± 11.0	54.5 ± 19.8	43.9 ± 10.4
Lysis 30	2.7 ± 1.0 <sup>a,b,c</sup>	100 ± 0.0 <sup>d</sup>	99 ± 2.0 <sup>d</sup>	100 ± 0.0 <sup>d</sup>	11.6 ± 18.6
Lysis 60	9.5 ± 2.1 <sup>a,b,c</sup>	100 ± 0.0 <sup>d</sup>	100 ± 0.0 <sup>d</sup>	100 ± 0.0 <sup>d</sup>	15.0 ± 21.4

FFP=fresh frozen plasma; Lysis 30=percent fibrinolysis at 30 minutes; Lysis 60=percent fibrinolysis at 60 minutes; MA= maximum amplitude; \*= K time not reached-deflection < 20 mm. P values: a= p<.02 vs. platelets; b= p<.02 vs. FFP; c= p<.02 vs. heparinase; d= p<.02 vs. aminocaproic acid

hyperfibrinolytic state was determined by performing a TEG with acceptance of lysis at 30 minutes of >50% and lysis at 60 minutes of >90%. Once a fibrinolytic state was achieved the coagulation assay was performed.

**Platelets.** To evaluate the platelet portion of the coagulation assay both a qualitative and quantitative platelet abnormality were created. A TEG and platelet count were obtained on the sample before alteration. To create a qualitative abnormality, 220 ul of nitroglycerin (1000 ug/ml) was added to 1 ml of the whole blood sample (15). A control sample containing 220 ul of normal saline was also created at this time. Both samples were then checked by performing a TEG. Qualitative platelet dysfunction was defined as a reduction in the TEG index of greater than one standard deviation from the normal baseline values. Once a platelet dysfunction was achieved the coagulation assay was performed.

To create a thrombocytopenic state, blood was centrifuged at 7200 RPM for 31 seconds to create a platelet-rich plasma. The plasma was then removed from the red blood cells and centrifuged at 7200 RPM for 4 minutes to create a platelet-poor plasma. The plasma supernatant was then separated from the platelets and combined with the red blood cells (this procedure was performed twice on each sample). Another platelet count was performed to assure a critical platelet count (< 50 K/ul). Once the critical platelet level was achieved the coagulation assay was performed.

**Hypofibrinogenemia.** To create hypofibrinogenemia a critical fibrinogen level (<50 mg/dl) was created. Blood samples were centrifuged at 7200 RPM for 4 minutes, a known quantity of plasma was removed and replaced with the same quantity of normal saline. After a critical level was obtained a platelet count was performed to assure that thrombocytopenia was not induced (>150 K/ul). Once the critical fibrinogen level was achieved the coagulation assay was performed.

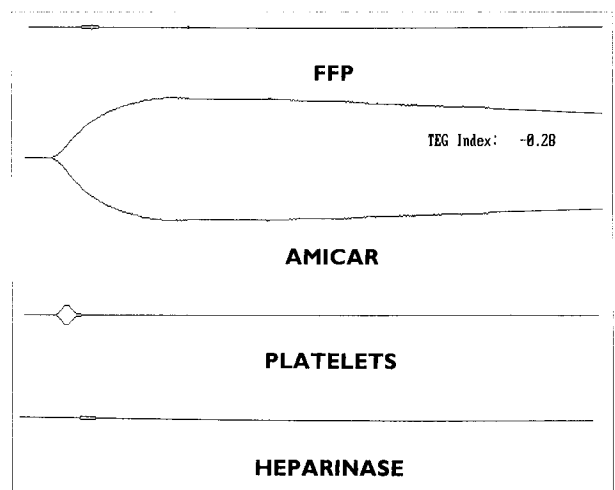
**Normal.** To provide a normal control for the coagulation assay non-treated whole blood samples were collected in the same fashion as the treated blood samples.

**Thrombelastography.** The TEG has been previously described (18). TEG parameters have been defined and are listed below:

**Reaction Time - (R time)** - Correlates with the Whole Blood Clotting Time. The R time marks the beginning of coagulation and occurs when the amplitude of the trace is equal to 2 mm.

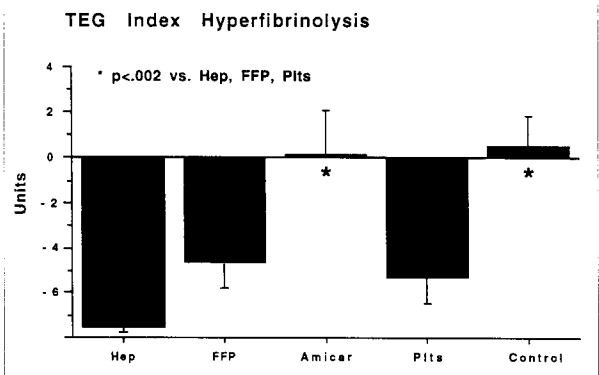
**Clot Growth Kinetics - (K time) and Alpha Angle** - The rate of clot growth is depicted as the time between initial clot formation (R time) and a 20 mm deflection in amplitude. Alpha angle and K time describe the polymerization of the structural elements involved in clotting. This is the rate of clot growth and is related to platelet function and plasma components resid-

Figure 1: Hyperfibrinolysis



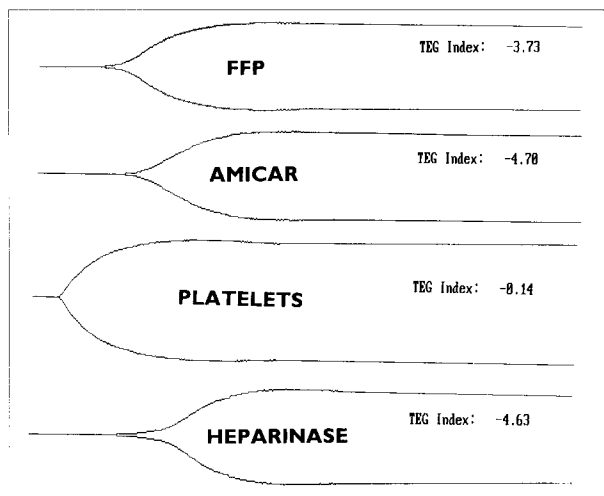
FFP = fresh frozen plasma

Figure 2: Hyperfibrinolysis



FFP = fresh frozen plasma; Hep = heparinase; Plts = platelets; TEG = thrombelastograph

Figure 3: Platelet dysfunction (Qualitative)



FFP = fresh frozen plasma

ing on the platelet surface.

**Clot Strength - Maximum Amplitude (MA)** - The strength of the clot is the ability of the clot to form hemostasis. This is a direct result of the function of platelets and plasma factors (fibrinogen) and their interaction.

**Clot Stability - Amplitude at 60 minutes (A 60)** - Refers to the potential of the clot to redissolve as a result of circulating fibrinolytic activators which activate the plasminogen incorporated in the clot. A steady or abrupt reduction in the MA over time represents clot dissolution and the presence of fibrinolysis.

**TEG index** - The TEG index is an equation, mathematically calculated from profiles of normal individuals, that combines the four primary variables of a TEG profile. The combination of these variables is used to assess the overall degree of coagulation (19).

**Lysis at 30 and 60 minutes** - The percent of clot lysis 30 and 60 minutes after complete clot formation. Used to identify fibrinolytic states.

The following is a list of abnormal values and their most likely clinical cause:

<u>TEG Values</u>	<u>Clinical Cause</u>
Prolonged R and K, and low alpha	Heparin
Decreased MA and normal R	Reduced platelet function
Decreased MA and extended R	Reduced platelet and clotting factors
Prolonged K and low alpha	Decreased platelet function, low plasma factors (fibrinogen), anticoagulants
Increased MA and short R	Hypercoagulable
Normal or reduced MA with reduced A 60	Clot fibrinolysis (Hyperfibrinolysis, DIC)

**Table 2: Platelet dysfunction (Qualitative) (n = 4)**

	Control	Heparinase	Platelets	FFP	Aminocaproic Acid
R time	23.6 ± 0.9 <sup>a</sup>	31.1 ± 8.6 <sup>a</sup>	8.2 ± 2.3	29.3 ± 7.4 <sup>a</sup>	28.6 ± 9.3 <sup>a</sup>
K time	11.6 ± 0.8	13.4 ± 5.9	11.1 ± 11.7	21.9 ± 13.4	16.6 ± 14.2
MA	53.8 ± 0.9	49.1 ± 9.4	50.3 ± 17.3	42.6 ± 17.0	43.5 ± 17.8
Alpha angle	36.3 ± 1.2	32.9 ± 10.5	51.6 ± 17.7	26.1 ± 11.2 <sup>a</sup>	36.8 ± 21.9

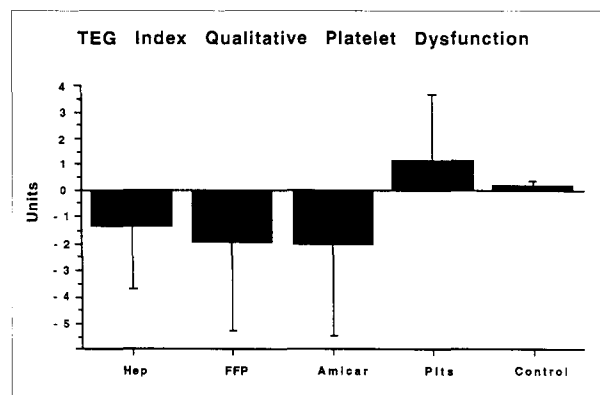
FFP=fresh frozen plasma; MA= maximum amplitude. P values: a= p .02 vs. platelets

**Table 3: Platelet dysfunction (Quantitative) – Platelet count = 46.5 ± 15.0 K/ul (n = 4)**

	Control	Heparinase	Platelets	FFP	Aminocaproic Acid
R time	29.4 ± 4.4 <sup>a,b,d</sup>	24.4 ± 5.5 <sup>a</sup>	14.4 ± 2.8 <sup>d</sup>	19.4 ± 2.8	21.9 ± 4.9
K time	12.3 ± 2.3 <sup>b,c,d</sup>	27.9 ± 8.3 <sup>a</sup>	15.4 ± 4.9 <sup>b</sup>	25.0 ± 5.9	24.0 ± 6.0
MA	48.6 ± 6.0 <sup>a,b,c,d</sup>	32.6 ± 5.2	36.0 ± 4.3	32.1 ± 4.3	32.9 ± 5.5
Alpha angle	34.5 ± 4.8 <sup>b,c,d</sup>	24.1 ± 11.6	33.6 ± 2.5	20.9 ± 3.9 <sup>a</sup>	20.4 ± 5.5

FFP=fresh frozen plasma; MA= maximum amplitude. P values: a= p .03 vs. platelets; b= p .03 vs. FFP; c= p < .05 vs. heparinase; d= p .02 vs. aminocaproic acid

**Figure 4: Platelet dysfunction (Qualitative)**



FFP = fresh frozen plasma; Hep = heparinase; Plts = platelets; TEG = thrombelastograph

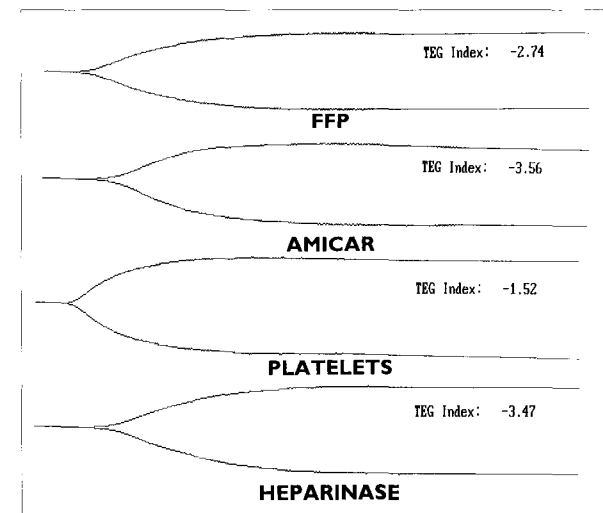
**Statistics.** All data were collected and loaded onto a personal computer in spreadsheet format. Data were analyzed with one way and two way ANOVA with a commercially prepared statistics program<sup>c</sup>. When significant f ratios were achieved the Fisher's protected least significant difference multiple comparison test was performed. Statistical significance was accepted at the p<0.05 level. All data are presented as mean ± standard deviation of the mean.

## RESULTS

The hyperfibrinolysis assay revealed that the FFP, aminocaproic acid, and platelet vials all reduced the R time significantly compared to the heparinase and control vials (Table 1). Fibrinolysis resulted in TEG profiles that failed to achieve a K time with the heparinase, FFP, or platelet vials. The aminocaproic acid vial, however, significantly reduced the K time by reversing the fibrinolytic condition. The aminocaproic acid vial also significantly increased the MA and improved the TEG index (Figure 1) compared to the heparinase, FFP, and platelet vials. The platelet and FFP vials did trend toward improving the TEG index (p=.06), but to a lesser degree than the aminocaproic acid vial (Figure 2). The

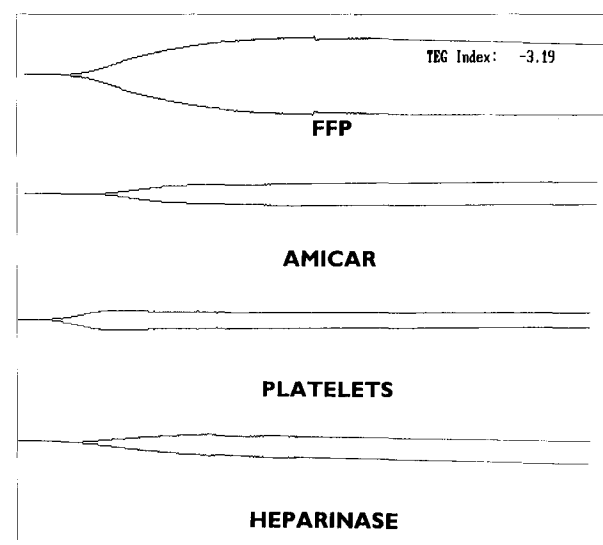
<sup>c</sup> SuperANOVA, Abacus Concepts, Berkeley, CA 94704

**Figure 5: Platelet dysfunction (Quantitative)**



FFP = fresh frozen plasma

**Figure 7: Hypofibrinogenemia**



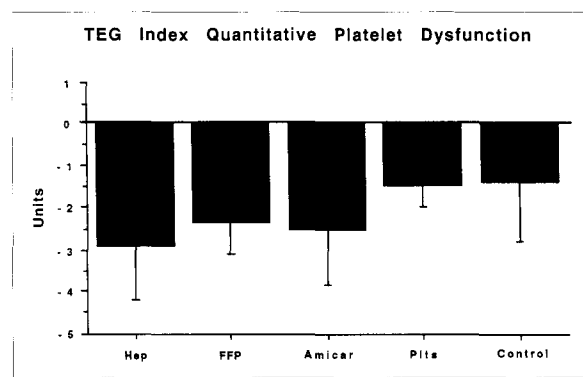
FFP = fresh frozen plasma

aminocaproic acid vial significantly reversed the clot lysis at both 30 and 60 minutes compared to the heparinase, FFP, and platelet vials.

For the qualitative platelet defect test, the platelet vial resulted in a significant shortening of R time compared to all other vials (Figure 3), and a significant increase in alpha angle compared to the FFP vial (Table 2). A trend in improvement was seen in the K time, MA, and TEG index, but it was not significant (Figure 4).

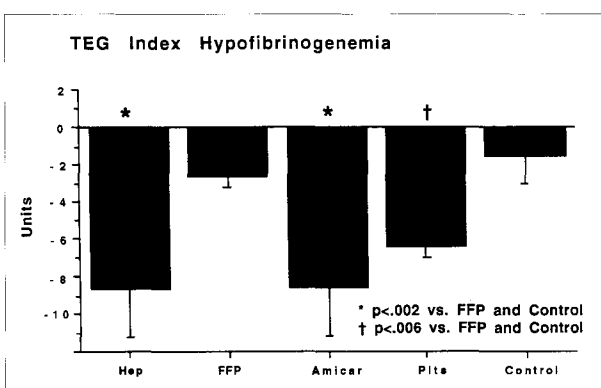
The R time of quantitative platelet defect (platelets=46.5 ± 15.0 K/u) assay was significantly shortened with the platelet vial compared to the amicar and heparinase vials (Table 3). The

**Figure 6: Platelet dysfunction (Quantitative)**



FFP = fresh frozen plasma; Hep = heparinase; Plts = platelets; TEG = thrombelastograph

**Figure 8: Hypofibrinogenemia**



FFP = fresh frozen plasma; Hep = heparinase; Plts = platelets; TEG = thrombelastograph

K time was significantly shortened, and the alpha angle was significantly increased with the platelet vial as compared to the FFP and amicar vials (Figure 5). The MA and TEG index were not significantly different between any of the vials except the control vial (MA) (Figure 6).

The hypofibrinogenemia assay showed a significant shortening in R time with the FFP and platelet vials compared to the heparinase and amicar vials (Table 4). Due to the critical levels of fibrinogen (23 ± 3.4 mg/dl), no K time was reached with the heparinase, platelet, or amicar vials, but a significant reduction was seen in the FFP vial (Figure 7). The alpha angle was significantly increased with the FFP vial compared to the amicar and control vials. The FFP and control vials showed significant differences compared to all other vials with respect to MA and TEG index (Figure 8).

The control assay revealed that the platelet vial significantly decreased the R time and K time and increased the alpha angle and TEG index (Figure 9), as compared to the amicar and heparinase vials. This was probably due to the thrombocytosis cre-

**Table 4: Hypofibrinogenemia. Fibrinogen concentration =  $23 \pm 3.4$  mg/dl (n = 4), platelet count =  $160 \pm 61$  K/ul (n = 4).**

	Control	Heparinase	Platelets	FFP	Aminocaproic Acid
R time	$30.1 \pm 3.5$	$37.9 \pm 17.6^{a,b}$	$17.8 \pm 2.4$	$21.1 \pm 1.4$	$37.8 \pm 15.3^{a,b}$
K time	$14.1 \pm 2.7^b$	*	*	$29.9 \pm 6.7$	*
MA	$47.1 \pm 7.2^{a,b,c,d}$	$6.88 \pm 2.8^b$	$6.0 \pm 2.35^b$	$30.8 \pm 2.7$	$7.25 \pm 5.4^b$
Alpha angle	$31.1 \pm 6.0^{a,b,c,d}$	$9.5 \pm 8.0$	$10.5 \pm 4.5$	$16.8 \pm 2.5$	$7.6 \pm 4.3^b$

FFP=fresh frozen plasma; MA= maximum amplitude; \* = K time not reached – deflection < 20 mm. P values: a= p < .01 vs. platelets; b= p < .05 vs. FFP; c= p < .05 vs. heparinase; d= p < .05 vs. aminocaproic acid

ated when the excess platelets from the platelet vial were added to the normal blood sample. The FFP vial also significantly decreased the R time compared to the amicar and heparinase, which was probably due to the increase in fibrinogen from the FFP vial. The values from the normal assay are summarized in Table 5.

## DISCUSSION

One of the major complications of CPB is excessive bleeding, caused by conditions resulting from extracorporeal circulation (3-5). To control bleeding it is often necessary to administer blood products to replace the components necessary for proper hemostasis (4,6,7). Many times the difficulty with treating coagulopathies is identifying the etiology, and if it cannot be readily determined, then the selection of interventional strategies is hindered. When homologous blood products are administered there is the potential for transmission of blood borne pathogens although the morbidity related to transfusion is much more prevalent (4,6,7). Our goal as clinicians is to minimize the usage of blood products by correctly identifying the etiology of bleeding and choosing appropriate interventions.

The most common method of monitoring a patient's full coagulation status includes the use of a coagulation profile. This is a series of tests that include both plasmatic (Prothrombin Time [PT], activated Partial Thromboplastin Time [aPTT], Thrombin Time [TT] and fibrinogen levels), and whole blood coagulation tests (bleeding time, platelet count, Activated Clotting Time [ACT], Heparin Dose Response [HDR] and heparin assay). For these tests to be effective it may be necessary to perform several of them together to obtain a complete hemostatic picture (18-21).

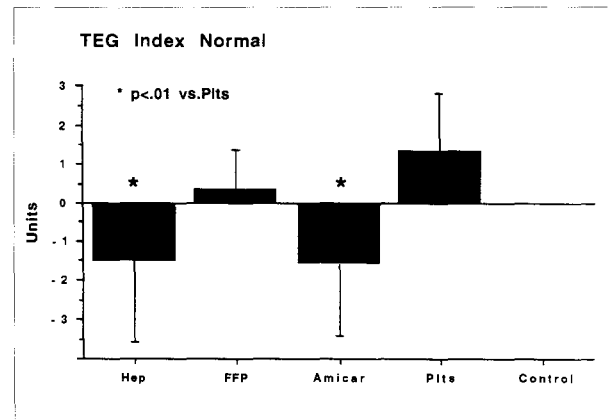
There are several limitations of plasmatic tests that prevent them from routinely being used in the operating room. The first limitation is the time required to perform the tests. The samples must be sent to the lab, centrifuged and then run on the various instruments. The next limitation is that the plasmatic tests can't assess platelet activity or fibrinolysis and the majority of the CPB induced coagulopathies are related to platelet de-

fects and fibrinolysis (20). The whole blood tests, such as the ACT, are ineffective because they are considered to be end-point assessments and will not identify coagulopathies such as fibrinolysis (19). Although bleeding time does appear to be a reliable assay in assessing platelet function, the Ivy bleeding time, which requires access to the patient's forearm, is not an appropriate test to perform in the

operating room because of the difficulty in obtaining this site (16,21,22). The other option would be to use the Duke's earlobe bleeding time (EBT); however, it has been shown that EBT has no predictive value for post-CPB bleeding (22).

Gravlee and associates have shown that routine coagulation testing is ineffective in predicting bleeding after cardiac operations (22). Despotis et al showed that on-site diagnosis of coagulopathies resulted in improved patient treatment (23). The present study was an attempt to take on-site monitoring one step further. Instead of using routine coagulation tests to determine the etiology of bleeding, abnormal patient samples were sub-

**Figure 9: Normal**



FFP = fresh frozen plasma; Hep = heparinase; Plts = platelets; TEG = thrombelastograph

**Table 5: Normal (n = 4)**

	Heparinase	Platelets	FFP	Aminocaproic Acid
R time	$37.2 \pm 11.8^{a,b}$	$13.7 \pm 6.2^c$	$21.5 \pm 3.4^c$	$34.2 \pm 12.3$
K time	$13.2 \pm 4.9^a$	$6.9 \pm 2.4^c$	$10.2 \pm 2.6$	$13.9 \pm 2.6$
MA	$52.6 \pm 6.9$	$55.8 \pm 6.7$	$54.1 \pm 5.7$	$49.7 \pm 6.0$
Alpha angle	$32.4 \pm 10.4^a$	$51.9 \pm 13.2^c$	$42.2 \pm 8.4$	$30.1 \pm 6.6$

FFP=fresh frozen plasma; MA= maximum amplitude. P values: a= p .01 vs. platelets; b= p < .05 vs. FFP; c= p < .05 vs. aminocaproic acid

jected to the TCA. Our data showed that significant improvement was seen, except in qualitative platelet dysfunction, in all of the TEG indices with the addition of the abnormal coagulation component. A trend in improvement, however, was seen in the quantitative platelet dysfunction tests which suggests that further analysis may be necessary to extrapolate these findings to clinical situations. Another advantage of the TEG over routine coagulation testing is cost. A single TEG test costs as much as 50% less than a coagulation profile (20).

Despotis and associates described a method of determining transfusion therapy with the use of routine coagulation tests. This method used an algorithm to determine the course of action in treating coagulopathies. The problem with this diagnostic process is that it can be difficult to understand and it requires distant laboratory assessment which may take additional time and personnel.

The use of the TEG has been shown to decrease the transfusion of homologous products in a retrospective study by Spiess et al (20). It has also been shown by Essell and colleagues that the TEG can discern between surgical and coagulopathic bleeding with greater than 90% confidence (21). This is clinically important because decreasing reoperations will decrease the cost to both the patient and hospital.

Our study used blood obtained from healthy patients under controlled conditions. We believe our results would correlate with clinical situations. The qualitative platelet defect assay showed the least amount of statistical significance with respect to correcting the induced coagulopathies. This may have been due to the method that was used to create the dysfunction. Had the platelet defect been natural the outcome may have been different. We also only looked at the coagulopathies individually. It is likely that clinically the coagulopathies will appear in combination. It should also be noted that the TEG will not differentiate between qualitative and quantitative disorders which means it may not correlate with platelet count when qualitative platelet dysfunction is seen. Other limitations of our study include performing the assays on whole blood from healthy volunteers. Since none of the samples were exposed to extracorporeal circulation, the absence of rheologic alterations may also be significant in attempting to apply our findings to clinical situations. We also chose to complete the study utilizing native whole blood samples that were not stimulated by the presence of a surface activator.

In conclusion, the TCA does appear to be effective in identifying the coagulopathies that were created. It will be necessary for further investigation to be done to validate this assay in a clinical setting since we only looked at the coagulopathies individually instead of in combination, which is how they will likely appear.

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