SOUTHERN SURGICAL ASSOCIATION ARTICLE

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

Hunter B Moore, MD, Ernest E Moore, MD, FACS, Ioannis N Liras, MD, Eduardo Gonzalez, MD, John A Harvin, FACS, MD, John B Holcomb, MD, FACS, Angela Sauaia, MD, PhD, Bryan A Cotton, MD, MPH, FACS

**BACKGROUND:** Fibrinolysis is a physiologic process that maintains microvascular patency by breaking down excessive fibrin clot. Hyperfibrinolysis is associated with a doubling of mortality. Fibrinolysis shutdown, 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 2 urban trauma centers.

**STUDY DESIGN:** Injured patients included in the analysis were admitted between 2010 and 2013, were 18 years of age or older, and had an Injury Severity Score (ISS) $>$ 15. Admission fibrinolysis phenotypes were determined by the clot lysis at 30 minutes (LY30): shutdown $\leq$ 0.8%, physiologic 0.9% to 2.9%, and hyperfibrinolysis $\geq$ 3%. Logistic regression was used to adjust for age, arrival blood pressure, ISS, mechanism, and facility.

**RESULTS:** There were 2,540 patients who met inclusion criteria. Median age was 39 years (interquartile range [IQR] 26 to 55 years) and median ISS was 25 (IQR 20 to 33), with a mortality rate of 21%. Fibrinolysis shutdown was the most common phenotype (46%) followed by physiologic (36%) and hyperfibrinolysis (18%). Hyperfibrinolysis was associated with the highest death rate (34%), followed by shutdown (22%), and physiologic (14%, $p < 0.001$). The risk of mortality remained increased for hyperfibrinolysis (odds ratio [OR] 3.3, 95% CI 2.4 to 4.6, $p < 0.0001$) and shutdown (OR 1.6, 95% CI 1.3 to 2.1, $p = 0.0003$) compared with physiologic when adjusting for age, ISS, mechanism, head injury, and blood pressure (area under the receiver operating characteristics curve 0.82, 95% CI 0.80 to 0.84).

**CONCLUSIONS:** Fibrinolysis shutdown is the most common phenotype on admission and is associated with increased mortality. These data provide additional evidence of distinct phenotypes of coagulation impairment and that individualized hemostatic therapy may be required. (J Am Coll Surg 2016;■:1−9. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

One in 3 severely injured trauma patients will have early evidence of impaired coagulation, which is associated with a 4-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 mechanisms.[3,4] Excessive clot degradation (hyperfibrinolysis) is associated with mortality rates that range from 40% to 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

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From the Departments of Surgery, University of Colorado Denver/Denver Health Medical Center, Denver, CO (H Moore, E Moore, Gonzalez, Sauaia) and the University of Texas Health Science Center at Houston/Memorial Hermann, Houston, TX (Liras, Harvin, Holcomb, Cotton).

Correspondence address: Hunter B Moore, MD, 655 Broadway, Suite 365, Denver, CO 80203. email: hunter.moore@ucdenver.edu





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**Abbreviations and Acronyms**

AIS = Abbreviated Injury Score
ED = emergency department
IQR = interquartile range
ISS = Injury Severity Score
LY30 = clot lysis at 30 minutes
OR = odds ratio
TEG = thromboelastography
tPA = tissue plasminogen

inhibition of fibrinolysis results in microvascular 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 nontrauma patients undergoing prehospital cardiopulmonary resuscitation[13] as well as in severely injured patients with profound hypotension at presentation to the hospital.[9] Although the molecular mechanism driving hyperfibrinolysis appears to be related to upregulation of tissue plasminogen activator (tPA) and depletion of its inhibitors,[14,15] few translational clinical data support 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 because empiric administration of antifibrinolytics to trauma patients may have adverse events in patients resistant to tPA. To date, 2 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 thromboelastography (TEG). Kaolin TEG is not used early during trauma resuscitations due to time delay in obtaining clotting measurements; this process can be expedited by adding tissue factor used in a rapid TEG. Consequently, our study had 3 major objectives: to determine the fibrinolysis spectrum using rapid TEG in a large, bi-institutional cohort of severely injured patients; to determine independent predictors of the 3 fibrinolysis phenotypes; and to determine the independent effect of the fibrinolysis phenotypes on post-injury outcomes.

## METHODS

Included in this study were acutely injured trauma patients enrolled in studies under IRB-approved protocols from 2012 to 2014 at the University of Colorado Denver/Denver Health Medical Center and the University of Texas Houston/Memorial Hermann. Patients meeting trauma activation criteria were included if they had an Injury Severity Score (ISS) > 15, were directly transferred from the injury scene to the emergency department, and had a rapid TEG drawn within 1 hour after injury. Patients taking anticoagulant medication including warfarin or direct factor inhibitors were excluded from the study. In addition, patients who received antifibrinolytics before rapid TEG were excluded.

Patient demographics, injury patterns, and blood product use were 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 ≥10 units of red blood cells within 6 hours post-injury).

Trained professional research assistants assayed blood with the TEG 5000 Hemostatic Analyzer (Haemonetics). Blood was obtained in 2.7-mL citrated tubes (Vacutainer, Becton-Dickinson) and assayed after recalcification within 2 hours of blood draw according to manufacturer's recommendations. The following measurements were recorded: thromboelastography-activated clotting time (T-ACT, seconds), angle ($\alpha$, degrees), maximum amplitude (MA, mm), and lysis 30 minutes after maximum amplitude (LY30, %).

Patients were categorized according to their admission fibrinolysis phenotypes, as determined by their rapid TEG 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.[5,8,9]

Statistical analysis was performed using SAS 9.4 for Windows (SAS Institute Inc). Normally distributed data were described as mean and standard deviation, and non-normally distributed data were described as the median value with the 25$^{th}$ to 75$^{th}$ 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 3-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 model 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. This model's performance was assessed using the area under the receiver operating characteristics curve with 95% confidence intervals (CI), and variable association was expressed as odds ratios (ORs) with 95% CI.

## RESULTS

There were 2,540 patients in the analysis, 21% of whom did not survive. Median age was 39 years (IQR 26 to 55 years) and median ISS was 25 (IQR 20 to 33). Fibrinolysis shutdown was the most common phenotype (46%), followed by physiologic (36%) and hyperfibrinolysis (18%). Although the hyperfibrinolytic phenotype was associated with a slightly higher overall ISS ($p = 0.024$), the AIS of different regions did not differ between the phenotypes (Table 1). Hyperfibrinolysis patients had a lower admission ED systolic blood pressure ($p < 0.001$) and lower Glasgow Coma Scale ($p < 0.001$). 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% physiologic, 14% shutdown; $p < 0.001$).

### Predictors of fibrinolysis phenotypes

Laboratory and specific TEG variables between fibrinolysis types are depicted in Table 2. The physiologic group had a lower median international normalized ratio ($p < 0.001$), shorter activated clotting time ($p < 0.001$), higher angle ($p < 0.001$), and maximum amplitude ($p < 0.001$) compared with 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 international normalized ratio $> 1.3$ was higher in the hyperfibrinolysis (32%) and shutdown groups (28%) compared with the physiologic group (18%, $p < 0.001$). The hyperfibrinolytic phenotype had nearly triple the rate of massive transfusion (14%) compared with the physiologic (5%) and shutdown types (5% $p < 0.001$). In the polytomous logistic regression model, shutdown was associated with male sex ($p = 0.024$) and advanced age ($p < 0.001$); the hyperfibrinolytic phenotype was associated with lower ED systolic blood pressure ($p = 0.001$), 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 (Fig. 1, $p < 0.001$). Although the mortality rate in the shutdown group was lower than in the hyperfibrinolysis group 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 to 4.6, $p < 0.0001$) and shutdown (OR 1.6, 95% CI 1.3 to 2.1, $p = 0.0003$) compared with physiologic fibrinolysis when adjusting for age, ISS, blunt vs penetrating mechanism, ED systolic blood pressure lower than

**Table 1.** Physiologic and Clinical Variables of Fibrinolysis Phenotypes

| | Fibrinolysis phenotypes | | | |
|---|---|---|---|---|
| **Variable** | **Shutdown** | **Physiologic** | **Hyper** | **p Value*** |
| Age, y | 43 (28–58) | 35 (24–50) | 34 (25–53) | <0.001 |
| SBP, mmHg | 119 (95–140) | 118 (96–138) | 110 (87–132) | <0.001 |
| HR, beats per 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 percentiles.
*p Values represent Kruskal-Wallis overall comparison between groups.
ABDPel, abdomen or pelvis; AIS, Abbreviated Injury Severity Score; Ext, extremity; GCS, Glasgow Coma Scale on arrival at emergency department; HR, heart rate on arrival at the emergency department; ISS, Injury Severity Score; SBP, systolic blood pressure on arrival at emergency department.

**Table 2.** Laboratory Variables Contrasted Between Fibrinolysis Phenotypes and Associated Resuscitation over the First 6 Hours after Injury

| | Fibrinolysis phenotypes | | | |
|---|---|---|---|---|
| **Variable** | **Shutdown** | **Physiologic** | **Hyper** | **p Value*** |
| Hgb, g/dL | 13 (12–14) | 13 (12–15) | 13 (11–14) | <0.001 |
| Plt count, $10^3$/μL | 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, % | 0.1 (0–0.4) | 1.6 (1.1–2.2) | 4.9 (3.6–10.8) | <0.001 |
| Crystalloid, mL | 500 (0–1,800) | 700 (0–2,000) | 500 (0–2,000) | 0.208 |
| RBC, U | 0 (0–3) | 0 (0–2) | 1 (0–5) | <0.001 |
| FFP, U | 0 (0–0) | 0 (0–3) | 1 (0–5) | <0.001 |
| PLT, U | 0 (0–0) | 0 (0–0) | 0 (0–1) | <0.001 |
| Cryo, U | 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 percentiles.
*p Values represent Kruskal-Wallis overall comparison between groups.
ACT, thromboelastography activated clotting time; Cryo, units of cryoprecipitate transfused in first 6 hours; Crystalloid, amount of crystalloid resuscitation in milliliters in first 6 hours; FFP, units of fresh frozen plasma transfused in first 6 hours; Hgb, hemoglobin; INR, international normalized ratio; LY30, the percent lysis at 30 minutes after the clot has reached maximum strength; MA, maximum amplitude; PLT, units of platelet transfused in first 6 hours; Plt count, platelet count in 100,000; RBC, units of red blood cells transfused in first 6 hours.

70 mmHg, AIS-head (area under the receiver operating characteristic curve 0.82, 95% CI 0.80 to 0.84).

Kaplan-Meier curves for the 3 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 with hyperfibrinolysis (hazard ratio [HR] 1.27, 95% CI 1.13 to 1.42, $p < 0.0001$) and shutdown (HR 1.10, 95% CI 1.01 to 1.20). Adjustment for mechanism, systolic blood pressure, and severe head injury did not alter this relationship. However, when adjusting for

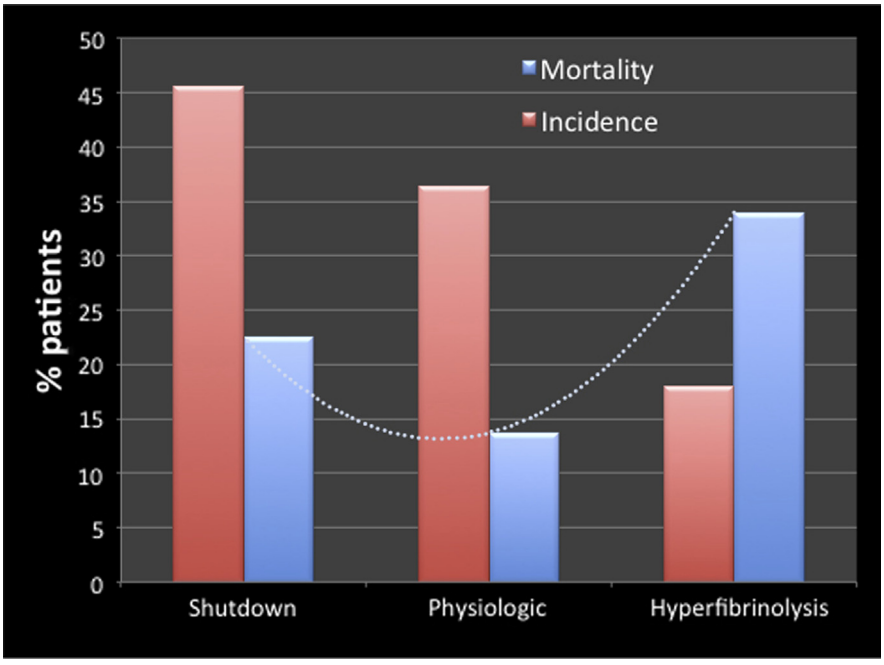


**Figure 1.** Incidence and mortality of severely injured trauma patients stratified by fibrinolysis phenotype.

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 vs physiologic.

### Fibrinolysis and cause of death

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

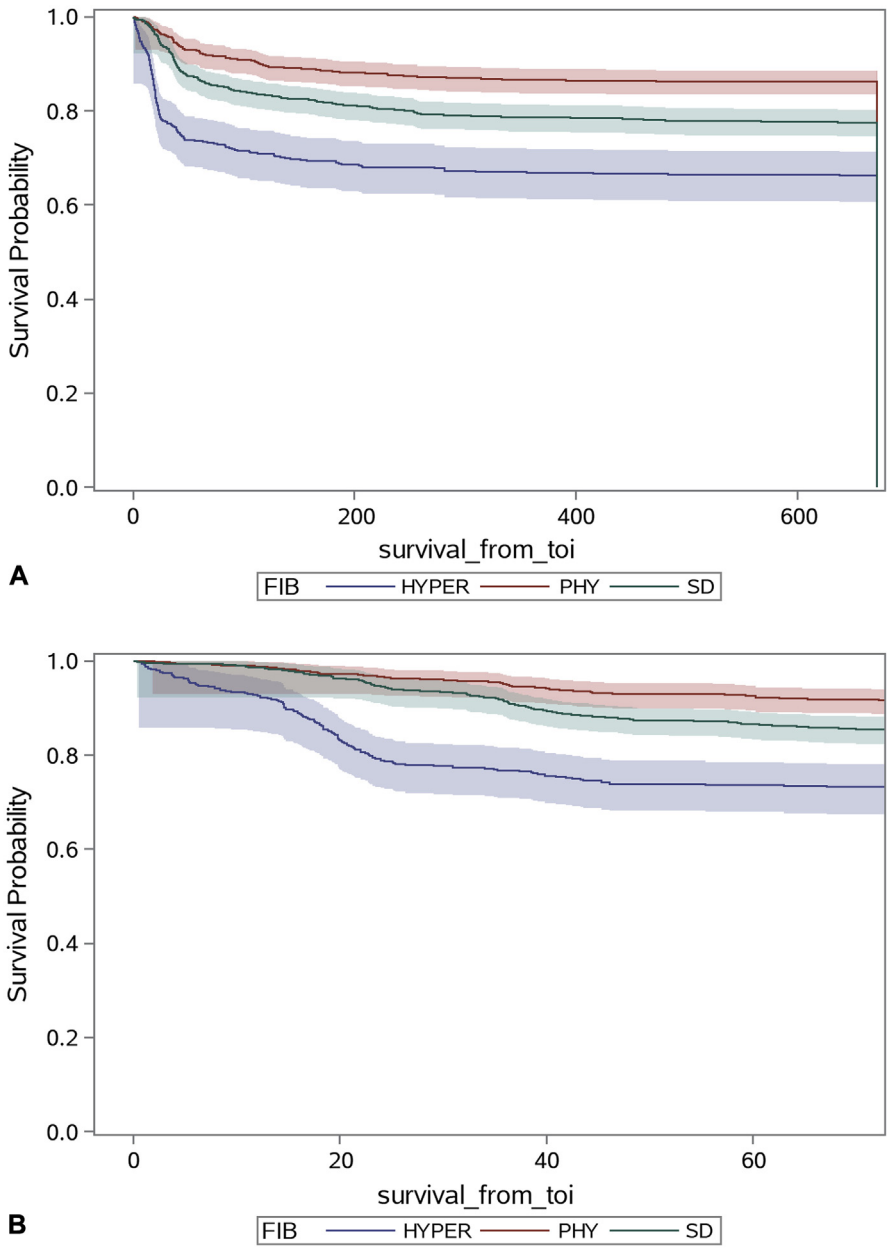


**Figure 2.** Survival time differences between fibrinolysis phenotypes. (A) Overall in-hospital survival; (B) a focused segment of the first 72 hours of survival after injury. Patients are stratified by fibrinolysis phenotype and vertical bars represent 95% CIs. Hyper, hyperfibrinolysis; Phy, physiologic;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

## DISCUSSION

The spectrum of post-injury fibrinolysis was first described in 2014.[9] The findings from this early study, limited to 180 patients using kaolin TEG, have now been validated with rapid TEG in a study population of more than 2,500 severely injured patients. The prevalence of the 3 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 is associated with mortality from hemorrhage.[5,6,8] Appreciation of the U-shaped association with LY30 and mortality is of clinical significance because 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[18] and MATTERs studies.[19,20] 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 tranexamic acid, with a reduction in mortality from 15% to 11%.[21] 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 mechanisms that drive derangements in the coagulation system. Hyperfibrinolysis diagnosed by TEG is associated with increased levels of tPA.[14,15] Although hemorrhagic shock does not uniformly provoke systemic hyperfibrinolysis in trauma patients, examples from nonsurgical patients suggest that inadequate tissue perfusion is a common feature of this phenotype.[13,22] Coagulopathy from malperfusion in nontrauma patients also appears to be driven by tPA rather than protein C.[22] This is supported by animal work demonstrating that 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 to drive this process,[23] which appeared to be validated in an animal model.[24] However, with the emergence of unique phenotypes of trauma-induced coagulopathy[25] 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 are evident.

Hypercoagulability is prevalent in trauma patients[2] and suggests why inhibition of fibrinolysis has pathologic consequences.[9] However, what drives the hypercoagulability and fibrinolysis shutdown after trauma remains to be identified. Recent work in sepsis indicated that cell free DNA contributes to fibrinolysis resistance.[26] These DNA fragments, which co-localize to histones, have been proposed to be drivers of microvascular thrombosis in septic shock.[27] Animal models have suggested that tissue injury in the absence of shock promotes a hypercoagulable state[28] and fibrinolysis resistance.[12] However, this translation to the human scenario remains a challenge because most patients have variable combinations of tissue injury and shock. Thromboelastography-detected

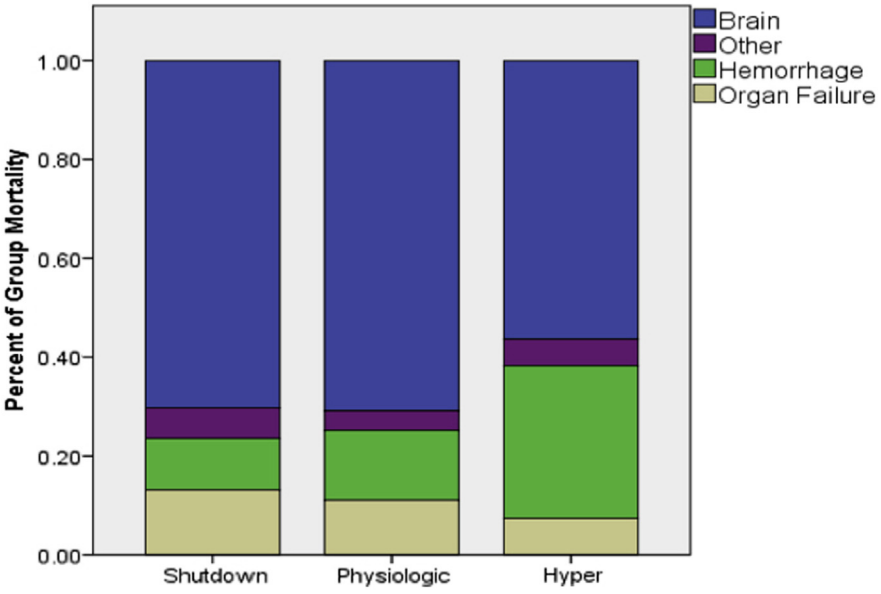


**Figure 3.** Differences in causes of mortality between phenotypes.

coagulopathy in a heterogeneous mix of trauma patients does not appear to correlate with anatomic ISS.[29] 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,[30] glycocalyx,[31] damage-associated proteins,[32] platelets,[33] tissue factor,[34] fibrinogen,[35] and even metabolites.[36,37] 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 of fibrinolytic activity in response to an acute release of tPA, including alpha 2 macroglobulin, C1-inhibitor, and alpha 2 anti-plasmin.[38] In addition, platelets can release stored fibrinolysis inhibitors and clot stabilizers.[39,40] In current clinical practice, early empiric plasma resuscitation appears to be a rational approach for hypotensive trauma patients because it is a buffer of fibrinolysis.[41] Animal models have shown that plasma attenuates hemorrhagic shock-induced hyperfibrinolysis[42] and reduces post-resuscitation hypercoagulability.[43] 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,[44] it was clear that time to plasma was associated with improved survival.

This study was limited to 1 time point before a trauma patient's resuscitation in the hospital. It is probable that the patient's initial fibrinolysis phenotype will change during the course of his or her resuscitation because there is a high prevalence of fibrinolysis resistance in the trauma ICU.[45] The relationship between initial fibrinolysis phenotype and progression to the hypercoagulable state after resuscitation is essential to further understand this process. This study was limited to mortality-related outcomes and does not necessarily predict that a patient will not develop organ dysfunction during his or her 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[46] and thrombotic complications, predicting poor outcomes after myocardial infarct.[47] We also appreciated that an increase in age was associated with an increase in the fibrinolysis shutdown phenotype. Levels of *PAI-1* have been associated with physiologic aging and disease processes.[48] It remains unclear if elderly patients do poorly after trauma because they are predisposed to fibrinolysis resistance, or from other physiologic derangements associated with advanced aged.

## CONCLUSIONS

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's initial blood draw using rapid TEG. Appreciation that fibrinolysis shutdown is the most common phenotype after severe injury warrants careful reconsideration of the empiric use of antifibrinolytics in trauma, and suggests a mechanism for the failure to document improved survival with the use of tranexamic acid in recent studies.

### Author Contributions

Study conception and design: HB Moore, EE Moore, Gonzalez, Holcomb, Sauaia, Cotton

Acquisition of data: HB Moore, Liras, Gonzalez, Harvin, Sauaia, Cotton

Analysis and interpretation of data: HB Moore, EE Moore, Liras, Gonzalez, Harvin, Holcomb, Sauaia, Cotton

Drafting of manuscript: HB Moore, EE Moore, Gonzalez, Sauaia, Cotton

Critical revision: HB Moore, EE Moore, Liras, Gonzalez, Harvin, Holcomb, Sauaia, Cotton

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