Fibrinolysis in Trauma: "Myth," "Reality," or "Something in Between"

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Abstract

The emphasis on fibrinolysis as an important contributor to trauma-induced coagulopathy (TIC) has led to a debate regarding the relative clinical significance of fibrinolysis in the setting of trauma. The debate has centered on two camps. The one camp defines fibrinolysis in trauma by standard coagulation tests as well as fibrin split products, D-dimers, and plasmin/antiplasmin levels. This camp favors a more liberal use of tranexamic acid and attributes more significance to hyperfibrinolysis in TIC. The other camp favors a definition of fibrinolysis based on the viscoelastic tests (VET), rotational thromboelastometry (ROTEM), and thromboelastography (TEG). These whole blood assays define hyperfibrinolysis at a higher threshold than plasma-based tests. Therefore, this VET camp reserves antifibrinolytic treatment for patients who demonstrate severe coagulopathy associated with hyperfibrinolysis. This bimodal attribution of the clinical relevance of fibrinolysis in trauma suggests that there may be an underlying "Myth" of the concept of TIC that was historically defined by plasma-based tests and a future "Reality" of the concept of TIC that is grounded on an understanding of TIC based on a VET-defined "fibrinolytic spectrum" of TIC. This narrative review explores this "Myth" and "Reality" of fibrinolysis in TIC and proposes a direction that will allow a "Future" interpretation of TIC that incorporates both the past "Myth" and present "Reality" of fibrinolysis TIC.

Keywords
- fibrinolysis
- trauma-induced coagulopathy
- tranexamic acid
- thromboelastography
- rotational thromboelastometry
- fibrinolytic spectrum
- fibrinolytic shutdown
- tissue injury phenotype
- hyperfibrinolysis
- hemorrhagic phenotype
- activated protein C

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> The coagulation, fibrinolysis, complement and kinin pathways are studied separately by scientists for their convenience. In life, they form a seamless web.
> —Ratnoff (1969)[1]

Fibrinolysis in Trauma: "Myth" or "Reality"

The relative clinical importance of fibrinolysis as a central mechanism of trauma-induced coagulopathy (TIC) has served as fertile ground for debate. This interest in fibrinolysis in trauma parallels a similar concern about the importance of fibrinolysis in sepsis that occurred more than two decades ago with the introduction of the much hoped for activated protein C (aPC) analog (Drotrecogin-α) in the treatment of sepsis.[2–5] The initial enthusiasm for aPC therapy was based on the assumption that the microvascular thrombosis caused by impaired fibrinolysis and anticoagulation associated with sepsis could be manipulated successfully by aPC. Similarly, the manipulation of fibrinolysis by the antifibrinolytic tranexamic acid (TXA) in traumatic resuscitation highlighted after the large randomized controlled trial known as the Clinical Randomization of an Antifibrinolytic in Severe Hemorrhage 2 Trail (CRASH-2) in 2010 was also met with unbridled enthusiasm.[6,7] However, subsequent post-CRASH-2 studies have revealed that the ubiquitous administration of TXA in trauma viewed through the lens of fibrinolysis as an important hemostatic derangement in TIC required a tempering of the view that the excessive fibrinolysis lay at the core of TIC.[7–13] Therefore, it is an appropriate time for a narrative review that focuses on the two ends of the spectrum of the "Myth" or "Reality" of the relative importance of fibrinolysis in TIC.

There are competing theoretical, pathophysiologic, and clinical assumptions related to the understanding of the coagulopathy of TIC.[3,4,8–10,14–17] We describe these competing assumptions as contributing to the "Myth" of fibrinolysis in trauma. These "Myths" will be considered in the light of what we will call the "Reality" of fibrinolysis in trauma, which refers to the successful practical and therapeutic approaches toward TIC.

Dysregulated fibrinolysis is one hemostatic abnormality that occurs in the bleeding trauma patient. There are a few leading and often overlapping hypotheses attesting to the pathophysiologic underpinnings of TIC, with shock, endothelial disruption, and inflammation as major contributors which differentially incorporate fibrinolysis primacy as the main driver of TIC.[8–10,17–22] Chang et al have very recently commented in their comprehensive review regarding TIC that as "TIC research proceeds, untangling its multiple interrelated pathways will not be straightforward"[17] (►**Fig. 1**).

Four Theories of TIC and Their Relation to Fibrinolysis

aPC Theory

The aPC theory stipulates that the combination of injury and hypotension causes tissue factor exposure with thrombin production and that shock-induced hypoperfusion causes upregulation of endothelial thrombomodulin (TM) with the binding of thrombin and activation of protein C.[4,18,23–25] aPC is the primary causal driver of TIC by inactivating factors V and VIII and by neutralizing plasminogen inhibitor 1 (PAI-1). These two mechanisms caused by aPC lead to impaired clot formation and increased clot lysis.[26] The overall result is a clot structure vulnerable to fibrinolysis due to reduced thrombin generation and increased fibrinolytic activity, culminating in dissolution of the fibrin mesh (►**Fig. 2**).[15,27–30]

The Disseminated Intravascular Coagulation /Fibrinolysis Hypothesis

The disseminated intravascular coagulation (DIC)/fibrinolysis hypothesis proposes that the propensity for hemorrhaging in trauma is secondary to hypoperfusion, resulting in vascular endothelial damage, creating first a consumptive coagulopathy from increased thrombin generation with subsequent higher fibrinolysis due to release of tissue plasminogen activator (tPA). This coagulopathy consumes clotting factors and fibrinogen and increases fibrin degradation products (FDPs) and D-dimers. The disproportionate amplification of plasmin compared with thrombin activation is central to explaining hyperfibrinolysis in trauma.[3,4,18,28,31–33]

In both the aPC and DIC/fibrinolysis theories, the DIC/fibrinolytic phase is followed 3 to 4 hours after trauma by a DIC/thrombotic phase due to high levels of PAI-1, resulting in the inhibition of fibrinolysis.[3,14,16,18,34–36]

Consumptive Fibrinogen-Centric Hypothesis

The consumptive fibrinogen-centric hypothesis focuses on the depletion of fibrinogen as the primary pathophysiologic driver of TIC. The consumption of fibrinogen results in diminished clot amplitudes as measured by viscoelastic tests (VETs) and elevated markers of fibrinolysis (FDP and D-dimer levels).[18,34] The lower fibrinogen levels may alter platelet function and increase protein C activation on the endothelial protein C receptor (EPCR)–TM–thrombin complex with resultant exacerbation of bleeding in the trauma patient.[18,34] A benefit of the fibrinocentric hypothesis is that it provides a treatable target, fibrinogen levels, using cryoprecipitate or fibrinogen concentrates to increase or maintain normal fibrinogen levels combined with antifibrinolytic agents to decrease fibrinolysis.[37–40]

Glycocalyx Injury Hypothesis

This hypothesis points to high levels of endothelial glycocalyx layer (EGL) disruption marked by high syndecan-1.[18,24] The shedding of two anticoagulant EGL components, chondroitin sulfate and heparan sulfate, increases the efficiency of TM and antithrombin, respectively, and may explain the TIC-associated protamine reversible "Autoheparinization."[17] The shedding of glycocalyx initiates a cross-talk between coagulation and immunologic entities due to activation of the endothelium.[25,28,31,41–44]

These hypotheses are not mutually exclusive and allow for a theoretical framework upon which to justify rational therapy.

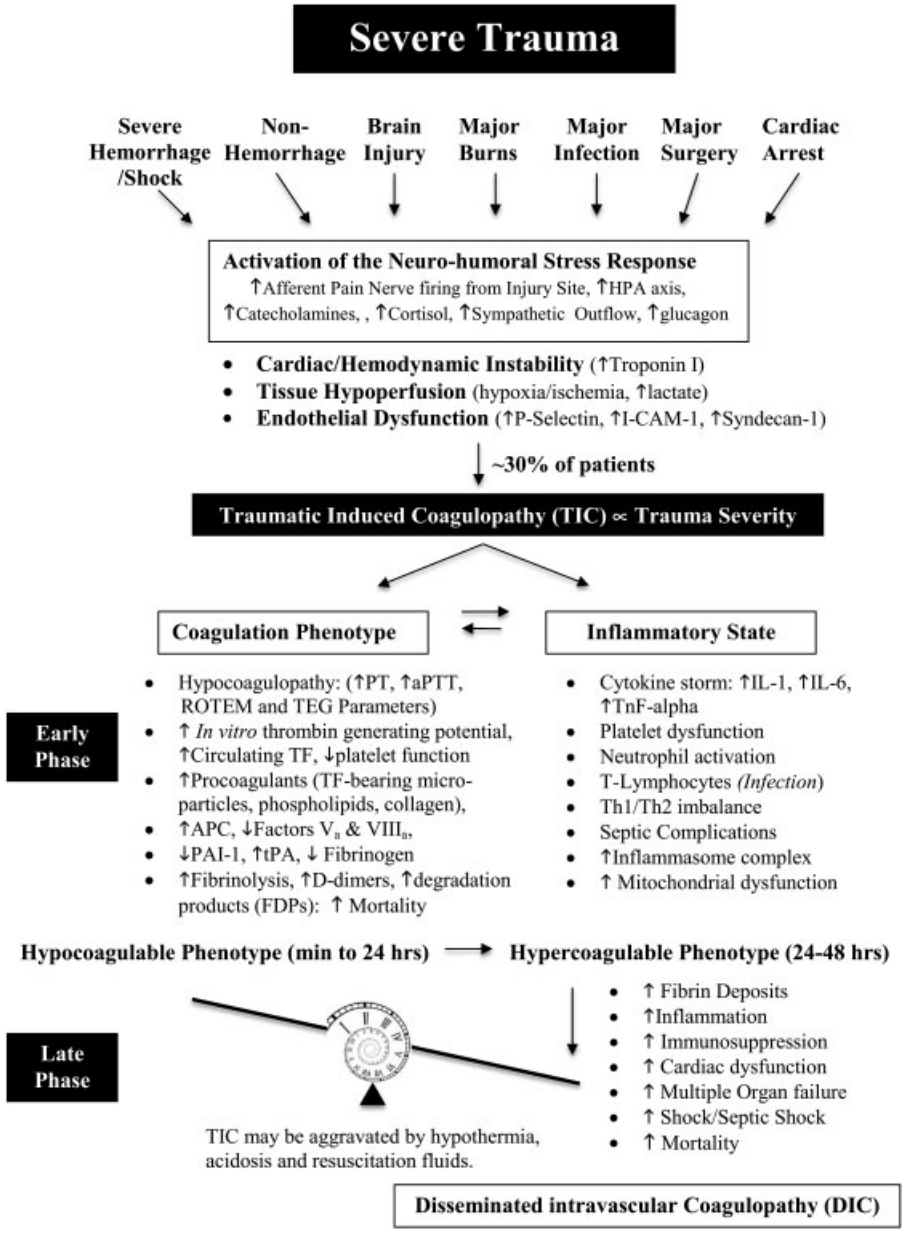


Fig. 1 Theoretical components of TIC. General scheme of TIC that occurs early after severe trauma. The upstream drivers of TIC seem to be the extent of tissue damage, hypoperfusion, and endothelial injury with different forms of trauma adding deep layers of complexity to its severity, progression, and clinical manifestation. Early TIC does not seem to be a consumptive coagulopathy but is characterized by multiple factors, including prolonged clotting times, systemic anticoagulation, local factor V inhibition, a paradoxical increase in TF-initiated thrombin-generating potential, increased activated protein C, dysfibrinogenemia, impaired platelet function, and hyperfibrinolysis. TIC may be aggravated further by hypothermia, acidosis, and resuscitation fluids. There seems to be two phases of TIC, an early and late phases, which may evolve into a DIC-like state. (Used with permission from Dobson et al.[18]) DIC, disseminated intravascular coagulation; TIC, trauma-induced coagulopathy.

Theories of TIC and Fibrinolysis: Myth versus Reality

These four hypotheses provide insight into the different coagulopathic as well as fibrinolytic phenotypes initiated by alterations in the TM–thrombin switch complex that develop within seconds to minutes of a traumatic event.[18] It is instructional to consider that there are an estimated hundreds of thousands of TM molecules and Annexin II, also known as Annexin A2, molecules (which bind to tPA and plasminogen through the Annexin A2 S100 complex) located in each of the 10^{13} endothelial cells lining all blood and lymphatic vessels within the body, covering a surface area of 3,000 to 7,000 m^2 which represents the size of a National Football League (NFL) football field or a standard soccer pitch. It has been proposed that hemostatic changes as a result of trauma in whole blood represent an evolutionary adaptation to a potential life-threatening condition.[18,45]

None of the aforementioned hypotheses explain the singular changes that occur instantly after significant tissue

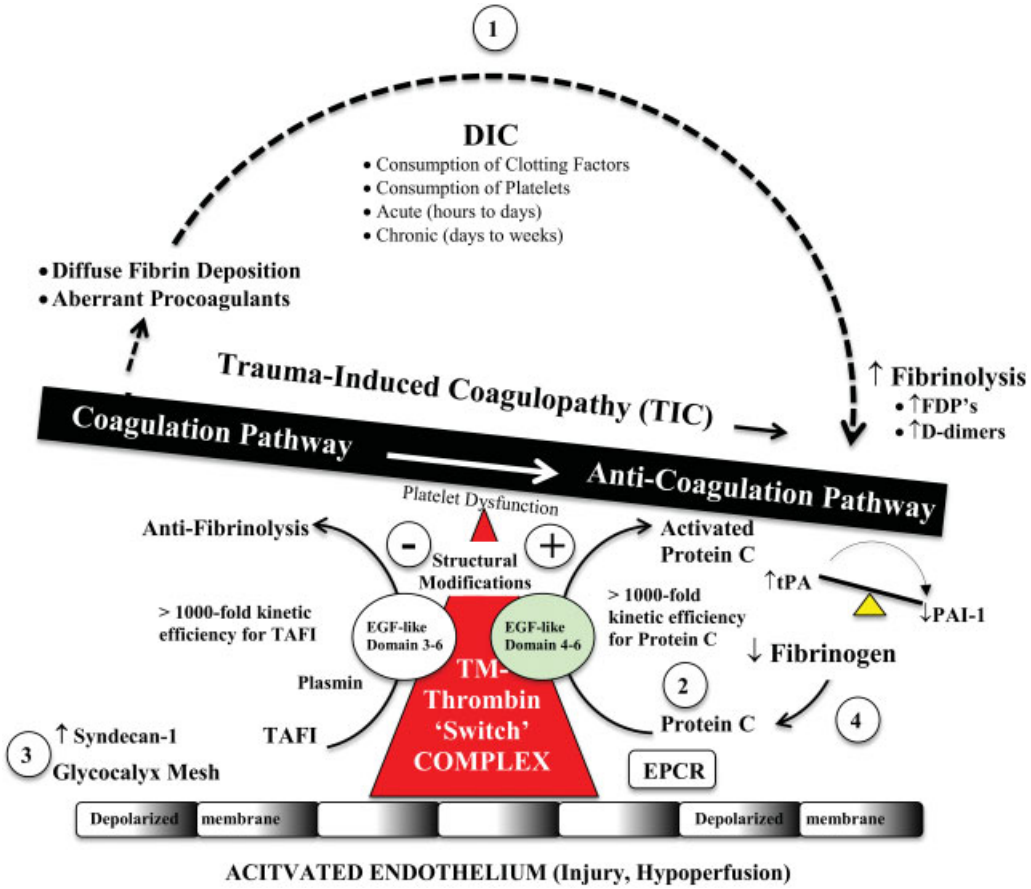


Fig. 2 The four theories of DIC in relation to the TM–thrombin switch complex. Broad schematic of the four TIC hypotheses and the TM–thrombin switch mechanism of hemostatic regulation. The current hypotheses to explain TIC include (1) the DIC-fibrinolysis hypothesis, (2) the activated protein C hypothesis, (3) the glycocalyx hypothesis, and (4) the fibrinogen-centric hypothesis. Central to the in vivo regulation of coagulation is the state of the endothelial TM–thrombin complex, which can either activate protein C anticoagulant or TAFI coagulation pathways. The switch, which occurs within seconds to minutes after trauma, may involve structural or posttranslational covalent modifications at the different sites on the TM–thrombin complex, which bind and activate protein C or TAFI in the presence of their respective cofactors and/or receptors. Protein C activation on TM–thrombin is further accelerated through binding to EPCR. An inverse relationship between fibrinogen levels and activated protein C has been reported and it has been proposed that at high levels, fibrinogen would inhibit TM–thrombin activation of protein C and, at low levels, would activate protein C activation and worsen the bleeding phenotype. DIC is separate from early TIC because it involves aberrant procoagulants and intravascular fibrin deposits. (Used with permission from Dobson et al.[18]) DIC, disseminated intravascular coagulation; TIC, trauma-induced coagulopathy.

injury or hypovolemic shock associated with trauma that leads to TIC.[17] This lack of mechanistic rationale for fibrinolysis as the main pathophysiologic agent for TIC has created a pathophysiologic vacuum that has led to attempts to classify TIC based on "Myths" of fibrinolysis in TIC.

Myths of Fibrinolysis in TIC

Myth No. 1: Plasma-Based Theory of Hemostasis Describes Fibrinolysis in Trauma

The first plasma-based unifying concept of a traumatic bleeding phenotype was proposed in 2003 by Brohi and colleagues who described what they called the acute coagulopathy of trauma/shock (ACoTS) also called acute traumatic coagulopathy (ATC), acute coagulopathy of trauma (ACoT), TIC, or early TIC.[5,16,18] The initial theoretical foundation of TIC was based on the plasma-based theory of hemostasis and was quantified by static fluid phase tests such as the prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), and fibrinogen levels known as standard coagulation tests (SCTs). In addition, platelet count and markers for fibrinolysis, such as FDP, D-dimer, and plasmin antiplasmin (PAP), were used to define clinically significant fibrinolysis. However, the FDP, D-dimer, and PAP tests would be expected to be elevated with any clot burden required for hemostasis, but they do not indicate the current capacity of the circulation to provoke systemic fibrinolysis.[4,15,18]

Myth No. 2: TIC Is DIC

Gando et al have described TIC as merely a final common pathway of coagulation dysregulation that leads to a DIC-like state. He described an early hemorrhagic phenotype where initial fibrinolysis and a later thrombotic phenotype of microvascular thrombosis prevail.[3,14,16] Traumatologists seeking a unified theory to delineate TIC from DIC were

warned by Gando that they were "Going down the wrong path."[3] The definition of DIC by Gando is based on plasma-based tests, FDP, D-Dimer, PTT, PT, fibrinogen, and platelet count, as well as other clinical parameters which form the basis for the International Society of Thrombosis and Hemostasis (ISTH) DIC scores. In trauma, these are neither sensitive nor specific tests to define the presence or absence of coagulopathy. Nor are these tests available in a timely fashion during the critical stages of trauma resuscitation. Gando's hypothesis of TIC as a manifestation of DIC has also been challenged as there is no histologic evidence of inappropriate disseminated clot formation,[10,18,46] and there are no correlations between ISTH DIC scores and anatomo-pathologic evidence of disseminated clot formation in early TIC.[46]

The clinical differences between septic and burn patients with hyperfibrinolysis/DIC and severely injured trauma patients with fibrinolysis epitomize this "Myth" versus "Reality." Aggressive fluid resuscitation is a vital therapeutic requirement for burn and septic patients with fibrinolysis. Antifibrinolytics do not improve clinical outcomes and can lead to worsening morbidity in septic patients.[18,47,48] In addition, many patients with sepsis have a relative hypofibrinolytic state, and resuscitation in the DIC of sepsis requires attention to maintaining microvasculature perfusion with crystalloids.[49–53] For patients with TIC, aggressive fluid management exacerbates fibrin breakdown and leads to worse outcome. A similar concern for excessive emphasis on the importance of fibrinolysis as a central mechanism for TIC has been noted by critics in the attempt to treat sepsis-induced coagulopathy with the aPC analog Drotrecogin-α more than 20 years ago.[2,8–10]

Myth No. 3: aPC Is Central to TIC

Cap and Hunt as well as other authors have challenged the importance of aPC in trauma with their analyses of platelet and plasma factor V resistance to aPC-induced cleavage which effectively challenged aPC's role as the central driving force of TIC.[8–10,17] The prevailing mechanistic rationale for TXA use in trauma resuscitation had been that aPC drives TIC through cleavage of factors Va and VIIIa and by binding PAI-1 and de-repressing t-PA, thus activating fibrinolysis.[4,5,15,27,29] This mechanism is problematic as platelet and plasma factor V are resistant to aPC cleavage at concentrations of aPC seen in TIC and that the levels of aPC noted in trauma are orders of magnitude less than those seen in therapeutic use of recombinant human aPC in sepsis.[8–10]

On the other hand, the addition of aPC to human blood in vitro also demonstrated increases in PT and PTT, decreased activation of factor V and VIII, and hypocoagulable parameters as determined by ROTEM in experimentally induced TIC.[26]

It has been proposed in the CRASH-2 trial that the benefit accrues from TXA's prevention of aPC-mediated fibrinolysis.[54] The CRASH-2 demonstrated a survival benefit of TXA given within 3 hours of injury to a broad range of trauma patients from low to moderate income countries mostly lacking established trauma systems.[6] This study provided clinical foundation for the administration of TXA in trauma without a theoretical basis as survivorship was not associated with less blood transfusion and a large number of patients in the study died of nonhemorrhagic shock-associated traumatic brain injury (TBI). Also, there were no markers for defining the incidence of fibrinolysis or coagulopathy.[7,55]

Recent utilization of VETs to stratify trauma patients based on the degree of fibrinolysis gives coherence to the observed findings of the effects of TXA in trauma patients who have evolved from the RCT CRASH-2 through subsequent nonrandomized control trials (nRCT). Post-CRASH-2 analyses have led to a middle ground whereby only trauma patients in shock-associated TIC are treated with antifibrinolytics. This middle ground was initially claimed by the Military Application of Tranexamic Acid in Traumatic Emergency Resuscitation studies (MATTERs I), which showed that TXA was beneficial in combat injuries requiring massive transfusion and that TXA increases this benefit, however, with the price of increase incidence of VTE.[6,11,12,56–59]

Therefore, it appears that the administration of antifibrinolytics to patients with TIC as a traumatologist's treatment paradigm is based on his or her theoretical view of the cause of TIC, which many clinicians and researchers center on fibrinolysis.[60,61] The debate is not whether fibrinolysis in trauma is "Myth" or "Reality," but how significant it is relative to outcome.[18,61]

Myth No. 4: Fibrinolysis and the 3-Hour TXA Paradox

It is not clear whether this 3-hour paradox represents "Myth" or "Reality." It has been suggested that this TXA 3-hour paradox is not "Myth" but has a likely explanation rooted in the comparative activity of tPA and urokinase plasminogen activator (uPA). It is known that tPA and uPA levels transiently increase in the brain soon after TBI and that tPA levels peak at 3 hours post-TBI, whereas uPA levels begin rising after tPA levels subside and peak at 8 hours (►**Fig. 3**). Although TXA effectively blocks tPA-mediated fibrinolysis, it is known that TXA promotes the ability of uPA to activate plasminogen, as the binding of TXA to plasminogen causes a conformational change which allows plasminogen to be more efficiently cleaved by uPA. It has

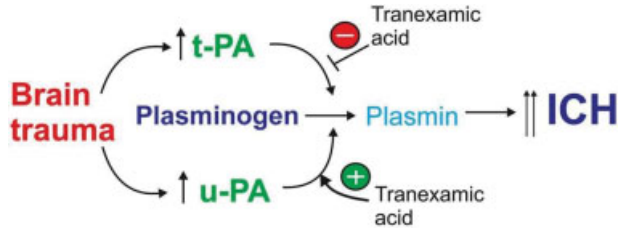


Fig. 3 Delayed uPA activity induced by TXA.[62] Following TBI, there is an increase in brain-derived tPA- and uPA-mediated fibrinolysis that promotes intracerebral hemorrhage (ICH). TXA blocks tPA-mediated fibrinolysis and ICH, but potentiates uPA-mediated plasminogen activation promoting ICH. TBI, traumatic brain injury; tPA, tissue plasminogen activator; TXA, tranexamic acid; uPA, urokinase plasminogen activator.

been suggested that the selective increase in uPA at the later time point explains the "TXA paradox."[17,62,63]

Relative Contribution of Coagulation Factors Fibrinogen, Platelets, and Endothelium to Clot Formation in TIC: Beyond Fibrinolysis

Fixed ratio coagulation therapy (FRCT) in TIC has recently been adopted as the method of choice for trauma resuscitation. A major concern of FRCT is that TIC is not a single coagulation disorder with one mechanism.[8–10] Studies have revealed that goal-directed coagulation therapy (GDCT) using point of care (POC) VETs provides individual therapy for each patient's hemostatic derangement and allows for dynamic changes during the early stages of resuscitation.[58,64–70]

Fibrinogen

The relative contribution of fibrinogen and platelets to promote clotting in normal samples using the TEG-measured functional fibrinogen and platelet mapping has been found to be 20% provided by fibrinogen and 80% by platelets with increasing percentage of platelet contribution occurring in patients in hemorrhagic shock.[71] The administration of cryoprecipitate or soluble fibrinogen with and without VET guidance improves mortality in patients with TIC. In addition, studies from Europe and the United States have shown that higher ratios of platelets to PRBC and FFP and earlier uses of cryoprecipitate and soluble fibrinogen provide protection in patients with TIC. The early administration of blood components, including fibrinogen, in TIC guided by VETs has been recently appreciated to improve patient outcomes by as much as 50% with TIC when compared with fixed ratios.[7,57,70,72–77]

Plasma

Recent emphasis on the early administration of the "Plasma First" strategy for the early treatment of TIC has focused attention on the protection of the endothelial glycocalyx barrier as well as the antifibrinolytic potential of FFP in patients with TIC. Regionalized fibrinolysis keeps the microvascular bed patent in the coagulopathic patient, while early administration of FFP prevents systemic hyperfibrinolysis as determined by the TEG.[78,79]

Platelets

Systemic fibrinolysis is impaired not only by PAI-1 but also by several additional proteins in human plasma and also inhibited in the presence of degranulated platelets.[79] Recent viscoelastic measurements in trauma patients have demonstrated that platelet function, not fibrinogen function, predicts sensitivity to tissue-type plasminogen activator in trauma patients and that early platelet dysfunction is an integral part of TIC. These findings support the clinical strategy of "Platelet First" resuscitation of trauma patients as adopted in the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial.[72,80,81]

Post-CRASH-2 Analysis and Reduced Emphasis on Fibrinolysis in Trauma

Following CRASH-2, several non-RCTs (nRCT) have provided conflicting evidence regarding the efficacy of TXA on a broad swath of trauma patients who were helped in CRASH-2.[12,56,59,82] It has been suggested that "exogenous inhibition of the fibrinolysis system in severely injured patients requires careful selection, as it may have an adverse effect on survival."[11] Similar conclusions regarding the ubiquitous use of TXA in mature trauma systems with limitation to its use in "shocked patients" have been noted by CRASH-2 authors in a nRCT, prospective observational study. Cole et al in their study "could not identify a clear outcome benefit to patients without shock," and therefore, "the findings give a clear signal for using TXA in severely injured, shocked civilian patients."[82] They also found that "VTE was more common in patients who received TXA. in the more severely shocked population." Their analysis states "There was a fourfold increase in the thromboembolic events in the TXA group (non-TXA: 2 vs. TXA: 8%, $p < 0.01$)."[82] These findings of injured and shocked patients with associated increased rates of VTE after TXA treatment are not consistent with the initial CRASH-2 results.[6,82]

The CRASH-2 trial has noted no difference with respect to vascular occlusive events, although the authors stated that owing to trial design they "might have under reported the frequency of these events."[6,83] The first nRCT for TXA in the prehospital setting has recently demonstrated a survival benefit for TXA, although this study is a retrospective analysis where TXA was given at the discretion of the emergency physician at the scene. In addition, survivors in this study had longer and more complicated hospital stays than controls. This finding validates the initial concerns of the possible under reporting of vascular occlusive complications made by the CRASH-2 authors and of the implications of administering an antifibrinolytic to patients with hypofibrinolysis that might result in increased incidence of multiorgan failure (MOF).[35,84] As a result of the controversy that has surrounded the CRASH-2 trial, formal recommendation for TXA use in the prehospital setting have been weak or discouraged.[83,85]

This duality of opinions centers on the significance of fibrinolysis in trauma and leads one to consider that there may be a spectrum of fibrinolysis that can be defined by VETs that will allow, when combined with clinical markers for severe shock, a more targeted administration of TXA.

Fibrinolysis in Trauma: Myth, Reality, or Spectrum

The Concept of "Spectrum of Fibrinolysis" in TIC

TEG analysis in trauma has recently described a spectrum of fibrinolytic disorders ranging from hypofibrinolytic to hyperfibrinolytic. The spectrum is dependent not just on the temporal sequence of the development of coagulopathy following trauma but also on the amount of tissue injury and/or the presence of severe hypoperfusion. Predominant tissue injury has been mostly associated with so-called

fibrinolytic shutdown, whereas the global hypoperfusion with markedly reduced oxygen delivery to the tissues has been linked with hyperfibrinolysis.[35,84,86]

Significance of Physiologic Fibrinolysis and Its Relation to the Spectrum

Physiologic maintenance of vascular patency is maintained by fibrinolysis. Disruption of the careful counterbalance of coagulation that is in part modulated by fibrinolysis has been described in trauma as early as 1794 by John Hunter. During the 1961–1975 Vietnam conflict, Hardaway and Drake proposed that irreversible shock occurs with the cessation of microvascular flow caused by microvascular fibrin deposition. They also proposed that irreversible hemorrhagic shock could be experimentally prevented by induced fibrinolysis.[18] This led to a Phase II trial that demonstrated reduced acute lung injury in trauma patients in the ICU who were treated with tPA.[87] Concomitant studies in the 1960s of coagulation abnormalities following elective surgery identified a subset of patients with inhibited fibrinolysis which was called "fibrinolytic shutdown."[88,89] This shutdown has been associated with an increased risk of VTE[90] and increased sepsis-related MOF.

Preventing clot degradation during acute injury offers a survival benefit as observed by the fact that shutdown of fibrinolysis is less lethal than hyperfibrinolysis.[35,84] This was recently noted by the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART).[91] In this trial, the increased rate of graft failure, renal failure, and death was noted with the direct antifibrinolytic agent, aprotinin, but not with epsilon aminocaproic acid or TXA (both of which work indirectly to block fibrinolysis). Empiric use of antifibrinolytics in the early history of liver transplantation led to increased incidence of VTE and the TEG was first used at that time in an attempt to predict those patients who would develop thrombotic complications.[92,93] It has been proposed that fibrinolytic shutdown (below) is a "missing link" in the pathogenesis of VTE in the surgical intensive care unit that offers a theoretical explanation for the increased rate of VTE with TXA in severely shocked trauma patients noted by many authors mentioned earlier.[11,12,35,56,84]

Fibrinolytic Shutdown

"Fibrinolytic shutdown" is the most prevalent phenotype found in severely injured trauma patients. These patients have lower incidences of massive transfusion and higher incidence of mortality attributed to MOF. The acute lung injury associated with MOF provides an example of how lack of fibrinolysis or "fibrinolytic shutdown" results in organ dysfunction. Tissue factor–mediated fibrin deposition occurs in the pulmonary vasculature in the setting of MOF associated with multiple traumas. Trauma patients who progress through acute lung injury to MOF and death have been found to have elevated levels of PAI-1 which reflects fibrinolytic shutdown.[94–97] Specific ratios of PAIs to activators may shutdown fibrinolysis after certain surgeries. For example, endothelial cells cultured in the plasma of postoperative hip replacement patients were associated with high levels of PAI-1. Also, elevated PAI-1 is associated with patients at risk for postoperative VTE in orthopedic surgery. Of note is the well-known lack of use of antifibrinolytics in acute hip fractures because of the increased rate of VTE in that group of patients.[90,98–100]

TBI enhances fibrinolytic shutdown and has been shown to result in significant release of tissue factor unbound to factor VIIa into the systemic circulation.[101] Sashindranath et al from the Medcalf laboratory have noted the influence of TBI on elevated PAI-1 levels and tPA in cerebrospinal fluid. The tPA/PAI-1 complexes are inactive, although these complexes exert a biological effect in TBI via low density lipoprotein receptor signaling. The tPA/PAI-1 complex alone is sufficient to disrupt neurovascular integrity by inducing matrix metalloproteinase 3 (MMP3) after TBI, providing a link between the plasminogen activator and MMP systems in TBI.[102] Recently, Chapman et al also showed evidence for tPA/PAI-1 complex formation in trauma.[33]

The relationships between levels of PAI-1 and fibrinolysis are not straightforward. The relative drop in PAI-1 shown in some trauma patients may simply be an increase in tPA causing a complex of tPA and PAI-1 which decreases the relative amount of free PAI-1. Free tPA, free PAI-1, and the tPA/PAI-1 complex should be measured simultaneously to fully characterize the imbalance that occurs during "fibrinolytic shutdown," physiologic fibrinolysis, and hyperfibrinolysis.[86]

Physiologic Fibrinolysis

Physiologic fibrinolysis is the least common of severely injured patients. In this less injured group of patients who do not have much physiologic stress, they do not require a higher level of fibrinolytic activity to maintain microvascular patency.

Hyperfibrinolysis

The definition of clinically significant fibrinolysis remains elusive. The lack of specificity of blood tests such as FDPs, D-dimer, and PAP levels have rendered them of little clinical use in predicting clinically significant fibrinolysis that requires treatment. TEG-defined fibrinolysis ranges from 3 to 7.5% lysis, while ROTEM-defined fibrinolysis ranges from greater than 7.5 to 15%. Lysis was defined using different terminology at 30 and/or 60 minutes for the TEG/ROTEM.[11,25,65,66,103–107] Addition of a TXA-reversible channel to the TEG to determine ex vivo reversibility of fibrinolysis may improve sensitivity in determining clinically significant clot burden and respective fibrinolytic response.[11,33]

The limitations of VETs to define fibrinolysis as mentioned earlier are amplified by the reduction of sensitivity of the VETs to define fibrinolysis by virtue of the activators kaolin for the TEG, elegiac acid for the ROTEM, and tissue factor for the rTEG and EXTEM version of ROTEM.[86] In addition, fluid mechanics of VETs do not replicate vascular hemodynamics. As a solution to these biomechanical differences between the TEG/ROTEM and in vivo clot formation, a method of rapid multichannel microfluidic detection has been proposed as a way of addressing the lack of venous and arterial shear forces on the endothelial surface with

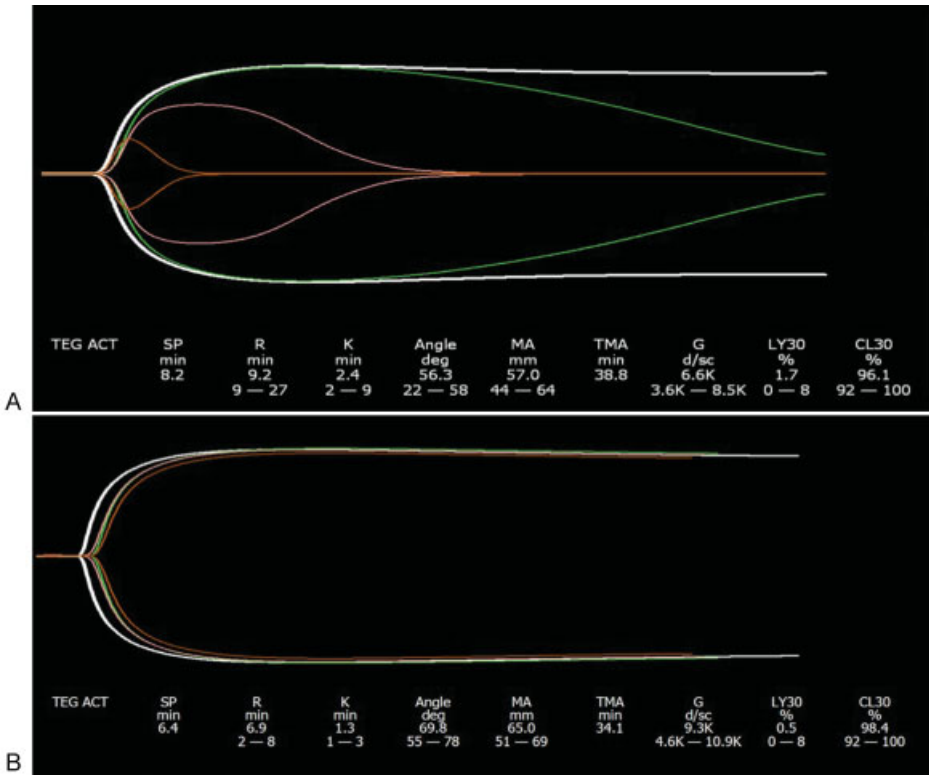


Fig. 4 (A) Physiologic fibrinolysis shows a dose response to tPA and magnitude of LY30: white, no TPA; green, low-dose TPA (75 μg/mL); pink, moderate-dose tPA (150 μg/mL); orange, high-dose tPA (300 μg/mL); tPA TEG challenge: http://links.lww.com/TA/A457.[33,35] Physiologic fibrinolysis (LY30 = 0.9–2.9; LY30 = 1.7). Fibrinolysis >2.9 native TEG. (**B**) Shutdown of fibrinolysis demonstrates overlapping curves despite increasing doses of tPA (75, 150, and 300 μg/mL) representing shutdown of the fibrinolytic system. tPA TEG challenge: http://links.lww.com/TA/A457.[33,35] Shutdown LY30 < 0.89 native TEG.

ex vivo testing that would reflect intravascular hemostasis. Rapid multichannel microfluidic detection has been shown to detect "(1) hemodilution-dependent impairment of clotting, (2) clot instability because of lysis, (3) blockade of fibrinolysis, and (4) platelet dysfunction during trauma." This more physiologic ex vivo recapitulation of in vivo hemostasis may provide novel diagnostic opportunities to predict trauma-induced coagulopathy (TIC) within 5 minutes.[108]

Defining patients with the hyperfibrinolytic group remains a challenge as there are no specific agreed upon parameters for ROTEM, TEG, or plasma-based assays which best define patients likely to benefit from TXA administration due to hyperfibrinolysis.[64,109–111] There has been much attention to PAI-1 activity as a marker for hyperfibrinolysis. However, PAI-1 activity has been shown not to be sensitive or specific in defining this group of patients if measured alone.[86] Recently, Moore et al have described a tPA TEG challenge test which allows early identification of trauma patients with clinically significant hyperfibrinolysis and defines trauma patients within the spectrum of fibrinolysis.[33] Using this technique, they have also described a latent hypersensitivity to exogenous tPA, which predicts the need for massive transfusion as well as defining those within the physiologic, shutdown, and hyperfibrinolytic spectrum.[33]

tPA TEG Challenge Test: Increasing the Sensitivity and Specificity of Defining Clinically Significant Fibrinolysis

The tPA TEG challenge is an ex vivo assay in which increasing doses of tPA are used to determine the level of fibrinolysis in whole blood. Moore et al have suggested that the mechanism of decrease in PAI-1 activity in hyperfibrinolytic (HF) trauma patients is not enzymatic degradation by aPC but is the result of complexity with tPA, driven by a massive increase in circulating tPA levels and tPA:PAI-1 complexes in response to shock. In this test, a native (non-Kaolin non-TF) TEG is challenged with a low dose of exogenous tPA (75-ng/mL human single-chain tPA in whole blood). The degree of lysis serves as a functional assessment of PAI-1 reserve. The principle of this assay is that as PAI-1 levels drop in trauma patients, the TEG LY30 in response to the low-dose tPA challenge increases. Therefore, with this exogenous tPA TEG challenge test, a spectrum of responses is observed in trauma patients from a marked increase in LY30 in those patient with hyperfibrinolysis and reduced PAI-1 levels to the absence of fibrinolysis or "fibrinolytic shutdown" with high PAI-1 levels (►**Fig. 4a**, **4b**).[33,86]

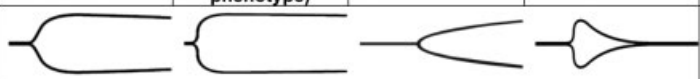
TYPE	Physiologic	Fibrinogen Shutdown (tissue injury phenotype)	Hypocoagulable (Non-shutdown, non-fibrinolytic)	Hyperfibrinolysis (hemorrhagic phenotype)	References
TEG REPRESENTATION					
rTEG LY30	0.81-2.9%	< 0.81%	0.81-2.9%	> 3%	
kaolin TEG LY30	3-8%	< 3%	3-7.4%	> 7.5%	
ISS	10-20	15-20	20-35	> 35	7,18,25,35,68,71,74 ,103,114-116
r-value	NL	NL	↑	↑↑	
α-angle	NL	NL	↓	↓↓	
MA	NL	↑	↓	↓↓	
MAFF	NL	NL	↓	↓↓	
Fg	NL	NL/↑	↓↓	↓↓	17,19,116,117
tPA	NL	NL	NL/↑	↑	17,19,86,118
uPA	NL	NL	↑	↑↑	17,43
PAI-1	NL	↑↑	NL/↓	↓	25,33,86
PLT Dysfunction	NL	↑	↑	↑↑	17,81,119,120
hcDNA	NL	↑	↑	↑↑	19,43,118
Clotting Factors	NL	NL	↓	↓↓	117
Tissue Factor	NL	NL	↑	↑↑	18,121
Plasmin Levels	NL	NL	↑↑	↑↑	25,109,110,112
tPA/PAI-1 complex	NL	NL	NL/↑	↑	18,86
Factors Va and VIIIa	NL	NL	NL/↓	↓	4,26,30
Factor XIII	NL	NL	NL/↓	↓	19
Autoheparinization	NL	NL	↑	↑↑	17,18,44
Syndecan-1	NL	NL	↑	↑↑	17,43-45,118
sTM	NL	NL	↑	↑↑	18,21,44,118
Catecholamine	NL	NL	↑	↑↑	17,20,45,118
BD / LA	None	None or ↑	↑↑	↑↑↑	18,25
aPC	NL	NL	NL/↑	↑	4,5,15,18,27
PT/PTT	NL	NL	↑	↑	19,43,44,118
sCD40L	NL	NL	↑	↑↑	19
PAP	NL	NL/↑	↑	↑↑	17,25,109,110,112
Interleukin 6	NL	NL	↑	↑↑	17,43,44
Antithrombin	NL	NL	↓	↓↓	21,54
P-selectin	NL	NL	↑	↑↑	18,54
HMGB1	NL	NL	↑	↑↑	43,118
TFPI	NL	NL	↓	↓↓	21,118
ICAM	NL	NL	↑	↑↑	18

Fig. 5 Theoretical and schematic table of markers as a function of trauma severity and position on the fibrinolytic spectrum as determined by rTEG and kaolin TEG. References are sample review articles and experimental studies.[114–121] Fg, fibrinogen; tPA, tissue plasminogen activator; uPA, urokinase plasminogen activator; PAI-1, plasminogen activator inhibitor-1; hcDNA, histone complexed DNA; sTM, soluble thrombomodulin; BD/LA, base deficit/lactic acid; aPC, activated protein C; sCD40L, soluble CD40 ligand; PAP, plasmin antiplasmin; HMGB1, high mobility group box 1; TFPI, tissue factor pathway inhibitor; ICAM, intercellular adhesion molecule. *TEG and ROTEM analysis of patients with sepsis-associated coagulopathy reveals a very low incidence of fibrinolysis when compared with patients with trauma-induced coagulopathy.[122,123]

Clinical Application of Fibrinolytic Shutdown through Physiologic and Hyperfibrinolysis in TIC: In Search of Reality

Mortality among trauma patients can be seen within the spectrum of fibrinolysis, manifest by a U-shaped distribution of mortality related to the fibrinolytic phenotype.[35,84,86] Clinical studies have confirmed the utility of this fibrinolytic spectrum with the well-known observation of high mortality in patients at the hyperfibrinolytic end of the spectrum as defined by VETs (►**Fig. 5**).

The historical and recently described clinical concern for antifibrinolytic-induced hypercoagulable complications is more than a theoretical concept, as post-CRASH-2 nRCTs have demonstrated increased rates of VTEs in subsets of patients given TXA for trauma resuscitation.[35,56,59,82,84] Military surgeons who used TXA to resuscitate mostly tissue injury phenotype "fibrinolytic shutdown" blast injuries in Afghanistan treated with TXA have noted "an entity of 'hyperacute venothromboembolic disease' occurring as early as six hours following massively destructive tissue trauma." Such procoagulant complications following severe trauma

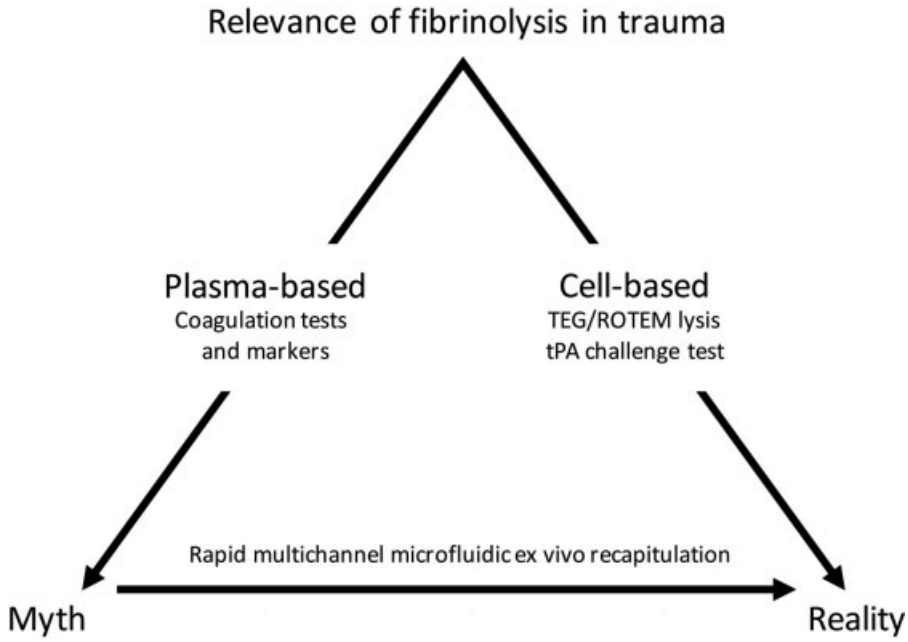


Fig. 6 Schematic diagram of relevance of fibrinolysis in trauma. Historical reliance on plasma-based coagulation tests and markers, such as D-dimer, FSP, PAP, PT, PTT, and fibrinogen, has leant to the myth of the central importance of fibrinolysis in TIC. The TEG/ROTEM-defined lysis is rendered more sensitive and closer to reality with the tPA challenge test. Rapid multichannel microfluidic ex vivo recapitulation combines plasma-based and cell-based theories of hemostasis on an endothelial platform and may provide a more realistic analysis of TIC.

and TXA use have received little notice in the literature.[54] The concept of a fibrinolytic spectrum of trauma allows a practical and theoretical explanation of the grades of coagulopathy observed in the early and late stages of severe trauma.[87] The unintended consequences of administering TXA ubiquitously to all prehospital trauma patients, which is associated with increased rates of VTE in specific populations, has been highlighted by the recent decision of the National Health Service (NHS) to deny payment for those patients who do not receive TXA when deemed appropriate.[112]

Rather than focus on the definition of significant fibrinolysis in TIC, a middle ground would be to use clinical indicators for initial prehospital or emergency department resuscitation subsequently guided by POC VET to determine not just fibrinolysis but also the need for other blood components that include FFP, platelets, cryoprecipitate as well as the hemostatic adjuncts—PCC, soluble fibrinogen, and TXA. This approach provides reconciliation between the "Myth" and "Reality" of fibrinolysis in trauma.[65,66,68–70,74,113]

Reconciliation of "Myth" and "Reality" of Fibrinolysis in Trauma: Seeking the Middle Ground

Future detection of coagulopathies in trauma patients may require both plasma-based SCTs as well as VETs complimented by multichannel microfluidic ex vivo recapitulation studies that reflect more accurately the hemostatic derangements in arterial and venous beds under shear forces similar to those found in vivo.[108] Somewhere in between the two pillars of plasma-based SCTs and VETs on the spectrum of tests that detect fibrinolysis lies a more balanced approach (►**Fig. 6**).

This heterogeneity of attributions of the significance of fibrinolysis in TIC highlights the fact that fibrinolysis is not an independent system. As Mutch and Booth have presciently noted concerning fibrinolysis in trauma: "Undoubtedly we choose our approaches and molecules of interest to us, and may well ignore other players, by virtue of the experimental system used. These choices may be convenient, but we must bear in mind the selection bias introduced into the system."[61]

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