Published in final edited form as:

J Am Coll Surg. 2016 April ; 222(4): 347–355. doi:10.1016/j.jamcollsurg.2016.01.006.

Acute Fibrinolysis Shutdown after Injury Occurs Frequently and Increases Mortality: A Multicenter Evaluation of 2,540 Severely Injured Patients

Hunter B Moore, MD¹, Ernest E Moore, MD, FACS¹, Ioannis N Liras, MD², Eduardo Gonzalez, MD¹, John A Harvin, FACS, MD², John B Holcomb, MD, FACS², Angela Sauaia, MD, PhD¹, and Bryan A Cotton, MD MPH, FACS²

¹University of Colorado Denver/ Denver Health Medical Center, Department of Surgery, Denver, CO

²University of Texas Health Science Center at Houston / Memorial Hermann, Department of Surgery, Houston, TX

Abstract

Background—Fibrinolysis is a physiologic process to maintain microvascular patency by breaking down excessive fibrin clot. Hyperfibrinolysis (HF) is associated with a doubling of mortality. Fibrinolysis shutdown (SD), an acute impairment of fibrinolysis, has been recognized as a risk factor for increased mortality. The purpose of this study was to assess the incidence and outcomes of fibrinolysis phenotypes in two urban trauma centers.

Study Design—Injured patients admitted 2010–2013, who were ≥18 years of age, had an injury severity score (ISS) >15 were included in the analysis. Admission fibrinolysis phenotypes were determined by the clot lysis at 30 minutes (LY30): SD 0.8%, physiologic 0.9–2.9%, HF 3%. Logistic regression was used to adjust for age, arrival blood pressure, ISS, mechanism, and facility.

Results—2540 patients met inclusion. Median age was 39 (IQR 26–55) and median ISS was 25 (IQR 20–33) with a mortality rate of 21%. Fibrinolysis shutdown was the most common phenotype (46%) followed by physiologic (36%) and hyperfibrinolysis (18%). HF was associated with the highest death rate (34%), followed by SD (22%), and physiologic (14%, $p < 0.001$). The risk of mortality remained increased for HF (OR=3.3, 95% CI: 2.4–4.6, $p < 0.0001$) and SD (OR 1.6 95% CI 1.3–2.1, $p = 0.0003$) compared to physiologic when adjusting for age, ISS, mechanism, head injury, and blood pressure (AUROC=0.82, 95% CI 0.80–0.84).

Correspondence address: Hunter B Moore, MD, 655 Bannock Street Denver, CO 80204, hunter.moore@ucdenver.edu, Phone: 303-724-2685, Fax: 303-720-2682.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosure Information: Nothing to disclose.

Disclosures outside the scope of this work: Dr Cotton is a paid consultant to Haemonetics Corp. Dr Sauaia's institution receives research support from the American Association for the Surgery of Trauma. Dr Moore receives research support from Haemonetics Corp and TEM.

Presented at the Southern Surgical Association 127th Annual Meeting, Hot Springs, VA, December 2015.

Conclusions—Fibrinolysis SD is the most common phenotype upon admission and is associated with increased mortality. Moreover, these data provide additional evidence of distinct phenotypes of coagulation impairment and that individualized hemostatic therapy may be required.

Introduction

One in three severely injured trauma patients will have early evidence of impaired coagulation, which is associated with a four fold increase in mortality(1). However, the majority of injured patients who present to the emergency department (ED) have hypercoagulability(2). Studies analyzing patterns of behavior of both coagulation factors and viscoelastic variables in severely injured patients suggest that clot formation and clot degradation (fibrinolysis) are mediated by unique mechanism(3, 4). Excessive clot degradation (hyperfibrinolysis) is associated with mortality rates that range from 40-90%(5-7), but is relatively infrequent(5, 8). Recently, it has been found that the majority of severely injured trauma patients have impairment of fibrinolysis within 12 hours of injury, which is associated with an increased risk of death from organ failure(9). This inhibition of fibrinolysis results in micro vascular thrombosis and has previously been implicated in the pathogenesis of organ failure(10) and venous thrombotic events(11).

The drivers of the pathologic extremes of the fibrinolytic system remain elusive. Animal work suggests that hemorrhagic shock drives hyperfibrinolysis while tissue injury promotes fibrinolysis shutdown(12). These experimental findings are consistent with clinical observations of a high prevalence of hyperfibrinolysis in non-trauma patients undergoing prehospital cardiopulmonary resuscitation(13) as well as in severely injured patient with profound hypotension at presentation to the hospital(9). While the molecular mechanism driving hyperfibrinolysis appear to be related to up regulation of tissue plasminogen activator(tPA) and depletion of its inhibitors(14, 15) little translation clinical data supports what provokes fibrinolysis shutdown.

In our previous description of the spectrum of post injury fibrinolysis no clinical indices or biomarkers of injury could be associated with the fibrinolysis shutdown phenotype(9). Identifying such indicators has significant clinical implications as empiric administration of antifibrinolytics to trauma patients may have adverse events in those patients resistant to tPA. To date, two large retrospective US studies found no survival benefit of administering tranexamic acid(TXA) to injured patients(16, 17). Our original study was limited to a single center and small number of patients using Kaolin TEG. Kaolin thrombelastography (kTEG) is not used early during trauma resuscitations due to time delay in obtaining clotting measurements, as this process can be expedited with the addition of tissue factor used in a rapid TEG (rTEG). Consequently our study had three major objectives: 1) to determine the fibrinolysis spectrum in a large, bi-institutional cohort of severely injured patients using rTEG; 2) to determine independent predictors of the three fibrinolysis phenotypes; and 3) to determine the independent effect of the fibrinolysis phenotypes on postinjury outcomes.

Methods

Acutely injured trauma patients enrolled in studies under IRB approved protocols from 2012-2014 from the University of Colorado Denver/ Denver Health Medical Center and University of Texas Houston/Memorial Hermann were included in this study. Patients meeting trauma activation criteria were included if they had an injury severity score (ISS) greater than 15, were directly transferred from the injury scene to the emergency department, and had a rapid thrombelastography (rTEG) drawn within one hour postinjury. Patients taking anticoagulant medication including warfarin or direct factor inhibitors were excluded from the study. In addition, patients who received antifibrinolytics before rTEG were excluded. Patient demographics, injury patterns, and blood product use was prospectively recorded in all patients. The primary outcome was in-hospital mortality. Secondary outcomes included cause of mortality (determined by senior investigators EEM and BAC based on morbidity and mortality meetings and clinical pathology report if available), survival time (from injury to death), and massive transfusion (defined as greater than or equal 10 units of red blood cells (RBC) within 6 hours postinjury).

Trained professional research assistants assayed blood with the TEG 5000 Hemostatic Analyzer (Heamonetics, Braintree, MA). Blood was obtained in 2.7 ml citrated tubes (Vacutainer, Becton-Dickison, Franklin Lakes NJ) and assayed after re-calcification within 2 hours of blood draw according to manufacturers recommendations. The following measurements were recorded: T-ACT (seconds), angle (α , degrees), maximum amplitude (MA, mm), and lysis 30 minutes after MA (LY30, %).

Patients were categorized according to their admission fibrinolysis phenotypes as determined by their rTEG LY30, as follows: hyperfibrinolysis was defined as LY30 >3%, fibrinolysis shutdown as LY30 of less than 0.8% and physiologic fibrinolysis as LY30 between 0.8% and 3%, based on the original description of the spectrum of post injury fibrinolysis defined by TEG (5, 9, 18).

Statistical analysis was performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). Normally distributed data were described as mean and standard deviation and non-normally distributed data were described as the median value with the 25th to 75th percentile values (IQR). Categorical data were contrasted between fibrinolysis phenotypes with a Chi-square test. Non-normally distributed and ordinal data were contrasted between groups with a Kruskal- Wallis test. Survival times were compared using Kaplan Meier curves (difference between strata tested using the log-rank and Wilcoxon tests). The differences between phenotype-associated survival times were adjusted for confounders using a Cox-proportional hazards model. A generalized logit model was used to determine independent predictors of fibrinolysis phenotypes fitting a polytomous logistic regression with a three-category dependent variable and physiologic phenotype serving as the reference group. The goodness of fit of this model was assessed by the Deviance and Pearson goodness of fit statistic (for which high p-values are desired). A logistic regression models was used to assess the independent effect of fibrinolysis phenotypes on mortality adjusted for confounders including: age, ISS, Head Abbreviated Injury Scale (AIS-head), and admission systolic blood pressure (ED SBP). This model's performance was assessed using

the area under the receiver operating characteristics curve (AUROC) with 95% confidence intervals (CI) and variable association was expressed as odds ratios (OR) with 95% CI.

Results

There were 2,540 patients in the analysis, of which 21% did not survive. Median age was 39 (IQR 26-55) and median ISS was 25 (IQR 20-33). Fibrinolysis shutdown was the most common phenotype (46%) followed by physiologic (36%) and hyperfibrinolysis (18%). While the hyperfibrinolytic phenotype was associated with a slightly higher overall ISS ($p=0.024$), the AIS of different regions did not differ between the phenotype (Table 1). Hyperfibrinolysis patients had a lower admission ED-SBP ($p<0.001$) and lower Glasgow Coma Scale (GCS, $p<0.001$). Advanced age was associated with higher incidence of fibrinolysis shutdown phenotype and a lower frequency of physiologic fibrinolysis ($p<0.001$). Hyperfibrinolytic patients more frequently had penetrating wounds (23% vs 19% PY 14%SD $P<0.001$).

Predictors of fibrinolysis phenotypes

Laboratory and specific TEG variables between fibrinolysis types are depicted in table 2. The physiologic group had a lower median INR ($p<0.001$), shorter ACT ($p<0.001$), higher angle ($p<0.001$), and MA ($p<0.001$) compared to other phenotypes. The shutdown cohort had a lower platelet count ($p<0.001$). The hyperfibrinolytic phenotype had a lower hematocrit ($p<0.001$), and required more blood products (Table 2). The proportion of patients with a coagulopathy defined as an INR > 1.3 was higher in the hyper (32%) and shutdown group (28%) compared to physiologic (18% $p<0.001$). The hyperfibrinolytic phenotype had a nearly triple the rate of massive transfusion (14%) compared to the physiologic (5%) and shutdown types (5% $p<0.001$). In the polytomous logistic regression model, shutdown was associated with male gender ($p=0.024$) and advanced age ($p<0.001$) while the hyperfibrinolytic phenotype was associated with lower ED-SBP ($p=0.001$), penetrating (vs. blunt) mechanism ($p=0.036$) and higher ISS ($p=0.005$). Model performance as indicated by the Deviance ($p=0.46$) and Pearson goodness-of-fit statistic ($p=0.45$) was good.

Fibrinolysis and outcomes

There were 543 deaths (21%). Overall crude mortality was 34% for hyperfibrinolysis, 14% for physiologic fibrinolysis, and 23% for fibrinolysis shutdown (Figure 1 $p<0.001$). While the mortality rate in the shutdown group was lower than hyperfibrinolysis, because it was such a frequent phenotype, it represented 48% of all deaths. The risk of mortality remained increased for hyperfibrinolysis (OR=3.3, 95%CI: 2.4-4.6, $p<0.0001$) and shutdown (OR 1.6 95%CI 1.3-2.1, $p=0.0003$) compared to physiologic when adjusting for age, ISS, blunt vs. penetrating mechanism, ED-SBP lower than 70mmHg, AIS-Head (AUROC=0.82, 95% CI 0.80-0.84).

The Kaplan Meier curves for the three phenotypes are shown in figure 2. The difference between strata was significant (Log-Rank test $p<0.0001$; Wilcoxon test $p<0.0001$). Survival analysis of the different phenotypes demonstrated a survival advantage of physiologic

compared to hyperfibrinolysis (Hazard Ratio, HR:1.27 95% CI 1.13 -1.42 $p<0.0001$) and shutdown (HR 1.10 95% CI 1.01-1.20). Adjustment for mechanism, systolic blood pressure, and severe head injury did not alter this relationship. However, when adjusting for age, there was a loss of survival benefit between physiologic and shutdown. There was no survival advantage in the first 24 hours with fibrinolysis shutdown versus physiologic.

Fibrinolysis and cause of death

The most common cause of death regardless of fibrinolysis phenotype was traumatic brain injury (TBI, 67%) followed by hemorrhage (17%) and organ failure (11%). The cause of mortality significantly differed by phenotype (Figure 3) $p<0.001$). The proportions of deaths due to TBI were 58%, 71%, and 70%, for hyperfibrinolysis, physiologic and shutdown, respectively. Death from hemorrhage was 30%, 14%, and 10% and organ failure 7%, 11% and 14% for hyperfibrinolysis, physiologic and shutdown.

Discussion

The spectrum of postinjury fibrinolysis was first described in 2014(9). The findings from this early study limited to 180 patients using kTEG, has now been validated in a study population of over 2,500 severely injured patients with rTEG. The prevalence of the three phenotypes of fibrinolysis are similar between both studies with fibrinolysis shutdown the most frequent. This study is consistent with earlier reports on hyperfibrinolysis detected by TEG, in that this phenotype is less frequent and associated with mortality from hemorrhage(5, 6, 18). Appreciation of the U shaped association with LY30 and mortality is of clinical significance as the physiologic levels of fibrinolysis have a survival benefit. These findings may help explain the recent retrospective studies in the United States(16, 17) that do not identify a survival benefit in using tranexamic acid as proposed by the CRASH II trial(19) and MATTERS studies(20, 21). The optimal use of antifibrinolytics is likely in a targeted population. A recent civilian study from England demonstrated that only severely injured patients in shock had a survival benefit with TXA, with a reduction in mortality from 15% to 11%(22). While we await the results of additional prospective clinical trials, the use of empiric antifibrinolytics in trauma patients should be selective.

A critical component to optimizing early trauma resuscitation is understanding the mechanism which drive derangements in the coagulation system. Hyperfibrinolysis diagnosed by TEG is associated with increased levels of tissue plasminogen activator(14, 15). While hemorrhagic shock does not uniformly provoke systemic hyperfibrinolysis in trauma patients, examples from non-surgical patients suggests that inadequate tissue perfusion is a common feature of this phenotype(13, 23). Coagulopathy from malperfusion in non trauma patients also appears to be driven by tPA rather than protein C(23). This is supported by animal work demonstrating tPA release is driven by shock and not tissue injury(12). Original work on trauma-induced coagulopathy hypothesized that both tissue injury and shock were necessary for driving this process (24), which appeared to be validated in an animal model(25). However, with the emergence of unique phenotypes of TIC(26) in the context that alteration in clot formation does not correlate with alteration in

clot degradation (3, 4), implications of coagulation abnormalities beyond protein C is evident.

Hypercoagulability is prevalent in trauma patients(2) and suggests why inhibition of fibrinolysis has pathologic consequences(9). However, it remains to be identified what drives the hypocoagulability and fibrinolysis shutdown after trauma. Recent work in sepsis indicated that cell free DNA contributes to fibrinolysis resistance(27). These DNA fragments, which co-localize to histones, have been proposed to be drivers of microvascular thrombosis in septic shock(28). Animal models have suggested that tissue injury in the absence of shock promotes a hypercoagulable state(29) and fibrinolysis resistance(12). However, this translation to the human scenario remains a challenge as most patients have variable combinations of tissue injury and shock. TEG detected coagulopathy in a heterogeneous mix of trauma patients does not appear to correlate with anatomic injury severity score(30). Our study also failed to identify a specific injury pattern associated with any of the fibrinolytic phenotypes.

Trauma induced coagulopathy cannot be adequately assessed from an isolated coagulation measurement. This complex process involves numerous factors including the endothelium(31), glycocalyx(32), damage associated proteins(33), platelets(34), tissue factor(35), fibrinogen (36), and even metabolites(37, 38). With emerging data that fibrinolysis resistance is also a pathologic response to trauma(9), additional mechanisms will likely be identified in the future. Plasma contains numerous proteins that directly alter the effect fibrinolytic activity in response to an acute release of tPA, including alpha 2 macroglobulin, C1-Inhibitor, and alpha 2 anti-plasmin (39). In addition, platelets can release stored fibrinolysis inhibitors and clot stabilizers (40, 41). In current clinical practice, early empiric plasma resuscitation appears to be a rationale approach for hypotensive trauma patients as it is a buffer of fibrinolysis(42). Animal models have shown that plasma attenuates hemorrhagic shock induced hyperfibrinolysis (43) and reduces post resuscitation hypercoagulability(44). Ultimately, the debate on the optimal ratios of blood components for initial resuscitation has not become as critical as the timing of early plasma administration. In the PROPPR trial it was clear that time to plasma was associated with improved survival(45).

This study was limited to one time point prior to a trauma patient's resuscitation in the hospital. It is probable that the patient's initial fibrinolysis phenotype will change during the course of their resuscitation as there is a high prevalence of fibrinolysis resistance in the trauma intensive care unit(46). The relationship between initial fibrinolysis phenotype and progression to the hypercoagulable state after resuscitation is essential to further understanding this process. This study was limited to mortality related outcomes and does not necessarily predict that a patient will not develop organ dysfunction during their hospitalization. There also may be a genetic predisposition to developing each of these phenotypes. Polymorphisms of the PAI-1 gene have been associated with bleeding complications during cardiac surgery(47) and thrombotic complications predicting poor outcomes after myocardial infarct(48). We also appreciated an increase in age was associated with an increase in the fibrinolysis shutdown phenotype. PAI-1 levels have been associated with physiologic aging and disease processes(49). It remains unclear if these

elderly patients do poorly following trauma because they are predisposed to fibrinolysis resistance, or from other physiologic derangements from advanced aged.

In conclusion, severely injured trauma patients present with a spectrum of post injury fibrinolysis. The pathologic extremes of this coagulation process predict the cause and timing of mortality, which can be assessed within 60 minutes of the patient initial blood draw using r TEG. Appreciation that fibrinolysis shutdown is the most common phenotype after severe injury warrants careful re-consideration of the empiric use of antifibrinolytic in trauma, and suggests a mechanism for the failure to document improved survival with the use of tranexamic acid in recent studies.

Acknowledgments

Support: This study was supported in part by National Institute of General Medical Sciences grants T32-GM008315 and P50-GM49222, and by National Heart, Lung, and Blood Institute grant UM1 HL120877. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIGMS, or National Institutes of Health.

References

1. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma*. 2003; 54:1127–1130. [PubMed: 12813333]
2. Schreiber MA, Differding J, Thorborg P, et al. Hypercoagulability is most prevalent early after injury and in female patients. *J Trauma*. 2005; 58:475–480. discussion 480–481. [PubMed: 15761339]
3. Kutcher ME, Ferguson AR, Cohen MJ. A principal component analysis of coagulation after trauma. *J Trauma Acute Care Surg*. 2013; 74:1223–1229. discussion 1229–1230. [PubMed: 23609271]
4. Chin TL, Moore EE, Moore HB, et al. A principal component analysis of postinjury viscoelastic assays: Clotting factor depletion versus fibrinolysis. *Surgery*. 2014; 156:570–577. [PubMed: 24962188]
5. Cotton BA, Harvin JA, Kostousouv V, et al. Hyperfibrinolysis at admission is an uncommon but highly lethal event associated with shock and prehospital fluid administration. *J Trauma Acute Care Surg*. 2012; 73:365–370. discussion 370. [PubMed: 22846941]
6. Ives C, Inaba K, Branco BC, et al. Hyperfibrinolysis elicited via thromboelastography predicts mortality in trauma. *J Am Coll Surg*. 2012; 215:496–502. [PubMed: 22766227]
7. Schochl H, Frietsch T, Pavelka M, Jambor C. Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. *J Trauma*. 2009; 67:125–131. [PubMed: 19590321]
8. Chapman MP, Moore EE, Ramos CR, et al. Fibrinolysis greater than 3% is the critical value for initiation of antifibrinolytic therapy. *J Trauma Acute Care Surg*. 2013; 75:961–967. [PubMed: 24256667]
9. Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg*. 2014; 77:811–817. discussion 817. [PubMed: 25051384]
10. Hardaway RM. The significance of coagulative and thrombotic changes after haemorrhage and injury. *J Clin Pathol Supplement*. 1970; 4:110–120.
11. Fearnley GR. Fibrinolysis. *Ann Royal Coll Surg Engl*. 1967; 41:51–54.
12. Moore HB, Moore EE, Lawson PJ, et al. Fibrinolysis shutdown phenotype masks changes in rodent coagulation in tissue injury versus hemorrhagic shock. *Surgery*. 2015; 158:386–392. [PubMed: 25979440]
13. Schochl H, Cadamuro J, Seidl S, et al. Hyperfibrinolysis is common in out-of-hospital cardiac arrest: results from a prospective observational thromboelastometry study. *Resuscitation*. 2013; 84:454–459. [PubMed: 22922072]

14. Cardenas JC, Matijevic N, Baer LA, et al. Elevated tissue plasminogen activator and reduced plasminogen activator inhibitor promote hyperfibrinolysis in trauma patients. *Shock*. 2014; 41:514–521. [PubMed: 24667610]
15. Chapman MC, Gonzalez E, Moore HB, et al. Overwhelming tPA release, not PAI-1 degradation, is responsible for hyperfibrinolysis in massively transfused trauma patients. *J Trauma Acute Care Surg*. 2015 in press.
16. Valle EJ, Allen CJ, Van Haren RM, et al. Do all trauma patients benefit from tranexamic acid? *J Trauma Acute Care Surg*. 2014; 76:1373–1378. [PubMed: 24854303]
17. Harvin JA, Peirce CA, Mims MM, et al. The impact of tranexamic acid on mortality in injured patients with hyperfibrinolysis. *J Trauma Acute Care Surg*. 2015; 78:905–911. [PubMed: 25909408]
18. Chapman MP, Moore EE, Ramos CR, et al. Fibrinolysis greater than 3% is the critical value for initiation of antifibrinolytic therapy. *J Trauma Acute Care Surg*. 2013; 75:961–967. discussion 967. [PubMed: 24256667]
19. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technology Assessment*. 2013; 17:1–79.
20. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg*. 2012; 147:113–119. [PubMed: 22006852]
21. Morrison JJ, Ross JD, Dubose JJ, et al. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERs II Study. *JAMA Surg*. 2013; 148:218–225. [PubMed: 23670117]
22. Cole E, Davenport R, Willett K, Brohi K. Tranexamic acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. *Ann Surg*. 2015; 261:390–394. [PubMed: 25412319]
23. Duvekot A, Viersen VA, Dekker SE, et al. Low Cerebral oxygenation levels during resuscitation in out-of-hospital cardiac arrest are associated with hyperfibrinolysis. *Anesthesiology*. 2015; 123:820–829. [PubMed: 26263429]
24. Brohi K, Cohen MJ, Ganter MT, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *J Trauma*. 2008; 64:1211–1217. discussion 1217. [PubMed: 18469643]
25. Chesebro BB, Rahn P, Carles M, et al. Increase in activated protein C mediates acute traumatic coagulopathy in mice. *Shock*. 2009; 32:659–665. [PubMed: 19333141]
26. White NJ, Contaiter D Jr, Martin EJ, et al. Early hemostatic responses to trauma identified with hierarchical clustering analysis. *J Thrombosis Haemostasis*. 2015; 13:978–988.
27. Gould TJ, Vu TT, Stafford AR, et al. Cell-free DNA modulates clot structure and impairs fibrinolysis in sepsis. *Arteriosclerosis Thrombosis Vascular Biology*. 2015; 35:2544–2553.
28. Gould TJ, Lysov Z, Liaw PC. Extracellular DNA and histones: double-edged swords in immunothrombosis. *J Thrombosis Haemostasis*. 2015; 13:S82–91.
29. Prat NJ, Montgomery R, Cap AP, et al. Comprehensive evaluation of coagulation in swine subjected to isolated primary blast injury. *Shock*. 2015; 43:598–603. [PubMed: 25643012]
30. Lee TH, Hampton DA, Diggs BS, et al. Traumatic brain injury is not associated with coagulopathy out of proportion to injury in other body regions. *J Trauma Acute Care Surg*. 2014; 77:67–72. discussion. [PubMed: 24977757]
31. Johansson PI, Sorensen AM, Perner A, et al. High sCD40L levels early after trauma are associated with enhanced shock, sympathoadrenal activation, tissue and endothelial damage, coagulopathy and mortality. *J Thrombosis Haemostasis*. 2012; 10:207–216.
32. Ostrowski SR, Johansson PI. Endothelial glycocalyx degradation induces endogenous heparinization in patients with severe injury and early traumatic coagulopathy. *J Trauma Acute Care Surg*. 2012; 73:60–66. [PubMed: 22743373]

33. Cohen MJ, Brohi K, Calfee CS, et al. Early release of high mobility group box nuclear protein 1 after severe trauma in humans: role of injury severity and tissue hypoperfusion. *Critical Care*. 2009; 13:R174. [PubMed: 19887013]
34. Wohlaer MV, Moore EE, Thomas S, et al. Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. *J Am Coll Surg*. 2012; 214:739–746. [PubMed: 22520693]
35. Howard BM, Miyazawa BY, Dong W, et al. The tissue factor pathway mediates both activation of coagulation and coagulopathy after injury. *J Trauma Acute Care Surg*. Aug 28.2015
36. Inaba K, Karamanos E, Lustenberger T, et al. Impact of fibrinogen levels on outcomes after acute injury in patients requiring a massive transfusion. *J Am Coll Surg*. 2013; 216:290–297. [PubMed: 23211116]
37. Wiener G, Moore HB, Moore EE, et al. Shock releases bile acid inducing platelet inhibition and fibrinolysis. *J Surg Res*. Jan 29.2015
38. Moore HB, Moore EE, Chapman MP, et al. Viscoelastic measurements of platelet function, not fibrinogen function, predicts sensitivity to tissue-type plasminogen activator in trauma patients. *J Thrombosis Haemostasis*. 2015; 13:1878–1887.
39. Bennett B, Croll A, Ferguson K, Booth NA. Complexing of tissue plasminogen activator with PAI-1, alpha 2-macroglobulin, and C1-inhibitor: studies in patients with defibrination and a fibrinolytic state after electroshock or complicated labor. *Blood*. 1990; 75:671–676. [PubMed: 1688722]
40. Declerck PJ, Alessi MC, Verstreken M, et al. Measurement of plasminogen activator inhibitor 1 in biologic fluids with a murine monoclonal antibody-based enzyme-linked immunosorbent assay. *Blood*. 1988; 71:220–225. [PubMed: 3257145]
41. Booth NA, Simpson AJ, Croll A, et al. Plasminogen activator inhibitor (PAI-1) in plasma and platelets. *Br J Haematol*. 1988; 70:327–333. [PubMed: 3264718]
42. Moore HB, Moore EE, Gonzalez E, et al. Plasma is the physiologic buffer of tissue plasminogen activator-mediated fibrinolysis: rationale for plasma-first resuscitation after life-threatening hemorrhage. *J Am Coll Surg*. Mar 31.2015
43. Moore HB, Moore EE, Morton AP, et al. Shock-induced systemic hyperfibrinolysis is attenuated by plasma-first resuscitation. *J Trauma Acute Care Surg*. 2015; 79:897–904. [PubMed: 26680132]
44. Cardenas JC, Cap AP, Swartz MD, et al. Plasma resuscitation promotes coagulation homeostasis following shock-induced hypercoagulability. *Shock*. Oct 12.2015
45. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015; 313:471–482. [PubMed: 25647203]
46. Gonzalez E ME, Moore HB, Pieracci FC, et al. Is fibrinolysis shutdown the missing link leading to post-injury hypercoagulability. *J Am Coll Surg*. 2014; 219:S47.
47. Ozolina A, Strike E, Nikitina-Zake L, et al. Polymorphisms on PAI-1 and ACE genes in association with fibrinolytic bleeding after on-pump cardiac surgery. *BMC Anesthesiol*. 2015; 15:122. [PubMed: 26340801]
48. Ye Z, Liu EH, Higgins JP, et al. Seven haemostatic gene polymorphisms in coronary disease: meta-analysis of 66,155 cases and 91,307 controls. *Lancet*. 2006; 367:651–658. [PubMed: 16503463]
49. Eren M, Boe AE, Klyachko EA, Vaughan DE. Role of plasminogen activator inhibitor-1 in senescence and aging. *Sem Thrombosis Hemostasis*. 2014; 40:645–651.

Figure 1.
Incidence and mortality of severely injured trauma patients stratified by fibrinolysis phenotype.

Figure 2. Survival time differences between fibrinolysis phenotypes. (A) Overall in-hospital survival; (B) a focused segment of the first 72 hours of survival after injury. Patients are stratified by fibrinolysis phenotype and vertical bars represent 95% confidence intervals. Hyper, hyperfibrinolysis; Phy, physiologic; SD, shutdown; Fib, fibrinolysis.

Figure 3.
Differences in causes of mortality between phenotypes.

Table 1

Physiologic and Clinical Variables of Fibrinolysis Phenotypes

Variable	Shutdown	Physiologic	Hyper	p Value *
Age, y	43 (28-58)	35 (24-50)	34 (25-53)	<0.001
SBP, mm HG	119 (95-140)	118 (96-138)	110 (87-132)	<0.001
HR, Beats pre min	98 (80-117)	97 (78-117)	100 (80-119)	0.325
GCS	3 (3-15)	10 (3-15)	3 (3-15)	<0.0001
ISS	25 (21-30)	25 (19-30)	26 (20-34)	0.024
AIS Head	3 (0-4)	3 (0-4)	3 (0-4)	0.091
AIS Chest	3 (0-3)	3 (0-3)	2 (0-3)	0.771
AIS ABDPel	0 (0-3)	0 (0-3)	0 (0-3)	0.671
AIS ExT	2 (0-3)	2 (0-3)	2 (0-3)	0.857

Each variable is displayed as the group median with brackets surrounding the 25th and 75th percentile.

SBP, systolic blood pressure on arrival to emergency department; HR, heart rate on arrival to the emergency department; GCS, Glasgow coma score on arrival to emergency department; ISS, injury severity score; AIS, abbreviated injury severity score; ABDPel, abdomen or pelvis; Ext, extremity

*p Values represent Kruskal-Wallis overall comparison between groups.

Table 2

Laboratory Variables Contrasted Between Fibrinolysis Phenotypes and Associated Resuscitation over the First 6 Hours after Injury

Variable	Shutdown	Physiologic	Hyper	p Value *
Hgb, grams per deciliter	13 (12-14)	13 (12-15)	13 (11-14)	<0.001
Plt Count, 10 ³ /microliter	215 (165-261)	240 (194-288)	223 (173-277)	<0.001
INR	1.15 (1.05-1.33)	1.10 (1.03-1.24)	1.16 (1.05-1.4)	<0.001
ACT, seconds	121 (105-128)	113 (105-128)	121 (113-136)	<0.001
ANGLE, degrees	72 (68-76)	73 (69-76)	72 (66-75)	<0.001
MA, mm	63 (58-67)	64 (60-68)	61 (54-66)	<0.001
LY30, percent	0.1 (0-0.4)	1.6 (1.1-2.2)	4.9 (3.6-10.8)	<0.001
Crystalloid, mL	500 (0-1800)	700 (0-2000)	500 (0-2000)	0.208
RBC, units	0 (0-3)	0 (0-2)	1 (0-5)	<0.001
FFP, units	0 (0-0)	0 (0-3)	1 (0-5)	<0.001
PLT, units	0 (0-0)	0 (0-0)	0 (0-1)	<0.001
Cryo, units	0 (0-0)	0 (0-0)	0 (0-0)	<0.001

Each variable is displayed as the group median with brackets surrounding the 25th and 75th percentile.

Hgb, hemoglobin; Plt Count, Platelet count in 100,000; INR, international normalized ratio; ACT, thrombelastography activated clotting time; MA, maximum amplitude; LY30, the percent lysis at 30 minutes after the clot has reached maximum strength; Crystalloid, amount of crystalloid resuscitation in milliliters in first 6 hours; RBC, units of red blood cells transfused in first 6 hours; FFP, units of plasma transfused in first 6 hours; PLT, units of platelet transfused in first 6 hours; Cryo, units of cryoprecipitate transfused in first 6 hours

* p Values represent Kruskal-Wallis overall comparison between groups.