Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: The spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy

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Author Disclosures: Michael P. Chapman: research support (Haemonetics). Anirban Banerjee: research support (Haemonetics).

Reviewer Disclosures: The reviewers have nothing to disclose.

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Submitted: January 15, 2014, Revised: April 9, 2014, Accepted: April 28, 2014, Published online: July 21, 2014.

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This study was presented at the 44th Annual Meeting of the Western Trauma Association, March 3, 2014, in Steamboat Springs, Colorado, and at the Annual Meeting of the American College of Surgeons' Committee on Trauma (ACS COT), March 20, 2014, in Philadelphia, Pennsylvania. The first author (H.B.M.) received the Best Clinical Research Manuscript award in ACS COT's 2014 Resident Trauma Papers Competition.

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DOI: 10.1097/TA.0000000000000341

BACKGROUND: Fibrinolysis is a physiologic process maintaining patency of the microvasculature. Maladaptive overactivation of this essential function (hyperfibrinolysis) is proposed as a pathologic mechanism of trauma-induced coagulopathy. Conversely, the shutdown of fibrinolysis has also been observed as a pathologic phenomenon. We hypothesize that there is a level of fibrinolysis between these two extremes that have a survival benefit for the severely injured patients.

METHODS: Thrombelastography and clinical data were prospectively collected on trauma patients admitted to our Level I trauma center from 2010 to 2013. Patients with an Injury Severity Score (ISS) of 15 or greater were evaluated. The percentage of fibrinolysis at 30 minutes by thrombelastography was used to stratify three groups as follows: hyperfibrinolysis (≥3%), physiologic (0.081–2.9%), and shutdown (0–0.08%). The threshold for hyperfibrinolysis was based on existing literature. The remaining groups were established on a cutoff of 0.8%, determined by the highest point of specificity and sensitivity for mortality on a receiver operating characteristic curve.

RESULTS: One hundred eighty patients were included in the study. The median age was 42 years (interquartile range [IQR], 28–55 years), 70% were male, and 21% had penetrating injuries. The median ISS was 29 (IQR, 22–36), and the median base deficit was 9 mEq/L (IQR, 6–13 mEq/L). Distribution of fibrinolysis was as follows: shutdown, 64% (115 of 180); physiologic, 18% (32 of 180); and hyperfibrinolysis, 18% (33 of 180). Mortality rates were lower for the physiologic group (3%) compared with the hyperfibrinolysis (44%) and shutdown (17%) groups ($p = 0.001$).

CONCLUSION: We have identified a U-shaped distribution of death related to the fibrinolysis system in response to major trauma, with a nadir in mortality, with level of fibrinolysis after 30 minutes between 0.81% and 2.9%. Exogenous inhibition of the fibrinolysis system in severely injured patients requires careful selection, as it may have an adverse affect on survival. (*J Trauma Acute Care Surg*. 2014;77: 811–817. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Prognostic study, level III.

KEY WORDS: Fibrinolysis; fibrinolysis shutdown; hyperfibrinolysis; antifibrinolytic; severe trauma.

Fibrinolysis is the physiologic counterbalance of coagulation, functioning to maintain vasculature patency.[1] With historical accounts of bleeding dysfunction related to trauma[2] dating back to 1794 and a hundred-year gap before the identification of fibrinolysis,[3] it is apparent that this system is complex. A complete understanding of the regulation of the fibrinolytic system remains elusive. Pathologic hyperfibrinolysis, excessive fibrinolytic activity, was appreciated by Starzl et al.[4] in 1963 using thrombelastography (TEG) during the early operative phase of liver transplantation. In the original series of transplantation in humans, these authors recommended empiric antifibrinolytics to reduce bleeding. However, 6 years later, when evaluating the coagulopathy of liver transplantation, Starzl's group[5] retracted their statement advocating empiric antifibrinolytics when they appreciated increased mortality from venous thromboembolism (VTE).

As a result of the recent widespread use of TEG in trauma, hyperfibrinolysis has been identified in severely injured patients, and this has been proposed as integral in trauma-induced coagulopathy (TIC).[6,7] Acutely injured patients with severe hyperfibrinolysis (>15% fibrinolysis after 30 minutes [Ly30]) are reported to have mortality rates exceeding 70%.[8–10] These findings prompted the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial[11] to determine the potential benefit of empiric antifibrinolytic therapy in injured patients. While there was a statistical improvement in survival with antifibrinolytics, less than half of the patients received a blood transfusion, and there was no overall reduction in blood product transfusions between treatment and placebo groups.[11] Perhaps the most concerning finding was increased mortality if the antifibrinolytic was given 3 hours after injury.[12] Despite the unclear mechanistic link of antifibrinolytic therapy (presumed inhibition of plasminogen activation) to reduced mortality despite no impact on transfusion requirements, centers in the United Kingdom have advocated empiric use for all trauma patients requiring resuscitation.[13] Activated protein C–mediated TIC has been associated with fibrinolysis.[7] However, recent component analyses of patients with TIC have identified a phenotypic distinction between those with global factor deficiency versus those with hyperfibrinolysis,[14,15] questioning the mechanistic relationship.

On the other end of the spectrum is inhibition of fibrinolysis. During the 1960s, studies of coagulation following elective surgery identified the inhibition of fibrinolysis and termed this clinical phenomenon *shutdown*.[2,3] Fibrinolysis shutdown has been associated with orthopedic surgery, resulting in increasing risk for deep venous thrombosis[16] and increased sepsis-provoked multiple organ failure.[17] We have observed in swine and rodent models that hemorrhagic shock and tissue injury have opposite effects on systemic fibrinolysis; that is, ischemia provokes hyperfibrinolysis, while tissue disruption inhibits fibrinolysis. Interestingly, the middle ground between the extremes of fibrinolysis (i.e., the potential benefit of physiologic fibrinolysis) has received little attention. Collectively, these findings indicate what appears to be a spectrum of fibrinolysis. We hypothesize that tissue injury and hemorrhagic shock produce distinct and opposing phenotypic effects on fibrinolysis, that untimely inhibition or hyperactivation may result in increased mortality, and that, between the two, there is a survival benefit.

PATIENTS AND METHODS

Study Population

TEG and clinical data were prospectively collected on acutely injured patients admitted to our Level I trauma center (Denver Health Medical Center) from 2010 to 2013 under Colorado Multiple Institutional Review Board protocol number 10-0477. Patients were excluded from the analysis if they had an Injury Severity Score (ISS) of less than 15, if the first TEG was obtained more than 12 hours after injury, or if they had taken preinjury anticoagulant medication. Patient demographics, emergency department vital signs, and initial laboratory values were obtained from this prospective registry.

Blood product administration was prospectively recorded in the same registry. Cause of death was determined based on the hospital mortality and morbidity conference records as well as death certificate data.

Thrombelastography

Blood was collected from patients in 2.7-mL buffered sodium citrate (3.2%) sample tubes (Vacutainer, Becton-Dickinson, Franklin Lakes, NJ). The median time for blood sampling was 96 minutes after injury (interquartile range, 46–260 minutes). Samples were run within 2 hours of collection. Citrated Kaolin TEG assays were recalcified and ran according to the manufacturer's instructions on a TEG 5000 Thrombelastograph Hemostasis Analyzer (Haemonetics, Niles, IL). Fibrinolysis was evaluated based on the percentage of clot lysis at 30 minutes after the clot achieved maximum strength (Ly30).

Data Analysis

Ly30 was stratified into three groups as follows: hyperfibrinolysis (≥3%), physiologic (0.81–2.9%), and shutdown (0–0.8%). The 3% cutoff was based on previously published studies that demonstrated increased mortality and blood product consumption higher than this value.[9,18] Ly30 lower than this level has not received as much attention, and we were unable to find literature to support a threshold for fibrinolysis shutdown. Thus, to identify a potential threshold for fibrinolysis shutdown, a receiver operating characteristic curve for mortality was generated using the remaining patients with an Ly30 of less than 3% . The point with the highest specificity and sensitivity for mortality on the receiver operating characteristic curve was 0.8%, based on the Youden index.[19] This Ly30 value was used as our upper boundary for fibrinolysis shutdown. The remaining patients with an Ly30 greater than this range and less than 3% were categorized as physiologic. Massive transfusion (MT) was defined as administration of red blood cells (RBCs) greater than 10 U within 6 hours of injury.

Data analysis was performed using the SPSS Statistics 22 software (IBM Corp., Somers, NY). Significance was set at an α of 0.05 with a two-tailed distribution. The Kruskal-Wallis test was used for continuous variables; when the experiment-wise p value was significant, pairwise comparisons were performed; the pairwise comparison p value was adjusted using the Bonferroni method. The χ^2 test was used for categorical variables. The Fisher's exact test was used for categorical variables when the frequency of 5 or less was represented in a stratum comparison (cause-specific mortality between pathologic fibrinolysis groups). Kaplan-Meier survival curves were compared using the log-rank and Wilcoxon tests.

RESULTS

The study cohort of 180 patients represented a severely injured population from an urban trauma center. The median age was 43 years (interquartile range [IQR], 28–55), 70% were men, and most injuries were due to motor vehicle crashes (Table 1). The median ISS was 29 (IQR, 22–36), with a median

TABLE 1. Stratified Fibrinolysis Phenotypes

	Hyperfibrinolysis	Physiologic	Shutdown	All Patients	p*
	Ly30 > 2.9%, n = 34 (18%)	Ly30, 0.81–2.9%; n = 38 (19%)	Ly30 < 0.8%, n = 121 (63%)	N = 193	
Age, y	40.5 (31–49)	37 (28–47.5)	46 (29–57)	42 (28–55)	0.16
Male	82%	71%	64%	70%	0.22
ISS	30 (25–36)	28 (22.5–35)	29 (20–38)	29 (22–36)	0.64
Penetrating	24%	21%	19%	21%	0.9
GSW	21%	8%	9%	10%	0.13
MVC	18%	40%	37%	30%	0.08
AutoPed	24%	13%	16%	15%	0.46
pH	7.23 (7.09–7.32)	7.24 (7.19–7.30)	7.26 (7.17–7.33)	7.25 (7.16–7.33)	0.37
BD, mEq/L	10 (8–16)	11 (6.5–14)	9 (6–12)	9 (6–13)	0.27
Lactate, mmol/L	6.4 (4–10.3)	4.4 (2.6–5.1)	4.1 (2.7–6.5)	4.4 (2.7–7.0)	0.07
INR	1.4 (1.1–1.6)	1.3 (1.2–1.4)	1.2 (1.1–1.4)	1.3 (1.1–1.5)	0.44
Temp, °C	36.5 (35.7–36.9)	36.6 (35.9–37)	36.6 (36.1–37.1)	36.6 (36.1–37.1)	0.83
SBP, mm Hg	92 (16–102)	99 (86–129)	110 (88–138)	104 (82–130)	0.005
GCS score	4 (3–15)	14 (6–15)	14 (3–15)	13 (3–15)	0.14
RBC	7 (0–24)	2 (0–6)	2 (0–10)	2 (0–10)	0.15
FFP	0 (0–5)	0 (0–4)	0 (0–6)	0 (0–6)	0.14
CRYO	0 (0–2)	0 (0–0)	0 (0–1)	0 (0–1)	0.65
PLTS	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0.57
MT	44%	5%	26%	28%	0.025

*χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables.
Continuous variables are represented as median (interquartile range).
AutoPed, auto-pedestrian crash; BD, base deficit; CRYO, cryoprecipitate units for 24 hours; FFP, fresh frozen plasma units for 24 hours; GCS, Glasgow Coma Scale; GSW, gunshot wound; INR, international normalized ratio; MT, 10 or greater RBC units within 24 hours; MVC, motor vehicle crash; pH, arterial pH; PLTS, platelet units for 24 hours; RBC, packed RBC units for 24 hours; Temp, temperature.

initial base deficit of 9 (IQR, 6–13). Overall mortality was 20%, with 67% occurring within 24 hours.

The spectrum of fibrinolysis was divided into three groups as previously defined. Fibrinolysis shutdown was the most prevalent, representing 64% (n = 115), while physiologic fibrinolysis (18% [n = 32]) and hyperfibrinolysis (18% [n = 33]) were similarly distributed. The fibrinolysis groups had similar age, ISS, and base deficit (Table 1). Transfusion between phenotypes had a similar distribution. However, when evaluating patients who received at least 1 U of RBCs, the hyperfibrinolytic phenotype had increased RBC ($p = 0.001$) and plasma transfusions ($p = 0.002$) compared with the other phenotypes, which predictably correlated to an increased rate of MTs ($p = 0.002$) (Fig. 1).

Mortality between groups had a U-shaped distribution, with the lowest rate in the physiologic group, and the highest rates of mortality were seen at the extremes of shutdown and hyperfibrinolysis ($p < 0.001$) (Fig. 2). Pairwise adjustment retained statistical significance for a decreased mortality rate in the physiologic phenotype versus shutdown ($p = 0.042$). The cause of mortality specific to the shutdown and hyperfibrinolysis groups had different patterns (Fig. 3). Exsanguination represented 66% of deaths in the hyperfibrinolysis group, which was significantly higher than the shutdown phenotype (15%, $p = 0.004$). The converse was appreciated in which the shutdown group experienced a higher percentage of mortality attributable to multiple organ failure (40% vs. 7%, $p = 0.048$). Death from traumatic brain injury was higher in the shutdown group, 45% versus 26%, but did not reach statistical significance ($p = 0.31$). Survival time also differed greatly between groups (Fig. 4). The hyperfibrinolysis group had a significant early drop in survival

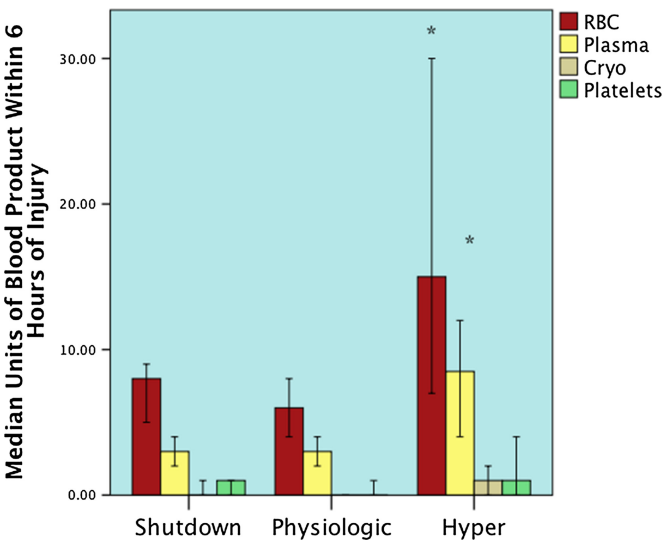

Figure 1. Blood product transfusions between phenotypes. The *y* axis represents the number of specific blood products transfused within 6 hours of injury. The figure includes only patients who received a transfusion. Overall RBC and plasma transfusion units were higher in the hyperfibrinolysis phenotype and remained statistically significant after pairwise adjustment between both the physiologic and shutdown groups. *$p < 0.05$ after pairwise adjustment. Cryo, croprecipitate.

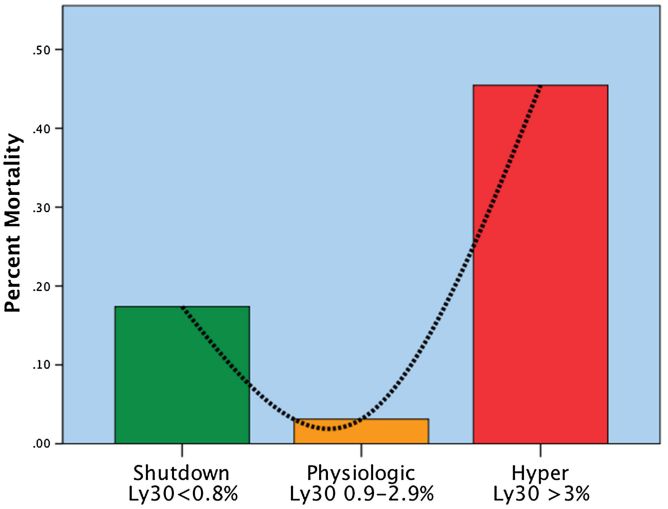

Figure 2. U-shaped distribution of mortality related to fibrinolysis phenotype. The *y* axis represents the percentage of mortality per phenotype. There is a U-shaped distribution of mortality, with a nadir in mortality identified in the physiologic group (Ly30 between 0.9% and 2.8%). Percentage of Ly30 higher and lower than this range had statistical increases in mortality. Hyper, hyperfibrinolysis; Ly30, percentage of fibrinolysis 30 minutes after reaching maximum amplitude measured by thombelastography; Physiologic, physiologic fibrinolysis; Shutdown, fibrinolysis shutdown.

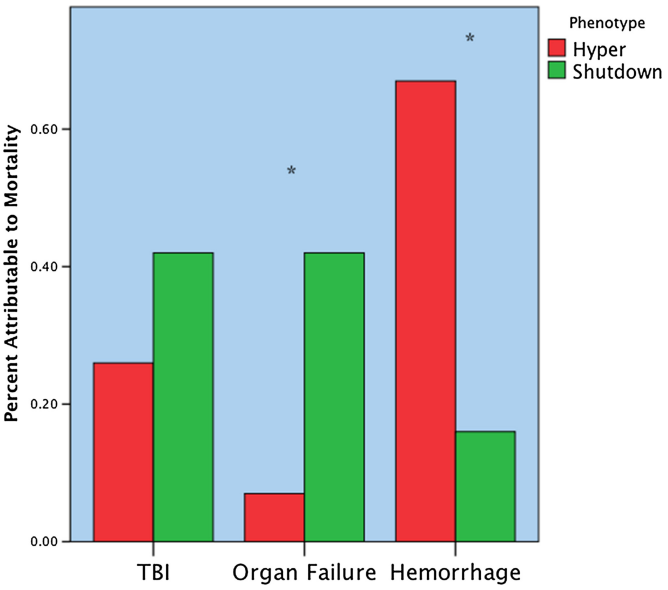

Figure 3. Distribution of mortality according to fibrinolytic phenotype. The *y* axis represents the percentage of total mortality per phenotype. The hyperfibrinolytic phenotype had a high frequency of mortality associated with hemorrhage. The shutdown phenotype has a high frequency of organ failure–related death. TBI did not reach statistical difference between phenotypes but was more common in the shutdown cohort. *$p < 0.05$. Hyper, hyperfibrinolysis; Shutdown, fibrinolysis shutdown; TBI, traumatic brain injury.

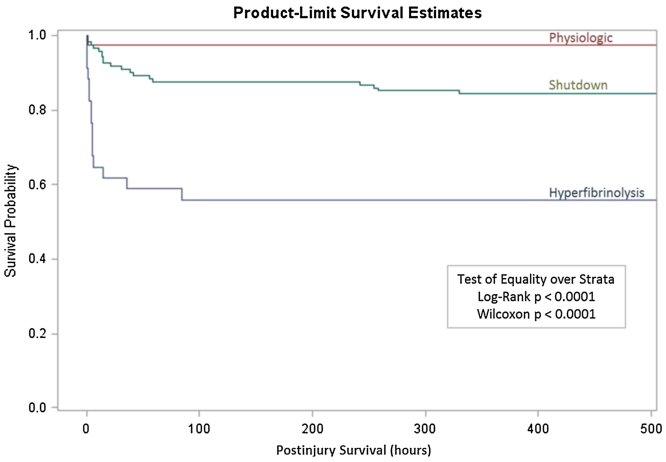

Figure 4. Survival curve of different phenotypes of fibrinolysis. Curve demonstrates the time from injury to survival patterns between the fibrinolysis phenotypes. The *y* axis represents the percentage of survival, and the *x* axis represents hours from injury. Survival, hours after injury.

compared with the shutdown cohort, which had delayed mortality ($p = 0.001$).

DISCUSSION

We have identified three distinct phenotypes of fibrinolysis in response to trauma. Despite having similar demographics and injury patterns (Table 1), mortality differs between groups (Fig. 2). Modest levels of fibrinolysis seem to be protective, compared with overactive fibrinolysis, as there is a nadir in morality between the 0.8% and 2.9% range. Hyperfibrinolytic patients die of exsanguination and early after injury, whereas shutdown patients have a delayed mortality more frequently from organ failure (Fig. 4). These findings support our experimental observation that tissue injury and hemorrhagic shock have opposing impact on systemic fibrinolysis.

The degree of fibrinolysis and trauma does not have a normal distribution. In our study population of severely injured patients, only 18% of the population had hyperfibrinolysis. Our results are consistent with previous reports in the literature that hyperfibrinolysis is relatively infrequent.[9,10,18] Interestingly, the more common response to injury is fibrinolysis shutdown, which accounted for more than 60% of our patients. While the concept of fibrinolysis shutdown during the acute injury phase in trauma has not received much attention, previous literature supports this concept. Raza et al.[20] identified a group of patients with elevated plasmin/antiplasmin complexes and minimal detectable fibrinolysis activity using an analogous TEG device. Elevated plasmin/antiplasmin complexes and lack of hyperfibrinolysis were identified in 57% of their patient population and were associated with increased mortality. In their article, perhaps paradoxically titled, "The incidence and magnitude of fibrinolytic activation in trauma patients," we believe that this group has elegantly shown the shutdown of fibrinolysis and confirmed a high prevalence.

Hyperfibrinolysis and shutdown have diverse pathologic sequelae. Hyperfibrinolysis is associated with early death from exsanguination, and shutdown is associated with delayed death due to organ failure (Fig. 4). It is interesting that both groups have similar distribution of demographics, injury patterns, and emergency department vital signs except systolic blood pressure (SBP) (Table 1). Kutcher et al.[21] also struggled to identify unique differences in patients who present with hyperfibrinolysis. Lower SBP differed between fibrinolysis phenotypes. These findings are consistent with the recent finding that prehospital cardiopulmonary resuscitation is associated with a high rate of hyperfibrinolysis.[22] Circulatory arrest clearly promotes fibrinolysis but is not uniform, as the previously mentioned study identified 36% of patients in circulatory arrest with hyperfibrinolysis. In our study, 14 patients presented in circulatory arrest, and 64% had hyperfibrinolysis. Our group's unpublished work with swine indicates that hemorrhagic shock is contributory to activation of fibrinolysis, although whether this is attributable to ischemia and/or no flow remains unclear. Interestingly, tissue injury in the swine produces fibrinolysis shutdown.

In our study, we failed to identify a specific injury pattern or patient demographics that predisposed patients to fibrinolysis shutdown. This is likely due to our lack of ability to quantify and specify tissue injury. Plasminogen activator inhibitor 1 (PAI-1) is produced rapidly after tissue injury during surgery,[23] and certain ratios of plasminogen inhibitors to activators to inhibitor may shut down the system. Bone fractures may be a dominant factor. Endothelial cells cultured in the plasma of postoperative hip replacement patients produced high levels of PAI-1.[24] Subsequently, prospective evaluation has identified elevated PAI-1 as a risk of postoperative deep venous thrombosis in orthopedic surgery.[16] The complexity of regulation of fibrinolysis is also compounded by at least a dozen receptors known to interact with plasminogen,[25] and there are likely many other unknown factors we currently overlook.

The shutdown of fibrinolysis is associated with organ failure. Nearly 90% of patients in our study who died of organ dysfunction had fibrinolysis shutdown. Acute lung injury provides an example of the failure of fibrinolysis resulting in organ dysfunction. Since the early 1980s, it has been known that fibrin deposition in the pulmonary vasculature is pathologic.[26] Idell et al.[27] in 1991 identified tissue factor as the perpetrator for excessive fibrin deposition that remained present for weeks because of decreased fibrinolysis activity. Ostrowski et al.[28] recently used TEG to demonstrate fibrinolysis shutdown in healthy volunteers by administrations of endotoxin, suggesting the cross talk between inflammation and fibrinolysis. These observations are not new, as it was appreciated in the 1960s that "stress" impacts the fibrinolytic system and that there is a complex interaction with inflammation.[29] Disseminated intravascular coagulopathy (DIC) may be an extreme example of fibrinolysis shutdown. Trauma patients who progressed through acute lung injury to multiple organ failures and ultimately death from DIC have been found to have progressively elevated levels of PAI-1,[30] indicative of fibrinolysis shutdown.

It seems intuitive that preventing clot degradation during the acute injury phase would have a survival benefit. Survival trends from our data support this concept, as shutdown of fibrinolysis is less lethal than hyperfibrinolysis (Fig. 3). However, between the two extremes, there is a survival advantage. This may

represent a physiologic protection following injury (Fig. 2). The Blood Conservation Using Antiibrinolytics in a Randomized Trial (BART) is an example of patients at high risk for bleeding who had increased mortality from medically inhibited fibrinolysis that may otherwise have been protective. There was an increased rate of coronary graft failure, renal failure, and death with empiric antifibrinolytics.[31] Even Groth et al.[5] retracted their position about the use of empiric antifibrinolytics during liver transplantation after 6 years of critically evaluating their experience and observing increased VTE. In fact, fibrinolysis shutdown may be the missing link in the pathogenesis of postinjury VTE in the surgical intensive care unit. Of note, Starzl's group advocated point-of-care testing for selective use of antifibrinolytics in 1969.

As with every retrospective clinical study, there are limitations. We were unable to identify previous reports in the literature that defined a physiologic protective level of fibrinolysis in response to trauma assayed with TEG. As a result, our current range of Ly30 from 0.81 to 2.9 is derived from a single-center study, and a multicenter trial would provide external validity. Because of the inherent variability of the TEG device, this range may differ between centers. We have recently developed a novel TEG assay that quantifies the degree of fibrinolysis shutdown. With this assay, we can more definitively differentiate shutdown from the physiologic phenotype (Supplemental Digital Content 1: tPA TEG assay, http://links.lww.com/TA/A457). Data from plasma processed within 1 hour of injury collected since the completion of this study demonstrate that PAI-1 levels in the shutdown phenotype are 20-fold higher than in healthy controls and suggest a mechanism for impairment of the fibrinolytic system. Because of the retrospective nature of this study, time from injury to TEG was different between groups. However, most of the TEGs were obtained within 3 hours of injury in all groups. More importantly, pre-TEG fluid and blood product transfusions were not different between groups (Table 1). With our ongoing prospective study of admission hospital blood values, we will reassess a threshold for defining cutoff points for the three phenotypes of fibrinolysis, augmented by our tPA TEG assay.

Severely injured patients were included in the study and eliminated more than half of all patients who had prospectively been evaluated during the past 3 years. We selected a patient population with severe injury, as our animal data suggested that tissue injury provokes the shutdown of fibrinolysis. The clinical importance of identifying the fibrinolysis shutdown is in patients at risk for organ failure and VTE. The ISS cutoff yielded a population of patients in which 98% of patients were either dead or required ICU care. Of patients who survived their initial resuscitation, 75% required ventilator support. We believe that this was an ideal population to identify the shutdown phenotype and to determine its relationship with organ failure.

It is possible that less injured patients have a different physiologic requirement of fibrinolysis, as they are not responding to as much stress and may not require a higher level of fibrinolytic activity to maintain the microvasculature patency. A previous report from Japan identified increased fibrinolysis activity to have a survival advantage during DIC.[32] This group measured proteins involved in the fibrinolysis pathway and did not use TEG. In our study, the focus was to identify clinical information to discuss fibrinolytic phenotypes. Our finding that the hyperfibrinolysis group predominantly bled to death was not surprising. We cannot definitively state that, had these patients survived, they would not have developed organ failure. However, it is intriguing that the physiologic levels of fibrinolysis lacked death from organ failure, and this poses the question of whether the shutdown population would benefit from fibrinolytic therapy, as described by Hardaway et al.[33] more than a decade ago.

AUTHORSHIP

H.B.M., E.E.M., E.G., and M.P.G. designed this study. H.G.M., E.G., M.P.G., and T.L.C. contributed to data collection. H.G.M., E.E.M., and A.S. performed data analyses. All authors participated in data interpretation. H.B.M. and E.E.M. wrote the manuscript, which all authors critically revised.

ACKNOWLEDGMENT

The authors thank Sarah Ammons, James Chandler, and Arsen Ghasabyan for their invaluable assistance in data procurement.

DISCLOSURE

This study was supported in part by National Institutes of Health grants T32-GM008315 (National Institute of General Medical Sciences), P50-GM0492221 (National Institute of General Medical Sciences), and UM 1HL120877 (National Heart, Lung, and Blood Institute) and in part by Colorado Clinical and Translational Science Award Grant UL1 TR001082 (National Center for Advancing Translational Science). Additional research support was provided by Haemonetics.

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EDITORIAL CRITIQUE

Drs. Moore and colleagues have performed a prospective observational study evaluating the association between early fibrinolysis as measured by LY30 on thrombelastogram (TEG) and clinical outcomes in a cohort of 186 severely injured patients. They have defined 3 ranges of fibrinolysis (shutdown, physiologic fibrinolysis and hyperfibrinolysis) that correlate with clinical outcomes. Mortality was increased in patients with shutdown and hyperfibrinolysis and patients with shutdown were more likely to die from multiple organ failure whereas patients with hyperfibrinolysis were more likely to die from exsanguination.

The study is an important contribution to the literature that appeals to the reader's common sense and introduces the concept of fibrinolysis shutdown with its potential negative effects. It also raises several concerns that need to be addressed in further study before the results can be widely accepted. The sample size is small with only 32 patients in the physiologic range and 33 patients with hyperfibrinolysis. The range of LY30 that spans across the distribution from fibrinolysis shutdown to hyperfibrinolysis is only 3% with fibrinolysis shutdown being defined as an LY30 from 0–0.8%. It is not clear that TEG technology can supply this degree of accuracy and reproducibility. Performance of the assays in duplicate with different machines would determine if the results are reproducible.

The median time to performance of the test was 96 minutes after injury with the interquartile range extending to 260 minutes. This indicates significant variability in timing suggesting that patients were in different phases of resuscitation. The authors report that there was no difference in the volume of fluid and blood products given to the 3 groups however they only report the volume of blood products given in the results. The study would be more powerful if the TEGs were performed upon admission of the patients prior to significant resuscitation.

In summary, the authors have potentially identified the very important phenomenon of fibrinolysis shutdown and associated it with the development of multiple organ failure. This has significant implications for the use of tranexamic acid in trauma patients. This preliminary study is highly suggestive however additional work is needed to confirm these findings.

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