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

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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;222:347–355.

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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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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 $\geq$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 (α, 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 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