Mechanisms of trauma-induced coagulopathy

Nathan J. White

1Division of Emergency Medicine, University of Washington, Seattle, WA

The identification and management of coagulopathy is a critical component of caring for the severely injured patient. Notions of the mechanisms of coagulopathy in trauma patients have been supplanted by new insights resulting from close examination of the biochemical and cellular changes associated with acute tissue injury and hemorrhagic shock. Acute intrinsic coagulopathy arising in severely injured trauma patients is now termed trauma-induced coagulopathy (TIC) and is an emergent property of tissue injury combined with hypoperfusion. Mechanisms contributing to TIC include anticoagulation, consumption, platelet dysfunction, and hyperfibrinolysis. This review discusses current understanding of TIC mechanisms and their relative contributions to coagulopathy in the face of increasingly severe injury and highlights how they interact to produce coagulation system dysfunction.

Introduction
Hemorrhagic shock from blood loss is a critical cause of mortality in severely injured patients. Contributing to blood loss is an intrinsic dysregulation of the blood coagulation system now named trauma-induced coagulopathy (TIC). TIC arises in the presence of both tissue hypoperfusion from blood loss and severe anatomical tissue injury and, when present, is strongly and positively associated with mortality. The physiological environment in which TIC arises is a complex mixture of inflammation, anticoagulation, and cellular dysfunction of mixed etiology. The coagulation system balance also changes rapidly during injury and resuscitation so that the TIC phenotype can evolve quickly over time from primarily an anticoagulant to a procoagulant state within hours to days if the patient survives. Given the complexity and rapidly changing nature of traumatic injury and TIC, underlying mechanisms have not been fully elucidated. However, several key processes, including dysfunction of natural anticoagulant mechanisms, platelet dysfunction, fibrinogen consumption, and hyperfibrinolysis, have been identified as primary components of TIC. In addition, specific effects of blood dilution from resuscitation fluids, environmental hypothermia, and acidosis can modulate clot formation, adding more layers of complexity to TIC. This review focuses on the initial intrinsic TIC phenotype found almost immediately after severe injury with tissue hypoperfusion. This phenotype arises quickly after injury with blood loss and is relatively independent of secondary influences. The individual underlying contributors and their interaction to produce TIC are highlighted, in addition to some of the key controversies in mechanism and current knowledge gaps.

Anticoagulation
Anticoagulation is a primary component of TIC. TIC was initially described as an increased international normalized ratio (INR) by Brohi et al in severely injured trauma patients measured on arrival at the emergency department.1 Activated partial thromboplastin times (aPTT) were also elevated in patients with severe injury and there was tissue hypoperfusion as measured by the base deficit, although changes in this assay lagged behind changes in INR. The investigators presumed that elevations in INR and aPTT were independent of dilution by fluid resuscitation or environmental influences due to the limited resuscitation fluids received by these patients before sampling.1 Later, several studies corroborated this assumption by showing TIC to be present at the scene of injury before onset of resuscitative treatment.2,3 From these data, the thrombin-thrombomodulin-protein C anticoagulant system was implicated as a potential primary mechanism of anticoagulation.4-5 Brohi et al found increased circulating thrombomodulin that correlated with decreased plasma protein C levels and attributed the decrease in protein C to its activation (activated protein C [aPC]) by thrombin bound to thrombomodulin.5 Interestingly, this anticoagulant pattern was only present in those patients demonstrating both severe anatomical injury and tissue hypoperfusion.3 Subsequent studies have confirmed an increase in aPC concentration in similar trauma patients.6,7 The anticoagulant properties of aPC are derived by its degradation of activated factors V and VIII, producing reduced concentrations and activities. Supporting this mechanism, Rizoli et al found that, among 110 trauma patients, factor V deficiency was always present as a component of critical factor deficiency.8 Experimental murine studies have confirmed that the anticoagulant property of aPC can mediate increased aPTT in the setting of combined injury and hemorrhagic shock.9 Investigators found that blocking of the anticoagulant function of aPC by monoclonal antibody reversed the trauma-induced elevation of aPTT in this murine model but had no impact on survival. Interestingly, blockade of the anticoagulant and endothelial interactions of aPC in the same model led to rapid mortality with massive intravascular thrombosis, suggesting a protective role for aPC in regulating endothelial interactions during traumatic shock in addition to its anticoagulant effects.9

Other anticoagulant mechanisms may contribute to the pathomechanism of TIC. Endogenous autoheparinization, possibly related to shedding of the endothelial glycocalyx, has been suggested by the ability to reverse anticoagulation in the presence of heparinase in whole blood from TIC patients.10 There is also disagreement regarding the contribution of disseminated intravascular coagulation (DIC) to the anticoagulated state of TIC. Gando et al contend that TIC is primarily a reflection of coagulation activation and fibrinolysis that they describe as DIC with fibrinolytic phenotype.11 Measuring fibrinopeptides liberated either by thrombin or from degradation by plasmin, they have shown a relatively greater increase of plasmin relative to thrombin activation during the initial encounter with trauma patients. These investigators propose that activation of plasmin fully accounts for the initially anticoagulated state and that there is no need to separate TIC from DIC with...
hyperfibrinolysis. They also point out that increased concentration of degradation products from cross-linked fibrin (D-dimer) argues for diffuse fibrin generation from thrombin generation. They also argue that increasing the concentration of soluble thrombomodulin in plasma does not necessarily conclude that it is responsible for anticoagulation because solubilized thrombomodulin demonstrates decreased activity versus thrombomodulin bound to endothelium. Nevertheless, it is clear that anticoagulation, either directly from the thrombin-thrombomodulin-aPC system or through thrombin activation and factor consumption, is an important component of TIC that deserves further focused study to fully understand.

**Platelet dysfunction**

There is a rapidly growing body of support for a prominent role of platelet dysfunction in the pathophysiology of TIC. Historically, platelet-specific transfusion and hemostatic management were based on critical thresholds in platelet counts and less so on platelet function. In trauma, platelet count does strongly influence hemostasis and a low or decreasing platelet count in trauma patients does predict greater mortality. However, platelet counts are typically within the normal range during early TIC, indicating that their consumption or dilution is not a major contributor to the early TIC mechanism.

Moderate or even mildly decreased platelet aggregation is strongly associated with mortality. Kutcher et al used impedance aggregometry to characterize platelet dysfunction in trauma patients on arrival at the emergency department. They found that of 101 patients, almost half (45.5%) showed decreased platelet aggregation in response to ADP, thrombin receptor-activating peptide, arachidonic acid (AA), and/or collagen. There was an astonishing 10-fold increase in mortality in patients having any one of these platelet aggregation deficits, and admission AA and collagen responsiveness were sensitive and specific predictors of mortality. Solomon et al showed similar results in 163 trauma patients of which 20 (12.3%) died and, again, even relatively minor defects in platelet aggregation detected by multiple electrode aggregometry were associated with mortality. They also found the platelet contribution to clot firmness measured using rotational thromboelastometry (ROTEM) to be significantly decreased in nonsurvivors. Using thrombelastography modified to detect platelet-specific effects (Platelet Mapping; Haemonetics) Wohlauer et al also found a pronounced inhibition of clot strength when activated with ADP and AA in 51 trauma patients within 30 minutes of injury.

These studies highlight the importance of intact platelet aggregation and contraction in the response to hemorrhage; however, they do not suggest a specific mechanism of action for platelet dysfunction. Some clues may be found in the relative increased tendency for decreased platelet aggregation in trauma patients on arrival. Some mechanisms of decreased platelet aggregation in trauma may include inhibition of multiple receptors, altered calcium influx in response to activation, or possibly even energetic defects arising downstream from receptor activation. Further focused study is required to elucidate the culprit molecular pathways.

**Fibrinogen consumption and fibrinolysis**

After its activation by thrombin, fibrinogen spontaneously polymerizes from its individual monomers to form an insoluble polymeric fibrin mesh to stop blood loss at sites of vascular injury. This process, along with platelet-induced clot contraction, is the primary component of secondary hemostasis. There is strong evidence that consumption of fibrinogen and fibrinolysis by the action of plasmin are key mechanistic components of TIC. Solomon et al demonstrated that fibrinolysis measured in patients with hemorrhagic shock was associated with increased rates of loss which was greater than liver production during hemorrhage and resuscitation. Others have demonstrated rapid decrease in functional fibrinogen concentration and clot strength during hemorrhage and before fluid resuscitation.

Fibrin clot formation is naturally counterbalanced by enzymatic clot breakdown or fibrinolysis. During fibrinolysis, tissue plasminogen activator (tPA) and the precursor plasminogen undergo high-affinity binding to fibrin, where tPA activates plasminogen to plasmin. Plasmin then cuts fibrin fibers at specific lysine residues. As a result, the scaffold of the formed clot is rapidly degraded and the clot is eventually destroyed. An increase in fibrinolysis, known as hyperfibrinolysis, is a known consequence of trauma with hemorrhagic shock. It was described as a critical mechanism of action of TIC by Brohi et al, who detected increased levels of tPA and the clot breakdown product D-dimer. They also demonstrated that fibrinolysis was associated with increased mortality rate in trauma patients. They found that overt lysis was rare (<5%), whereas moderate fibrinolytic activation, defined as plasmin-antiplasmin complex concentration > 2× the control levels was common, having been present in 57% of patients in this cohort. In addition, those with fibrinolytic activation demonstrated higher mortality (12% vs 1%, P < .001) and had more complications. Increased tPA antigen concentration and reduced fibrinogen concentration has also been found in trauma patients meeting the criteria for early DIC. Using viscoelastic methods of measurement, overt hyperfibrinolysis is associated with an exceedingly high (60%-100%) mortality rate in trauma patients with rapid primary clot lysis and is often associated with a perimortem state. Mortality is also directly and positively associated with degree of fibrinolysis, as demonstrated by Schoch et al, who found that mortality increased with the speed of clot breakdown.

The mechanism of hyperfibrinolysis in trauma is attributed to activated protein C-mediated inactivation of plasminogen activator inhibitor-1 (PAI-1), leaving tPA unchecked. Brohi et al have provided evidence for this mechanism by demonstrating that activation of protein C by thrombin-thrombomodulin is associated with reduced PAI-1 concentration and elevated D-dimer. They conclude that this association is mediated by an inhibitory action of aPC on PAI-1, which has also been demonstrated in vitro. However, Ueda et al used the euglobin lysis time assay to show that recombinant aPC inhibited cleavage and inactivation of PAI-1, concluding that aPC appears to normalize hyperfibrinolysis by inhibiting thrombin-dependent PAI-1 degradation. Therefore, aPC may alternatively enhance fibrinolysis by its thrombin-reducing...
effects rather than by a direct inhibitory effect on PAI-1. Destruction of PAI-1 via neutrophil elastase may also enhance fibrinolysis in trauma. In a smaller series of 57 trauma patients, Hayakawa et al found that those meeting the criteria for early DIC also displayed increased neutrophil elastase concentrations and neutrophil elastase-specific fibrin degradation products in addition to markers of plasmin activation and IPA release on day 1 of treatment. In addition to direct cleavage of fibrin and fibrinogen, neutrophil elastase can also degrade and inactivate PAI-1, so it may act similarly to the aPC system by altering PAI-1 availability during traumatic shock. Obviously, these data raise more questions than answers and further specific study of the mechanisms involved in hyperfibrinolysis during trauma are needed to reach definitive conclusions.

Combining injury and shock to produce TIC

Observational clinical data have demonstrated that TIC is most common in severely injured trauma patients who are subjected to a high degree of both anatomical tissue injury and hypoperfusion from hemorrhagic shock. A multicenter retrospective study of over 3646 trauma patients confirmed that the severity of TIC is strongly associated with combined severe injury and shock. A synergistic effect of materials released from tissue injury with inflammation and anticoagulant factors induced by endothelial injury and tissue hypoxia likely mediate this relationship to produce TIC.

There is evidence that circulating intracellular contents such as histones, known to be released from injured tissue, are associated with TIC. Kucher et al examined plasma histone concentration in 132 trauma patients on hospital arrival, finding a high degree of circulating histone burden in patients with higher anatomical injury severity. Increased histone concentration was present in patients with abnormal coagulation tests, increased markers of fibrinolysis, and elevated aPC. Rapid measurement of extracellular DNA levels in the plasma of trauma patients also revealed a significant elevation within 20 minutes of injury. In a small study of 37 multiple trauma patients, patterns of elevated histones and extracellular DNA derived from activated neutrophils followed leukocyte counts, IL-6 levels, and myeloperoxidase levels and were associated with subsequent sepsis, multiple organ failure, and death. These early investigations suggest that circulating material from direct tissue trauma and leukocyte activation may be primary candidates to explain the critical role of anatomical injury severity in the development of TIC.

Neurohormonal and endothelial activation in response to acute blood loss may also be involved in the development of TIC. Johansson et al examined 75 victims of trauma and found that neurohormonal response in the form of increased circulating adrenaline concentration was significantly elevated in nonsurvivors and was independently associated with mortality, coagulation dysfunction, and markers of tissue and endothelial damage. This relationship may be mediated by products of endothelial or platelet activation, such as soluble vascular endothelial growth factor receptor 1 or soluble CD40 ligand, both of which have been shown to be predictive of shock, coagulopathy, and mortality in trauma patients.

Although specific mechanisms of shock-induced endothelial activation and dysfunction have not yet been elucidated, there is emerging evidence that disruption of the endothelial glycocalyx barrier (indicated by syndecan-1 release) plays an important role in the endothelial response to traumatic shock. Haywood-Watson et al found elevated plasma syndecan-1 concentration in severely injured trauma patients in hemorrhagic shock. They also found that 3 proinflammatory cytokines, IFN-γ, IL-1β, and fractalkine, were negatively associated with plasma syndecan-1 levels, presumably by their binding and activation of endothelium. These investigators then showed that endothelial barrier function was reduced in association with shedding of syndecan-1 and that this process was inhibited by application of fresh frozen plasma in vitro. Glycocalyx shedding and associated loss of endothelial barrier function also presumably promotes leukocyte recruitment and activation, liberation of injurious reactive oxygen species, and endothelial cell damage, as demonstrated by the damaging effect of incubating leukocytes captured from trauma patients on endothelial progenitor cells in vitro.

Summary

Clearly, TIC arises from a complex interplay among coagulation, inflammation, and cellular dysfunction (platelets, leukocytes, endothelium). Recent evidence points toward several interconnected mechanisms, including anticoagulation by the thrombin-thrombomodulin-protein C system, platelet dysfunction, and hyperfibrinolysis. New evidence regarding the prominent role of inflammation and endothelial activation/dysfunction as orchestrators of TIC continues to add to our understanding of this important and complex pathology. Although our understanding of this disease has improved immensely in recent years, there remain many questions yet to be answered.

Disclosures

Conflict-of-interest disclosure: The author is on the board of directors or an advisory committee for Stasys Medical Corporation; has received research funding from the National Institutes of Health, the Department of Defense, the Wallace H. Coulter Foundation, and the Washington State Life Sciences Discovery Fund; has consulted for Stasys Medical Corporation; holds patents with or receives royalties from Stasys Medical Corporation; and has equity ownership in Stasys Medical Corporation. Off-label drug use: None disclosed.

Correspondence

Nathan J. White, Harborview Medical Center, Emergency Dept, Box 359702, 325 9th Ave, Seattle, WA 98104; Phone: 206-744-8465; Fax: 206-744-4095; e-mail: whiten4@uw.edu.

References