Acute Coagulopathy of Trauma: Hypoperfusion Induces Systemic Anticoagulation and Hyperfibrinolysis

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Background: **Coagulopathy is present at admission in 25% of trauma patients, is associated with shock and a 5-fold increase in mortality. The coagulopathy has recently been associated with systemic activation of the protein C pathway. This study was designed to characterize the thrombotic, coagulant and fibrinolytic derangements of trauma-induced shock.**

Methods: **This was a prospective cohort study of major trauma patients admitted to a single trauma center. Blood was drawn within 10 minutes of arrival for analysis of partial thromboplastin and prothrombin times, prothrombin fragments 1 + 2 (PF1 + 2), fibrinogen, factor VII, thrombomodulin, protein C, plasminogen activator inhibitor-1 (PAI-1), thrombin activatable fibrinolysis inhibitor (TAFI), tissue plasminogen activator (tPA), and D-dimers. Base deficit was used as a measure of tissue hypoperfusion.**

Results: **Two hundred eight patients were studied. Systemic hypoperfusion was associated with anticoagulation and hyperfibrinolysis. Coagulation was activated and thrombin generation was related to injury severity, but acidosis did not affect Factor VII or PF1 + 2 levels. Hypoperfusion-induced increase in soluble thrombomodulin levels was associated with reduced fibrinogen utilization, reduction in protein C and an increase in TAFI. Hypoperfusion also resulted in hyperfibrinolysis, with raised tPA and D-Dimers, associated with the observed reduction in PAI-1 and not alterations in TAFI.**

Conclusions: **Acute coagulopathy of trauma is associated with systemic hypoperfusion and is characterized by anticoagulation and hyperfibrinolysis. There was no evidence of coagulation factor loss or dysfunction at this time point. Soluble thrombomodulin levels correlate with thrombomodulin activity. Thrombin binding to thrombomodulin contributes to hyperfibrinolysis via activated protein C consumption of PAI-1.**

Key Words: **Coagulopathy, Shock, Hypoperfusion, Protein C, Plasminogen activator inhibitor-1, Thrombin activatable fibrinolysis inhibitor, Fibrinolysis, Anticoagulation.**

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Coagulopathy is present immediately at admission in 25% of trauma patients and is associated with a 5-fold increase in mortality.[1] Accepted causes of traumatic coagulopathy are consumption of clotting factors, acidosis and hypothermia leading to reduced activity, and dilution from intravenous fluids and packed cell administration. However acute coagulopathy is present early in the postinjury phase, before fluid administration and in normothermic patients.[1] Further, while acidosis per se affects coagulation protease function, clot time and maximum clot firmness are only impaired at very low pH (<6.8).[2]

We have recently demonstrated that only patients who are in shock are coagulopathic on admission.[3] Increased severity of hypoperfusion was associated with an increase in plasma thrombomodulin and a reduction in protein C levels. This suggests that acute coagulopathy is due to systemic anticoagulation through activation of the protein C pathway.

The overall goal of this study was to fully characterize the coagulopathy of shock, and in particular to examine the interplay of shock, anticoagulation and the fibrinolytic system. Second, we wished to analyze whether coagulation factor consumption or dysfunction because of acidosis was responsible for coagulopathy before massive fluid and blood transfusion. Third, we hypothesized that thrombomodulin has a central role in traumatic coagulopathy, complexing thrombin and resulting in anticoagulation and hyperfibrinolysis. Finally, there has been some debate from basic science studies as to whether the hyperfibrinolysis resulting from thrombin–thrombomodulin (T-TM) formation is due to activation of thrombin activatable fibrinolysis inhibitor (TAFI)[4] or activated protein C con-

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sumption of plasminogen activator inhibitor-1(PAI-1).[5,6] We sought to understand which pathway was more important in clinical practice.

PATIENTS AND METHODS

This was a prospective cohort study of consecutive major trauma patients admitted to a single level I trauma center. The methodology has been described previously.[3] Briefly, a 10 mL sample of blood was drawn immediately on admission to the emergency department. The sample was spun down, plasma extracted, and then frozen at −80°C.

For this study, we assayed plasma levels of Factor VII, tissue plasminogen activator (tPA; Asserachrom tPA, Diagnostica Stago, Inc., Parsippany, NJ) (normal range, 3 ng/mL–13 ng/mL) and TAFI enzyme-linked immunosorbent assay (Enzyme Research Laboratories, Ltd., South Bend, IN) (normal range, 2.8 mcg/mL–9.2 mcg/mL) in addition to previously described measurements of prothrombin fragments 1 + 2 (PF1 + 2), fibrinogen, soluble thrombomodulin (sTM), protein C, PAI-1, and D-Dimer levels. For the D-Dimer assay, levels above 0.22 μg/mL were reported as 0.22 μg/mL. Factor VII activity levels were measured by a one stage clotting assay using factor VII deficient plasma on a STA-R automated analyzer (Roche Diagnostics, Almere. The Netherlands) and pooled normal plasma as a reference.

Data were collected prospectively on patient demographics, injury time, mechanism (blunt or penetrating) and severity, prehospital fluid administration, the time of arrival in the trauma room, and admission vital signs. In the absence of a biochemical marker, the injury severity score was used as a surrogate measure of the degree of tissue injury. A full blood count, coagulation profile and arterial blood gas were drawn at the same time as the research sample as part of the standard management of major trauma patients. The degree of shock and systemic tissue hypoperfusion was assessed with the base deficit. Admission base deficit is a clinically useful early marker of tissue hypoperfusion in trauma patients and an admission base deficit greater than 6 mEq/L has previously been identified as predictive of worse outcome in trauma patients.[7,8]

Statistical analyses were performed with Microsoft Excel 2003 with the WinSTAT plug-in (Microsoft, Inc., Redmond, WA). Normal-quantile plots were used to test for normal distribution. Parametric data are expressed as mean ± 95% confidence intervals. Nonparametric data are given as median (interquartile range). Two-group analysis was performed with a two-tailed unequal variance Student's t test. The χ^2 test was used for dichotomous data analysis. A p value of 0.05 was chosen to represent statistical significance.

RESULTS

Blood was drawn on 208 consecutive patients immediately on arrival to the trauma room. Median prehospital time was 28 minutes (interquartile range, IQR: 23 minutes–29 minutes) and 150 mL of crystalloid fluid (0 mL–200 mL) were administered in the field. Median injury severity score was 17 (9–26) and 25% were penetrating.

Patients without significant hypoperfusion [base deficit (BD) ≤6] were not coagulopathic, regardless of injury severity (Fig. 1, A, B). A total of 2.6% of patients with a BD ≤6 had a clinically important prolonged prothrombin time [(PT) >18 seconds] compared with 19.6% of patients with BD >6 mEq/L ($p = 0.001$, χ^2) and only 1.9% of patients with a BD ≤6 mEq/L had a clinically important prolonged partial thromboplastin time [(PTT) >60 seconds] compared with 12.5% of patients with BD >6 ($p = 0.007$, χ^2). Forty-one percent of patients with a systolic blood pressure less than 100 mm Hg on admission had a clinically important coagulopathy (PT >18 seconds or PTT >60 seconds). Systolic blood pressure was only weakly correlated to the base deficit ($r^2 = 0.15$, $p < 0.001$), 15% of patients had a BD >6 mEq/L despite a normal blood pressure (systolic blood pressure ≥100 mm Hg) and 8% of these were coagulopathic.

For patients in shock, both PT and PTT were prolonged as injury severity increased (Fig. 1, A, B). In contrast, there was activation of fibrinolysis without shock (Fig. 1, C). However shock increased the degree of fibrinolysis in all patients (Fig. 1, C). Acute coagulopathy is, therefore, a consequence of shock and is characterized by systemic anticoagulation and hyperfibrinolysis.

PF1 + 2 were assayed to assess the degree of thrombin generation. PF1 + 2 increased with injury severity (Fig. 2, A). There was no reduction in PF1 + 2 levels as acidosis increased (Fig. 2, B), suggesting that reduction in coagulation factor activity because of acidosis does not make a significant contribution to the coagulopathy of shock. Factor VII levels were also unchanged by acidosis (Fig. 2, C), and sufficient for clot generation. Combined, these data also suggest that consumption of factors is not clinically significant at this time point and does not contribute to acute coagulopathy.

Hypothermia did not contribute to the incidence or degree of admission coagulopathy. Forty (19%) patients arrived with a temperature below 35°C and 5 (2%) below 34°C. Only three patients with a temperature below 35°C were coagulopathic (PT >18 seconds. PTT was normal in all patients <35°C). There was no significant difference in PT (15 seconds versus 15 seconds) or PTT (32 seconds versus 29 seconds) between normothermic and hypothermic (temperature <35°C) patients. Additionally thrombin generation was not reduced by hypothermia (PF1 + 2: 3.5 nM, ≥35°C; 4.0 nM <35°C).

We previously demonstrated that increasing shock with hypoperfusion was associated with a rise in plasma levels of sTM and a decrease in protein C levels.[3] Thrombomodulin complexes with thrombin and switches thrombin to an anticoagulant function, as the complex activates protein C. In addition, thrombin bound to thrombomodulin is not free to cleave fibrinogen to form fibrin or to activate platelets. As thrombomodulin levels rise, fibrinogen levels are maintained (Fig. 3, A). Figure 3, B shows how with low thrombomodulin

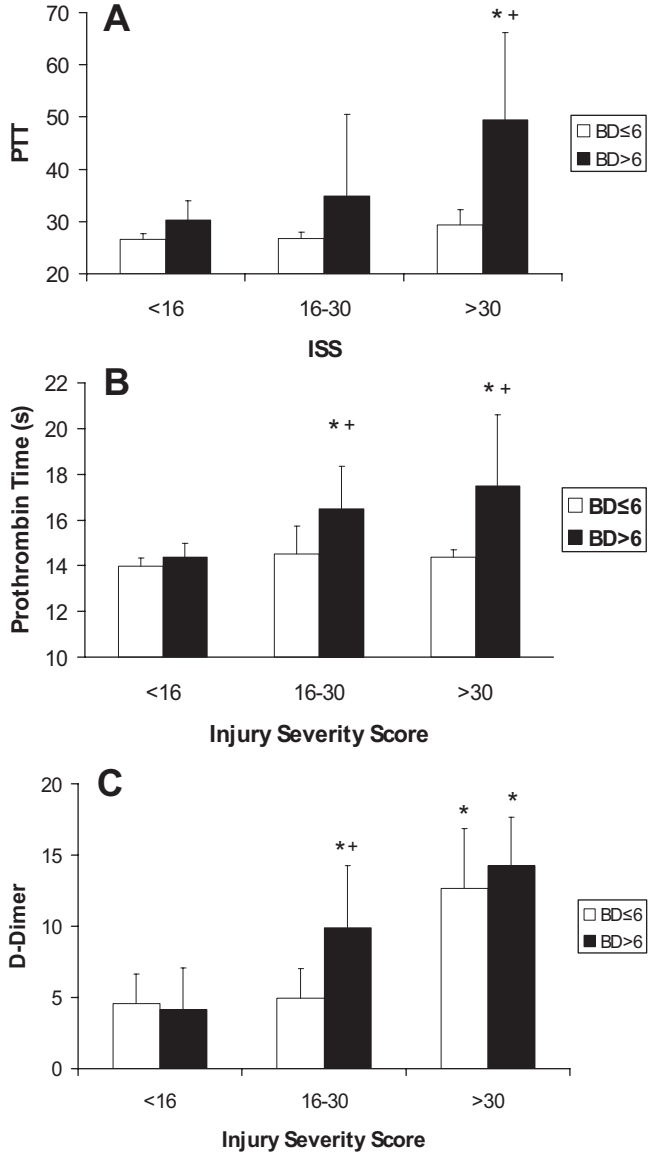

Fig. 1. *Shock induces anticoagulation and hyperfibrinolysis. (*A*) Partial thromboplastin time (PTT) is prolonged only in the presence of a raised BD. Although the BD remains low (*white bars*), increasing injury severity has no effect on the PTT. With a raised BD (*black bars*), prolongation of the PTT is seen with increasing injury severity score (ISS). ISS in tertiles. *p = 0.04 compared with ISS <16 for BD >6 mEq/L. $^{+}$p = 0.05 comparing BD ≤6 and >6 mEq/L. (*B*) Prothrombin time (PT) is prolonged only in the presence of a raised BD. Although the BD remains low (*white bars*), increasing injury severity has no effect on the PT. With a raised BD (*black bars*), prolongation of the PT is seen with increasing injury severity score (ISS). ISS in tertiles. *p < 0.05 compared with ISS <16 for BD >6 mEq/L. $^{+}$p < 0.05 comparing BD ≤6 and >6 mEq/L. (C) D-Dimers are increase as ISS increases. With hypoperfusion (BD >6 mEq/L,* black bars*), there is hyperfibrinolysis. ISS in tertiles. *p < 0.05 compared with ISS <16. $^{+}$p < 0.05 comparing BD ≤6 and >6 mEq/L. D-dimer assay reported with a ceiling of 0.22 μg/mL.*

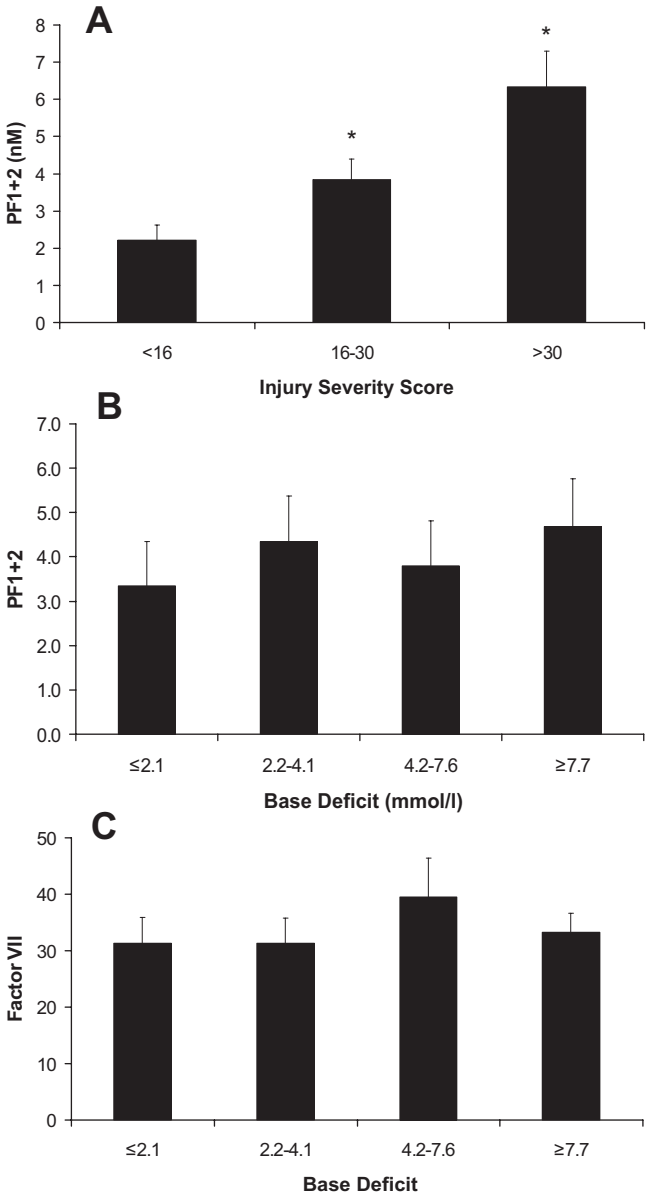

Fig. 2. *Injury leads to activation of coagulation but levels of coagulation proteins are not affected by acidosis. (*A*) Thrombin generation increases as injury severity increases. ISS in tertiles. *p < 0.001 compared with ISS <16. (*B*) Thrombin generation is not affected by the degree of acidosis. (*C*) Factor VII activity is not affected by the degree of acidosis.*

levels, there is a dose-dependent reduction in fibrinogen levels, indicating activation and consumption of fibrinogen. This effect is abolished when thrombomodulin is high. Only one patient with an admission coagulopathy (PT >18 seconds or PTT >60 seconds) had a fibrinogen <100 mg/dL. In the presence of shock and high thrombomodulin levels, fibrin production is minimal, regardless of clotting factor activity.

Further consequences of formation of the T-TM complex include activation of protein C. We did not measure activated protein C in this study but can demonstrate falling protein C

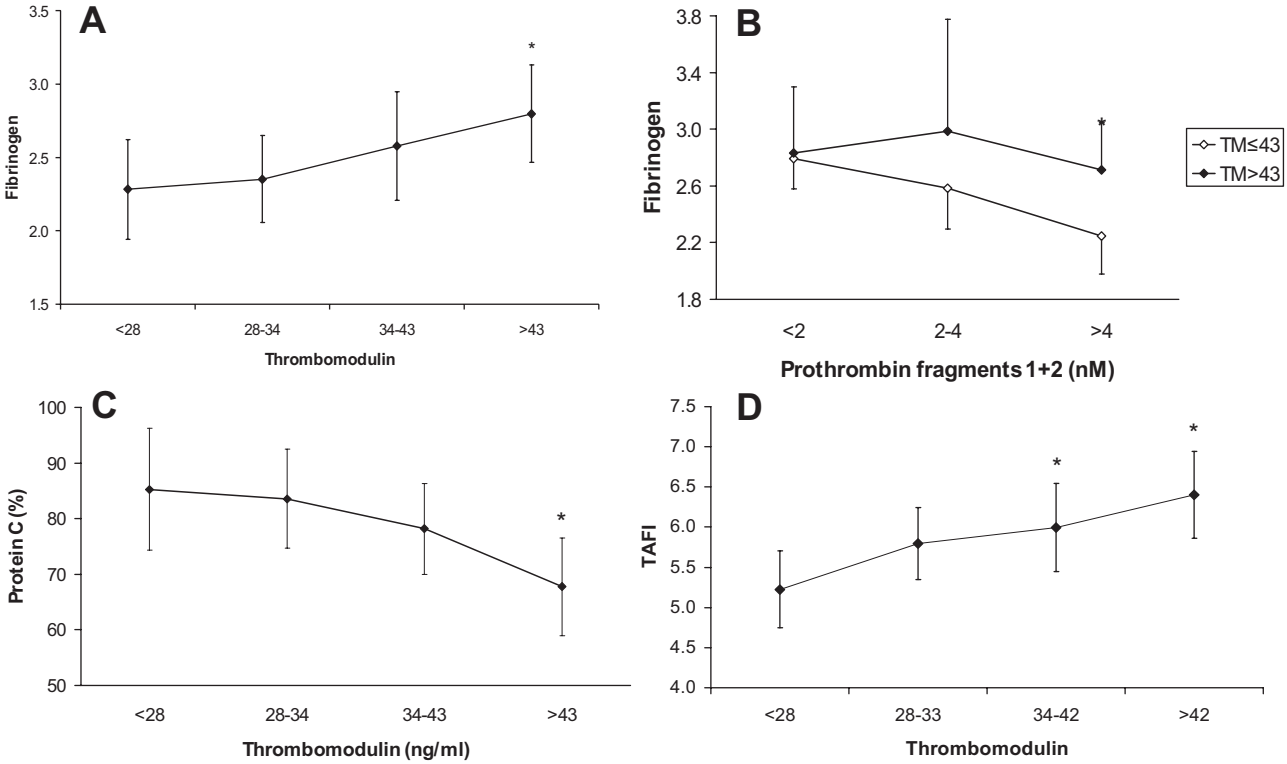

Fig. 3. *Increased soluble thrombomodulin is associated with reduced fibrinogen utilization, reduction in protein C (activation) and an increase in TAFI. (*A*) Decreased fibrinogen utilization as thrombomodulin levels increase. Thrombomodulin in quartiles. *p = 0.04 compared with TM <28 ng/mL. (*B*) Dose-dependent utilization of fibrinogen with thrombin generation is abolished in the presence of raised TM. PF1 + 2 in tertiles. *p = 0.04 comparing fibrinogen levels for TM ≤43 and >43 ng/mL. (*C*) Decrease in Protein C levels (increased activation) as TM increases. TM in quartiles. *p = 0.02 compared with TM <28 ng/mL. (*D*) Increase in TAFI with increasing TM. *p < 0.05 compared with TM <28 ng/mL.*

levels with increasing sTM (Fig. 3, C) and have previously shown that this is likely to represent protein C activation because of observed effects on anticoagulation.[3] Thrombin complexed to thrombomodulin also activates TAFI, and we can demonstrate an increase in TAFI levels with increasing sTM (Fig. 3, D). Together these results support a central role for thrombomodulin in acute traumatic coagulopathy.

We have demonstrated that systemic fibrinolysis is also a component of this coagulopathy (Fig. 1, C). tPA is released from the endothelium, and was significantly elevated in patients with shock, irrespective of the amount of thrombin generated (Fig. 4, A,). tPA levels were significantly higher when PAI-1 was low (Fig. 4, C) and increasing tPA levels were correlated with increasing D-Dimers, as expected (Fig. 4, D).

When present in excess, activated protein C is a potent inhibitor of PAI-1[4] and we have previously shown that patients in shock have low levels of PAI-1 and a direct correlation between protein C and PAI-1 levels, suggesting that protein C activation leads to PAI-1 consumption.[3] It has previously been suggested that the deinhibition of fibrinolysis seen with protein C is not due to this mechanism but to a competitive reduction in TAFI activation by the T-TM complex.[5,6] We can demonstrate this competitive binding of T-TM to either protein C or TAFI by an inverse correlation between protein C and TAFI levels (Fig. 5, A). However, although we can demonstrate an inverse relationship between PAI-1 and the D-Dimer level (Fig. 5, B) there is no such correlation between TAFI and D-Dimers (Fig. 5, C) suggesting that in the clinical setting the protein C—PAI-1 interaction is more important for the observed hyperfibrinolytic state.

DISCUSSION

Acute traumatic coagulopathy occurs in patients who are shocked and is not due to coagulation factor consumption or dysfunction because of acidosis, moderate hypothermia, or dilution. These factors may be important later in the clinical course, after massive transfusion or the development of severe hypothermia or acidosis. However shock itself is associated with a coagulopathy that is due to the systemic activation of anticoagulant and fibrinolytic pathways.

We have demonstrated previously that the protein C pathway is implicated in this process,[3] and show here the central role of thrombomodulin in the conversion of thrombin from its coagulant role to a regulator of clot formation. Thrombomodulin is an endothelial protein that is present in normal endothelial cells. Theoretically, activation leads to

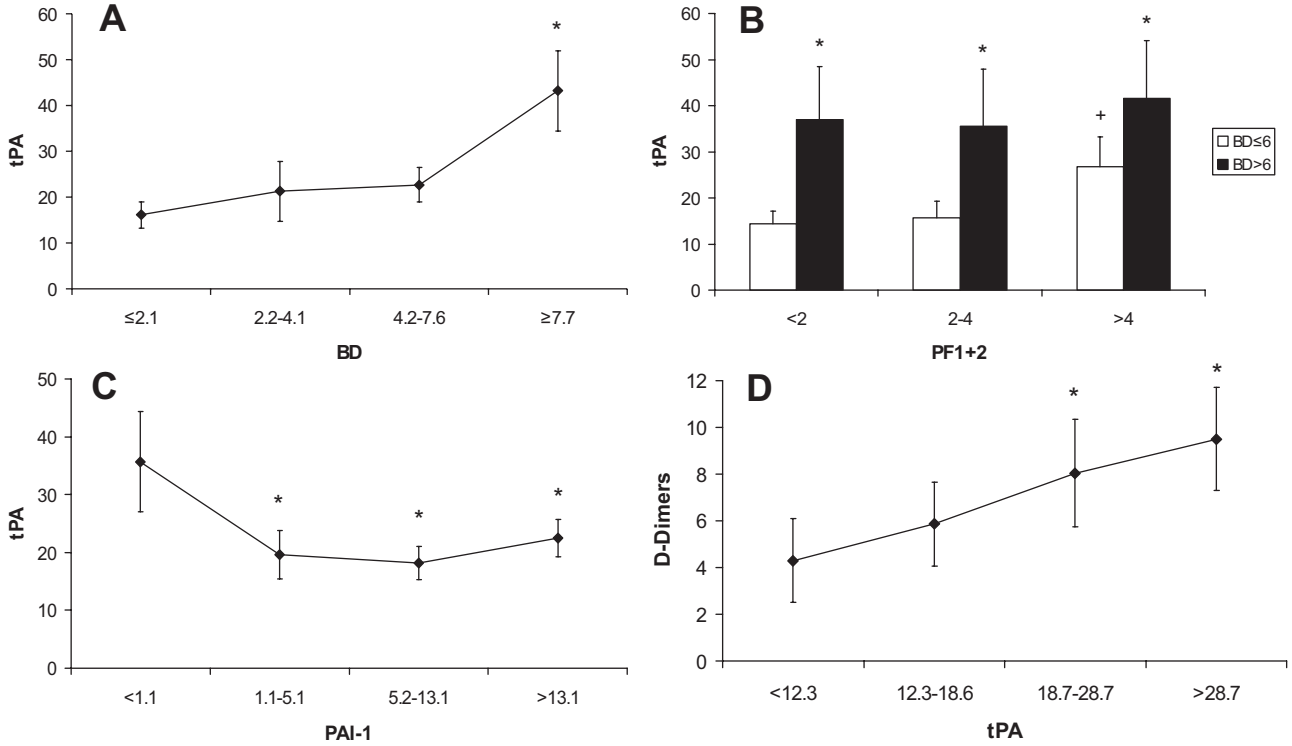

Fig. 4. *Activation of fibrinolysis.* (A) *tPA increases as the degree of hypoperfusion increases. BD in quartiles.* *p $<$ *0.001 compared with BD* $\leq$*2.1.* (B) *Hypoperfusion results in hyperfibrinolysis (increased tPA levels) for all degrees of thrombin generation. PF1 + 2 in tertiles.* *p $<$ *0.001 comparing BD* $\leq$*6 mEq/L and BD* $>$*6 mEq/L.* $^{+}$p $<$ *0.001 compared with PF1 + 2* $<$*2 nM.* (C) *Low PAI-1 levels result in deinhibition of fibrinolysis (increased tPA). PAI-1 in quartiles.* *p $<$ *0.01 compared with PAI-1* $<$ *1.1 AU/mL.* (D) *Expected increased fibrinolysis with increasing levels of tPA. tPA in quartiles.* *p $<$ *0.01 compared with tPA* $<$*12.3 ng/mL.*

increased thrombomodulin expression on the surface of the endothelium, where it complexes thrombin which then activates protein C at the endothelial protein C receptor. This "anticoagulant thrombin" is no longer available to cleave fibrinogen to form fibrin, as we have demonstrated.

This has significant implications for current practice. All current efforts to correct traumatic coagulopathy are currently directed at augmenting the clotting factor pathway, through the administration of fresh frozen plasma[9] or recombinant factor VIIa.[10] In theory, while patients are shocked and thrombomodulin is present in excess, thrombin that is generated will be anticoagulant, and stable clot will not be formed. Although it may be possible to overwhelm thrombomodulin with massive thrombin generation, this would also be associated with widespread activation of protein C. This would lead to consumption of PAI-1 and increased fibrinolysis, breaking down the clot that had formed. Further, activated protein C has a relatively long half-life,[11] and the anticoagulant environment might persist and result in rebleeding. Further studies will be needed to ascertain whether this mechanism is of clinical consequence after augmentation of the extrinsic pathway during the shocked state.

There has been some debate in the literature about the relationship between sTM and endothelial-bound thrombomodulin. Studies variously suggest that sTM does not reflect endothelial TM activity but is simply a marker of endothelial injury,[12] is itself active[13,14] or that it is in fact inhibitory to the accepted role of thrombomodulin.[15,16] Our data would suggest that plasma sTM levels do reflect overall thrombomodulin activity, as increased sTM levels appear to be associated with decreased fibrinogen utilization and activation of protein C and TAFI.

Finally, we have demonstrated that fibrinolysis associated with injury is exacerbated by shock and this is mediated by deinhibition of tPA through the consumption of PAI-1. Low levels of PAI-1, in combination with the increased release of plasminogen activators from the vessel wall will result in hyperfibrinolysis. As mentioned above, it has been suggested that TAFI is the main driver of fibrinolysis inhibition, and that reduction in TAFI activation by the competitive binding of protein C to T-TM is the mechanism for derepression of fibrinolysis with activation of protein C. Although we can demonstrate an increase in TAFI levels with thrombomodulin, and a competition between TAFI and protein C, there was no observable correlation between TAFI and D-Dimer levels. Further confirmatory studies are required, but the consumption of PAI-1 by activated protein C appears to be the more clinically important cause of hyperfibrinolysis.

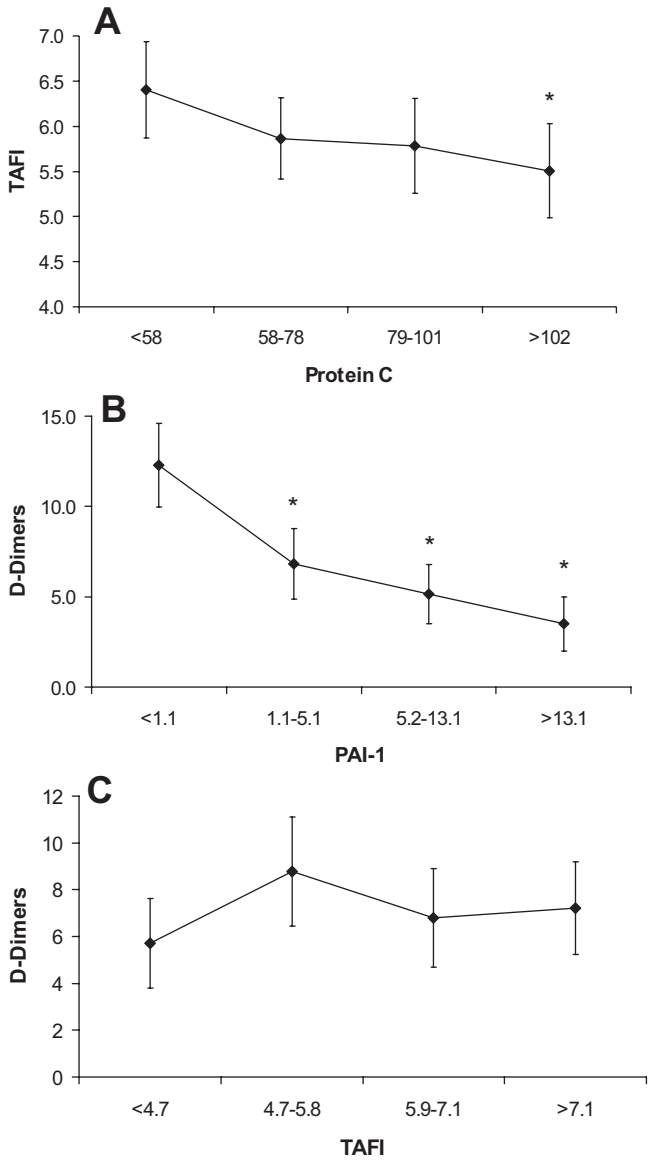

Fig. 5. *Hyperfibrinolysis is due to consumption of PAI-1, not a reduction in TAFI. (*A*) Competitive activation of Protein C and TAFI (by the Thrombin-TM complex). TAFI falls as Protein C levels fall (increased activation). Protein C in quartiles.* *p = 0.02 *compared with Protein C <58%. (*B*) Reducing PAI-1 leads to a hyperfibrinolysis. PAI-1 in quartiles.* *p < 0.01 *compared with PAI-1 <1.1 AU/mL. (*C*) No effect of TAFI on overall fibrinolytic state. TAFI in quartiles.*

This study has several limitations that have been alluded to previously.[3] The PT and PTT are crude methods of identifying coagulopathy, and do not describe the global fibrinolytic state at all. Comparing these biochemical markers to more functional methods such as thromboelastometry might reveal more clinically relevant changes in coagulation. Further, this is an investigation of the state of the coagulation system at a single time point. The response of the coagulation system to continued hemorrhage or successful resuscitation is important areas of further study. Previous investigations at later time points have identified that patients become hypercoagulable[17,18] and are at risk of thromboembolic complications.[19] It is possible that this is a result of depletion of protein C after systemic activation; indeed a previous study has identified admission coagulopathy as an independent risk factor for later venous thromboembolism.[20]

Thrombomodulin is normally present in the endothelium,[15] and protects the vasculature by sequestering thrombin and generating adequate levels of activated protein C to prevent thrombosis.[21] Increased thrombomodulin presentation in low-flow conditions would generate a local anticoagulant milieu and protect vascular beds. When there was systemic low-flow and widespread activated protein C generation, this appropriate response would become pathologic. However, the cause and mechanism of increased thrombomodulin presentation on the endothelial surface during hypoperfusion is currently unknown. The rapid increase in thrombomodulin levels observed in this study appears to exclude a transcriptional upregulation of gene expression. Thrombomodulin is found in endothelial membrane caveolae and in sub-membrane vesicles.[22,23] These may be presented on the endothelial cell surface after activation or alternatively, endothelial damage may result in presentation of thrombomodulin on the cell surface or release of active soluble thrombomodulin into the plasma. These mechanisms and their initiators are currently the subject of further study in our laboratory.

In summary, we have identified that acute traumatic coagulopathy occurs only in the presence of shock and is characterized by systemic anticoagulation and hyperfibrinolysis mediated through the activation of thrombomodulin. This has significant implications for the management of traumatic hemorrhage, and suggests that hypoperfusion must be corrected before the coagulation system's hemostatic balance can be restored.

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EDITORIAL COMMENT

The stimulating review by Brohi et al.,[1] represents a continuation of this group's landmark work which has illuminated novel mechanisms to explain the acute, coagulopathy of trauma independent of traditional concepts suggesting clotting factor deficiency. This work is particularly timely, as this unique phenomenon is a robust independent predictor of mortality. In fact, this process likely establishes the stage for further evolution of the classic "bloody vicious cycle" (hypothermia, acidosis, coagulopathy) described by our group over 25 years ago.[2] The clear significance of these findings for clinical practice are well emphasized by the authors: efforts at augmenting the clotting factor pathway through pre-emptive fresh frozen plasma (FFP) or recombinant factor VIIa may prove ineffective until shock and associated hypoperfusion are corrected. In fact, we recently suggested a revised "bloody vicious cycle" with an "FFP resistant" pathway, (acute endogenous coagulopathy) as opposed to a later "FFP sensitive" route leading to progressive systemic coagulopathy with associated clotting factor deficiency.[3]

The authors assert that systemic hypoperfusion was associated with anticoagulation and hyperfibrinolysis, and their mechanistic theory via the thrombomodulin pathway is supported by their data, emphasizing the central role of activated protein C and consumption of plasminogen activator inhibitor-1 (PAI-1). In addition, it does appear likely that tissue injury is also a major contributor to this process.

These findings emphasize the growing complexity of the coagulation process, but fall short of the author's stated goal to "fully characterize the coagulopathy of shock." Currently, little is known about how thrombomodulin is upregulated within this early post-injury time frame, or the precise instigators of the process. Furthermore, it is unclear whether the hyperfibrinolysis from thrombin-thrombomodulin formation is due to activation of thrombin activatable fibrinolysis inhibitor (TAFI) or via activated protein C consumption of PAI-1. In addition, the "anticoagulant thrombin" that is formed via thromobomodulin expression on the surface of the endothelium with subsequent complex and cleaving with protein C remains to be documented in clinical practice via measurements of activated protein C levels. Lastly, this study represents a "snapshot" of coagulation early after injury, and the dynamic mechanisms leading to subsequent factor depletion and progressive coagulopathy seen in clinical practice remain to be elucidated. In sum, we commend Brohi and colleagues for their unique contributions to the science of post-injury coagulation management, and look forward to their continued work to unravel the mysteries of this fundamental biologic process.

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