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Functional Fibrinogen Assay Indicates That Fibrinogen is Critical in Correcting Abnormal Clot Strength Following Trauma

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Abstract

BACKGROUND—Thrombelastography (TEG) is emerging as the standard in the management of acute coagulopathies in injured patients. While TEG is sensitive in detecting abnormalities in clot strength, one short-coming is differentiating between fibrinogen and platelet contributions to clot integrity. Current American algorithms suggest platelet transfusion, while European guidelines suggest fibrinogen concentrates for correcting low clot strength. Therefore, we hypothesized that a TEG-based functional fibrinogen assay would assess the contribution of fibrinogen and platelets to clot strength, and provide insight to transfusion priorities.

METHODS—Blood samples were obtained from trauma patients on arrival to the emergency department or who were admitted to the SICU (n=68). Citrated Kaolin TEG, FF, and von Clauss fibrinogen levels (plasma-based clinical standard) were measured. Correlations were assessed using linear regression models. In vitro studies were also performed with adding fibrinogen concentrates to blood collected from healthy volunteers (n=10). FF and citrated Kaolin TEG parameters were measured.

RESULTS—FF strongly correlated with von Clauss fibrinogen levels ($R^2=0.87$) and clot strength ($R^2=0.80$). The mean fibrinogen contribution to clot strength was 30%; however, there was a direct linear relationship with fibrinogen level and % fibrinogen contribution to clot strength ($R^2=0.83$). Traditional TEG parameters associated with fibrinogen activity (α -angle and k-time) had significantly lower correlations with FF ($R^2=0.70$ and 0.35). Furthermore, platelet count only had a moderate correlation to clot strength ($R^2=0.51$). The addition of fibrinogen concentrate in in vitro studies increased clot strength (MA) (60.44 ± 1.48 to 68.12 ± 1.39) and percent fibrinogen contribution to clot strength ($23.8\pm1.8\%$ to $37.7\pm2.5\%$).

CONCLUSION—FF can be performed rapidly with TEG, and correlates well with the standard von Clauss fibrinogen assay. Both fibrinogen and platelet contribution of clot strength can be derived from FF. Moreover, FF had a stronger correlation to clot strength and increased levels

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were directly associated with increased % contribution to clot strength. In vitro studies also demonstrated an increase in FF, clot strength, and percent fibrinogen contribution to clot strength with the addition of fibrinogen concentrate. These data suggest fibrinogen should be addressed early in trauma patients manifesting the acute coagulopathy of trauma.

Keywords

Functional Fibrinogen; TEG; Clot Strength; Trauma; Fibrinogen Concentrate; Platelets; Resuscitation

INTRODUCTION

Uncontrolled hemorrhage is the second leading cause of death following trauma, accounting for nearly 40% of early mortality, and patients who have a coagulopathy on arrival to the emergency department are four-times more likely to die than those without a coagulopathy.^{1,2} Therefore, early recognition of the acute coagulopathy of trauma (ACOT) is imperative, and viscoelastic hemostatic assays have proven useful in the identification and treatment of ACOT.³⁻⁷ Consequently, viscoelastic hemostatic assays have been widely adopted, and are emerging as the standard-of-care in the management of trauma patients.

Although viscoelastic hemostatic assays have been reported to be superior to traditional plasma-based tests (i.e. aPTT, INR),^{4,6,8,9} there remains debate regarding therapeutic interventions for correcting abnormal parameters. This debate stems from the understanding of the cell-based model of hemostasis. Clot strength is the ultimate measure of hemostatic capacity, and reflects the interaction between platelets and fibrin(ogen); both critical for stable clot formation. With the availability of fibrinogen concentrates, many European trauma centers infuse fibrinogen early to correct for abnormalities in clot strength since fibrinogen concentrates are easily stored, and thus, available for immediate use.¹⁰⁻¹² However, in the United States, platelets are used preferentially to correct abnormal clot strength following trauma, since platelets provide the surface for coagulation complexes to form, increasing thrombin generation.¹³

The TEG® 5000 is the most widely used viscoelastic hemostatic assay in the United States, but a potential short-coming of this device is differentiating between platelet and fibrin(ogen) contribution to clot integrity. Traditionally, the k-time and α -angle have been used to assess fibrinogen function, but correlations to clinical fibrinogen levels have been inadequate.^{14,15} However, with the recent development of the TEG® Functional Fibrinogen assay, this limitation can be addressed, but has not yet been evaluated in the trauma population. With this assay, the fibrinogen that is actively involved in thrombus formation can be measured and be compared to overall clot strength. Therefore, we hypothesized that the TEG® Functional Fibrinogen assay would assess the contribution of fibrinogen and platelets to clot strength in severely injured patients, and provide insight to transfusion regimens.

MATERIALS AND METHODS

Prospective Observational Study

This prospective observational study was conducted at the Denver Health Medical Center, the academic level-1 trauma center for the University of Colorado Denver, and was approved by the Colorado Multiple Institutional Review Board. Citrated whole blood samples were obtained from trauma patients (n=68), meeting field criteria for a trauma alert or activation status, on arrival to the emergency department or within the first five days of admission to the surgical intensive care unit in order to capture a broad range of fibrinogen

levels. Patients with known coagulopathies, on anti-platelet therapy, under the age of 18 years, prisoners, and pregnant women were excluded from this study. No patients in this study received colloid resuscitative fluids with known effects on coagulation, such as hetastarch. All blood samples were collected in 3.5 mL plastic Vacutainers® containing 3.2% citrate.

The von Clauss assay is the clinical gold standard for measuring plasma fibrinogen levels and was performed by the clinical laboratory.¹⁶ For this assay, a standard curve is generated by performing a thrombin time on different dilutions of plasma with a known fibrinogen level. Citrated whole-blood is then collected from a patient, centrifuged, and the plasma portion is obtained. The plasma is then diluted 1:10, and a thrombin time is performed. The measured thrombin time is then noted on the standard curve, and the fibrinogen concentration is extrapolated.

The Functional Fibrinogen and Kaolin TEG assays were provided by Haemonetics® (Niles, IL, USA), and performed on the TEG® 5000 device in the trauma research laboratory. The samples for both thrombelastography and the von Clauss assay were collected simultaneously, and trained research personnel performed the thrombelastography within 30 minutes following blood collection. For the Kaolin TEG assay, 1 mL of citrated blood was added to the designated Kaolin-vial, and gently mixed. A 340 µL aliquot was transferred from the Kaolin-vial to a 37°C TEG cup preloaded with 20 µL 0.2 mol/L CaCl₂. To perform the Functional Fibrinogen (FF) assay, 0.5 mL of citrated blood was added to the designated FF-vial containing a mixture of Kaolin and a monoclonal GPIIb/IIIa receptor antagonist, and gently mixed. A 340 µL aliquot was transferred from the FF-vial to a 37°C TEG cup preloaded with 20 µL 0.2 mol/L CaCl₂. The FF-assay measures the functional fibrinogen level (FLEV), which is extrapolated from the MA_{Fibrinogen} value. In performing both the Kaolin TEG and FF TEG, the independent contribution of fibrinogen and platelets to overall clot strength (MA) can be determined by the equation $MA = MA_{Platelet} + MA_{Fibrinogen}$ (Figure 1).

In Vitro Studies

In vitro studies were performed on citrated whole-blood samples obtained from healthy volunteers (n=10) to demonstrate the causal role of fibrinogen on clot strength. Venipuncture was performed with a 21-gauge needle in an antecubital vein, and blood was collected into two separate 3.5 mL plastic Vacutainers® containing 3.2% citrate. In one citrated whole-blood sample, 20 mg of lyophilized human fibrinogen concentrate (Sigma-Aldrich Co., St. Louis, MO, Product F3879) was slowly added directly to the Vacutainer® and gently inverted until the powder was completely dissolved. This method limited the volume change as well as the change in concentration of citrate in the Vacutainer®. Pre-study experiments were performed to determine the optimal addition of fibrinogen to roughly double the functional fibrinogen concentration. Both Kaolin and FF TEGs were performed within 30 minutes of collection as above on each sample, and all TEG parameters were recorded. Normal TEG parameters for our clinical laboratory include: k-time (1.1-3.5 min), α-angle (55.0-78.0 degrees), MA (55.8-73.3 mm), FLEV (200-445 mg/dL).

Statistical Analysis

Patient demographics are reported as the mean ± standard deviation or the median with interquartile range (IQR) if the variable did not follow a normal distribution. TEG parameters in the in vitro study are reported as the mean ± standard error of the mean. Correlations in the prospective observational study were assessed using linear and polynomial regression models, and a two-tailed, paired student t-test was used to determine

significance in the in vitro studies. A p-value less than 0.05 was considered statistically significant.

RESULTS

In this clinical study, 66% of patients were male, with a mean age of 38 ± 12.3 years. The median ISS and base deficit were 23.5 (IQR; 17-33) and 12 mEq/L (IQR; 8-15.25) respectively, and 55% of patients sustained blunt trauma. Von Clauss fibrinogen levels ranged from 59 to 840 mg/dL. Functional fibrinogen FLEV values ranged between 100 and 734 mg/dL. There was a significant correlation between the von Clauss fibrinogen assay and the FF assay ($R^2=0.87$, $p<0.0001$) (Figure 2). Furthermore, both the von Clauss fibrinogen levels and the FLEV had a significant correlation to clot strength (MA) ($R^2=0.75$ and 0.80 respectively, $p<0.0001$), with FLEV having a modestly higher correlation coefficient than the von Clauss fibrinogen level (Figure 3). Both assays appeared to show that fibrinogen levels greater than 200 mg/dL correlated with normal clot strength values, and reached a plateau at levels greater than 500 mg/dL. On the other hand, platelet count did not correlate as well as fibrinogen levels. Although significant, the platelet count had only a moderate correlation to clot strength ($R^2=0.51$, $p<0.0001$) (Figure 4). Moreover, an increase in platelet count did not appear to contribute to clot strength at numbers greater than 300,000 per μL . In addition, there was no association with R-time with either von Clauss fibrinogen or FLEV ($R^2=0.001$ and 0.026 respectively).

With regard to individual component contributions to clot strength, von Clauss fibrinogen levels appeared to have a direct linear correlation to the percent fibrinogen contribution to clot strength ($R^2=0.83$, $p<0.0001$) (Figure 5). Therefore, as fibrinogen levels increased, so did the fibrinogen component to clot strength. Moreover, there was no evidence of a plateau in this relationship. Conversely, platelet count had a poor correlation to the percent platelet contribution to clot strength ($R^2=0.07$, $p=0.047$). In fact, an increase in platelet count appeared to decrease the platelet contribution to clot strength.

To determine the association of FLEV to traditional TEG measures of fibrinogen function, correlations to k-time and α -angle were also examined. K-time had a moderate, inverse linear correlation to FLEV ($R^2=0.35$, $p<0.0001$). However, at FLEV levels less than 115 mg/dL, k-time lost its association, accounting for the decrease in the correlation coefficient, but this sample size is limited. Consequently, α -angle had a stronger association to FLEV, but also had a decreased association for FLEV levels less than 115 mg/dL, and reached a plateau at FLEV levels greater than 400 mg/dL ($R^2=0.70$, $p<0.0001$) (Figure 6).

In the in vitro studies, healthy volunteers had a mean age of 35 ± 6 years and 50% were male. Addition of fibrinogen concentrate to citrated whole-blood increased FLEV from 263.1 ± 20.5 to 468.1 ± 31.4 mg/dL ($p=0.0008$). In addition, an increase in FLEV increased clot strength from 60.44 ± 1.48 to 68.12 ± 1.39 dynes/cm² ($p=0.0009$). This subsequently increased the percent fibrinogen contribution to clot strength from $23.8 \pm 1.8\%$ to $37.7 \pm 2.5\%$ ($p=0.003$). Traditional TEG parameters of fibrinogen function also significantly changed. K-time shortened from 3.06 ± 0.33 to 2.02 ± 0.18 min ($p=0.005$), and α -angle increased from 52.78 ± 2.28 to 60.84 ± 2.54 degrees ($p=0.0153$), which corresponded to the clinical study values. In addition, the R-time shortened from 8.57 to 5.84 minutes ($p=0.002$) indicating that the addition of fibrinogen enhances all aspects of clot formation and stability.

DISCUSSION

These data show that the TEG®-based Functional Fibrinogen assay correlates well to the standard von Clauss assay, and that fibrinogen is critical in correcting abnormal clot strength

in trauma patients. ACOT contributes to increased morbidity and mortality following severe injury, and rapid diagnosis and appropriate blood component treatment are crucial to improving outcomes. The role of fibrinogen in ACOT has not been well characterized, and is generally considered impaired from a combination of endogenous factors (activated protein C and release of tPA from the endothelium),¹⁸⁻²⁰ as well as dilution from crystalloid and packed red blood cell resuscitation. Typically, fibrinogen levels are not obtained in the initial evaluation of severely injured patients at risk for significant coagulopathy. The implementation of viscoelastic hemostatic assays in trauma management offers a superior assessment of coagulation that can be achieved more rapidly than plasma-based assays. Similarly, results of the FF assay can be achieved in less than 15 minutes and can be run simultaneously with a Rapid or Kaolin TEG.

In our prospective observational study, the FF assay correlated well with the most common clinical assay used to measure fibrinogen levels, and demonstrated that the FF assay can be accurately employed for use in the management of severely injured patients. Furthermore, the FF assay was able to determine the relative fibrinogen and platelet contributions to clot strength, and correlated fibrinogen levels to increased clot strength, as well as increased fibrinogen contribution to clot strength. These associations were subsequently confirmed by in vitro studies. Platelets, which are known to contribute up to 80% of total clot strength in normal individuals, had a much poorer correlation to clot strength, which likely reflects the fact that platelet count and platelet function are separate entities. Therefore, platelet function may ultimately be a better parameter to use to guide resuscitation. Moreover, platelet counts greater than 100,000 per μL were associated with normal clot strength parameters, and counts greater than 300,000 per μL were associated with no increase in clot strength. Interestingly, there was a decrease in percent platelet contribution to clot strength with an increase in platelet count. This may be partly explained by the cell-based model of hemostasis. Since coagulation complexes form on the surface of the platelet, increasing the amount of platelet surface area may ultimately increase thrombin generation, even in the setting of trauma when platelets become inhibited.²¹ This increase in thrombin generation, and subsequent fibrin production, likely increases the fibrinogen contribution to clot strength disproportionately greater than the platelet contribution to clot strength, which plateaus. Therefore, this decreases the relative platelet contribution to clot strength, and is not reflective of platelet inhibition.

The traditional TEG parameters of measuring fibrinogen function (k-time and α -angle) have some value, since k-time had a moderate correlation to fibrinogen levels, and α -angle had a much stronger correlation. In fact, almost all α -angle values above 55.0° , the minimal normal reference value, had fibrinogen levels greater than 200 mg/dL. Therefore, α -angle may be used to assess fibrinogen function. However, the FF assay had similar correlations to clinically measured fibrinogen levels as well as clot strength. Furthermore, k-time and α -angle were poorer predictors of fibrinogen function with fibrinogen levels less than 115 mg/dL and greater than 400 mg/dL, and therefore, is a limitation of using these parameters to assess fibrinogen function. Lastly, k-time and α -angle do not allow for the assessment of platelet function, as well as fibrinogen and platelet contributions to clot strength.

The in vitro studies further demonstrated that fibrinogen is directly responsible for an increase in clot strength, as well as increased fibrinogen contribution to clot strength. Interestingly, data from our in vitro studies were very similar to data from our clinical studies. The changes observed in TEG parameters from increasing functional fibrinogen levels in vitro corresponded to similar changes in clot strength, percent fibrinogen contribution to clot strength, k-time, and α -angle in our observational study. Therefore, we are re-assured of the validity of our in vitro work, suggesting that TEG results from clinically relevant in vitro studies may translate to the clinical arena.

A limitation to this study is that we have not defined the acute coagulopathy of trauma, but the most described definition is an INR > 1.5. Of this patient population studied, 29.4% had an INR > 1.5 on arrival to the ED, but with limited FF and Kaolin TEG data on patients arriving to the ED, we cannot make any conclusions on initial fibrinogen level and ACOT defined by INR in this study. We also recognize that plasma-based assays are not the optimal tool to detect coagulopathies, and at our institution, we use TEG parameters below our clinical reference range in patients who are actively bleeding to characterize patients with ACOT. These parameters include R-time, K-time, α -angle, MA, or LY30. However, these reference ranges may differ between institutions or some may only characterize patient with ACOT who have a low MA or significant lysis. Therefore, we feel a standard TEG definition is required and future studies are needed, as TEG is becoming the standard of care.

The direct clinical implication of these data suggests that fibrinogen levels should be addressed early in severely injured patients at risk for ACOT. The von Clauss assay is not a rapid point-of-care test, but the FF-assay can be easily performed in institutions already employing TEG, which can be run simultaneously with a Rapid TEG. Although normal values for k-time and α -angle are associated with FLEV greater than 115 mg/dL, FLEV is a better predictor of clot strength, and also derives platelet contribution to clot strength. Consequently, data from this clinical study demonstrates that fibrinogen levels greater than 100 mg/dL may not be adequate in addressing severely injured patients with abnormally low clot strength, and suggests levels greater than 200 mg/dL to achieve normal clot strength parameters. Moreover, platelet counts greater than 100,000 per μ L appear adequate to achieve normal clot strength parameters. Therefore, patients with a platelet count greater than 100,000 per μ L and an abnormal clot strength, may need to be given fibrinogen in order to address the coagulopathy. Another advantage of the FF-assay is that all other TEG-assays are affected by patients on anti-platelet therapy, except for the FFassay. Therefore, if patients with known, or unknown, anti-platelet therapy use present with an abnormally low MA on a Rapid or Kaolin TEG, with a normal platelet count and a normal FF, platelets should be the next blood component given in the setting of an actively bleeding patient. However, if this same patient also has an abnormally low FF, then blood components containing fibrinogen should be considered earlier in the management of this patient. The FF-assay allows for more precision in component-specific resuscitation.

In summary, our results demonstrate that the FF assay is an accurate and rapid point-of-care assay, and that fibrinogen is critical to clot strength. Therefore, these data further suggest that fibrinogen levels should be addressed early in severely injured trauma patients presenting with abnormal clot strengths. Although fibrinogen concentrates have a known, high concentration of fibrinogen that is easily stored and rapidly available to transfuse, they are not currently approved by the United States Food and Drug Administration for use in trauma. Options to increase fibrinogen levels include fresh frozen plasma (FFP) and cryoprecipitate. A unit of FFP ($\approx$ 250 mL) contains approximately 725 mg (2.9 mg/mL) of fibrinogen, where a unit of cryoprecipitate ($\approx$ 20 mL) contains approximately 183 mg (8.8 mg/mL).²¹ These data also suggest that platelets should only be transfused for platelet counts of less than 100,000 per μ L in patients with abnormal clot strength, and that platelet function may be a better parameter to guide platelet transfusions. Overall, the TEG® Functional Fibrinogen assay provides clinically useful data that may guide cost-effective transfusions.

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REFERENCES

1. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, Pons PT. Epidemiology of trauma deaths: a reassessment. *J Trauma*. 1995; 38(2):185–193. [PubMed: 7869433]
2. Macleod JBA, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. *J Trauma*. 2003; 55(1):39–44. [PubMed: 12855879]
3. Kheirabadi BS, Crissey JM, Deguzman R, Holcomb JB. In vivo bleeding time and in vitro thrombelastography measurements are better indicators of dilutional hypothermic coagulopathy than prothrombin time. *J Trauma*. 2007; 62(6):1352–1359. [PubMed: 17563647]
4. Park MS, Martini WZ, Dubick MA, Salinas J, Butenas S, Kheirabadi BS, Pusateri AE, Vos JA, Guymon CH, Wolf SE, Mann KG, Holcomb JB. Thromboelastography as a better indicator of hypercoagulable state after injury than prothrombin time or activated partial thromboplastin time. *J Trauma*. 2009; 67(2):266–275. [PubMed: 19667878]
5. Plotkin AJ, Wade CE, Jenkins DH, Smith KA, Noe JC, Park MS, Perkins JG, Holcomb JB. A reduction in clot formation rate and strength assessed by thrombelastography is indicative of transfusion requirements in patients with penetrating injuries. *J Trauma*. 2008; 64(2 Suppl):S64–S68. [PubMed: 18376174]
6. Martini W, Cortez D, Dubick M, Park MS, Holcomb JB. Thrombelastography is better than PT, aPTT, and activated clotting time in detecting clinically relevant clotting abnormalities after hypothermia, hemorrhagic shock and resuscitation in pigs. *J Trauma*. 2008; 65(3):535–543. [PubMed: 18784565]
7. Doran CM, Woolley T, Midwinter MJ. Feasibility of using rotational thromboelastometry to assess coagulation status of combat casualties in a deployed setting. *J Trauma*. 2010; 69(Suppl 1):S40–S48. [PubMed: 20622618]
8. Counts RB, Haisch C, Simon TL, Maxwell NG, Heimbach DM, Carrico CJ. Hemostasis in massively transfused trauma patients. *Ann Surg*. 1979; 190(1):91–99. [PubMed: 464685]
9. Lucas CE, Ledgerwood AM. Clinical significance of altered coagulation tests after massive transfusion for trauma. *Am Surg*. 1981; 47(3):125–130. [PubMed: 7212456]
10. Schochl H, Nienaber U, Hofer G, Voelckel W, Jambor C, Scharbert G, Kozek-Langenecker S, Solomon C. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care*. 2010; 14(2):R55. [PubMed: 20374650]
11. Schochl H, Cotton B, Inaba K, Nienaber U, Fischer H, Voelckel W, Solomon C. FIBTEM provides early prediction of massive transfusion in trauma. *Crit Care*. 2011; 15(6):R265. [PubMed: 22078266]
12. Schochl H, Nienaber U, Maegele M, Hochleitner G, Primavesi F, Steitz B, Arndt C, Hanke A, Voelckel W, Solomon C. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. *Crit Care*. 2011; 15(2):R83. [PubMed: 21375741]
13. Hoffman M, Monroe DM. A cell-based model of hemostasis. *Thromb Haemost*. 2001; 85(6):958–965. [PubMed: 11434702]
14. Jeger V, Willi S, Liu T, Yeh DD, De Moya M, Zimmermann H, Exadaktylos AK. The rapid TEG α -angle may be a sensitive predictor of transfusion in moderately injured blunt trauma patients. *Scientific World Journal*. 2012; 2012:821794. [PubMed: 22547997]
15. White NJ, Martin EJ, Brophy DF, Ward KR. Coagulopathy and traumatic shock: characterizing hemostatic function during the critical period prior to fluid resuscitation. *Resuscitation*. 2010; 81(1):111–116. [PubMed: 19854556]
16. Fluger I, Maderova K, Simek M, Hajek R, Zapletalova J, Lonsky V. Comparison of functional fibrinogen assessment using thromboelastography with the standard von Clauss method. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2011 10.5507/bp.2011.035, 2011.
17. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Ann Surg*. 2007; 245(5):812–818. [PubMed: 17457176]

18. Cohen MJ, Call M, Nelson M, Calfee CS, Esmon CT, Brohi K, Pittet JF. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. *Ann Surg.* 2012; 255(2):379–385. [PubMed: 22133894]
19. Kooistra T, Schrauwen Y, Arts J, Emeis JJ. Regulation of endothelial cell t-PA synthesis and release. *Int J Hematol.* 1994; 59(4):233–255. [PubMed: 8086618]
20. Wohlaer MV, Moore EE, Thomas S, Sauaia A, Evans E, Harr J, Silliman CC, Ploplis V, Castellino FJ, Walsh M. Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. *J Am Coll Surg.* 2012; 214(5):739–746. [PubMed: 22520693]
21. Caudill JS, Nichols WL, Plumhoff EA, Schulte SL, Winters JL, Gastineau DA, Rodriguez V. Comparison of coagulation factor XIII content and concentration in cryoprecipitate and fresh-frozen plasma. *Transfusion.* 2009; 49(4):765–770. [PubMed: 19192257]

Figure 1. Normal citrated Kaolin TEG and Functional Fibrinogen tracings demonstrating both the fibrinogen and platelet contribution to clot strength.

Figure 2. Functional Fibrinogen levels (FLEV) strongly correlate with the clinical standard von Clauss fibrinogen levels. $R^2=0.87$ ($p<0.0001$).

Figure 3. Functional Fibrinogen levels (FLEV) strongly correlates with TEGmeasured clot strength (MA). $R^2=0.80$ ($p<0.0001$). Normal clot strength parameters appear to be associated with FLEV values greater than 200 mg/dL. Normal values are shaded.

Figure 4.

Platelet count has a moderate correlation to clot strength (MA). $R^2=0.51$ ($p<0.0001$). A platelet count greater than 100,000 per μL was associated with normal clot strength parameters. An increase in platelet count does not appear to significantly contribute to clot strength at numbers greater than 300,000 per μL . Normal values are shaded.

Figure 5. von Clauss fibrinogen levels are strongly correlated to the percent fibrinogen contribution to clot strength. $R^2=0.83$ ($p<0.0001$). Therefore, as fibrinogen levels increase, the percent fibrinogen contribution to clot strength also increases.

Figure 6.

Functional Fibrinogen levels (FLEV) strongly correlate with α -angle. $R^2=0.7$ ($p<0.0001$). FLEV values greater than 115 mg/dL are associated with normal α -angle values. However, FLEV values greater than 400 mg/dL are not associated with significant increases in α -angle. Normal values are shaded.