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Trauma-Induced Coagulopathy: The Past, Present, and Future

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Abstract

Trauma remains a leading cause of death worldwide, and most early preventable deaths in both the civilian and military settings are due to uncontrolled hemorrhage, despite paradigm advances in modern trauma care. Combined tissue injury and shock result in hemostatic failure, which has been identified as a multi-dimensional molecular, physiologic, and clinical disorder termed trauma-induced coagulopathy (TIC). Understanding the biology of TIC is of utmost importance as it is often responsible for uncontrolled bleeding, organ failure, thromboembolic complications, and death. Investigations have exposed that TIC is characterized by multiple phenotypes of impaired hemostasis due to altered biology in clot formation and breakdown. These coagulopathies are attributable to tissue injury and shock and encompass underlying endothelial, immune, and inflammatory perturbations. Despite the recognition and identification multiple mechanisms and mediators of TIC and the development of targeted treatments, the mortality rates and associated morbidities due to hemorrhage after injury remain high. The purpose of this review is to examine the past and present understanding of the multiple distinct but highly integrated pathways implicated in TIC to highlight the current knowledge gaps and future needs in this evolving field, aimed at reducing morbidity and mortality after injury.

Keywords

Blood Coagulation Disorders; Exsanguination; Hemorrhagic Shock; Hemostasis; Trauma

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Introduction

Trauma remains a leading cause of death worldwide(1), and it is expected that rates of death due to injury will continue to rise as populations age (2). In the 1970s, Trunkey described a trimodal distribution of trauma deaths (3), with immediate deaths thought to be non-preventable and due to hemorrhage. However, since that time there have been paradigm changes in our understanding of death due to hemorrhage including the recognition of trauma-induced coagulopathy (TIC), as well as advances in resuscitation techniques designed to mitigate the effects of TIC (4). It is now clear that one-quarter to one-third of hemorrhaging trauma patients suffer from TIC, a multi-phenotypic disease state that encompasses disorders of coagulation and inflammation characterized by impairments in clot formation, breakdown, and overall vascular homeostasis. TIC is associated with increased early transfusion requirements, the development of organ failure, and mortality (5, 6). Death from hemorrhage is not the sole consequence of TIC. Due to the innate crosstalk between coagulation and inflammation, there are widespread adverse downstream inflammatory and immune consequences associated with early trauma coagulopathies, including organ dysfunction and thromboembolic complications(6).

Despite these focused investigations into the mechanisms and mediators of TIC and improvements in care related to identification and treatment, hemorrhage related mortality continues to be the most common cause of preventable deaths after injury (7). Therefore, targeted scientific focus on advancing our understanding of TIC across molecular and clinical realms remains of utmost importance to rescue a large percentage of injured patients from death due to early hemorrhage and late organ failure. Although substantial advances have been made, the links between the injury induced impairments of each of the various mechanisms that contribute to the failure of clot formation, lysis, and vascular homeostasis remain open science. In addition, the field is desperate for clear causal and intervenable pathways between coagulation, inflammation, and immune dysfunction. However, mechanistic studies related to TIC are fraught with the limitations of analyzing blood and vascular homeostasis in ex-vivo environments that often lack endothelium, flow, and local tissue injury milieu while extrapolating microvascular environments into macro measurements. The overall purpose of this review is to understand the past and present in order to highlight the needed future directions of this evolving field.

History

Injury induced disordered clotting that is associated with bleeding and death is not a modern concept. Historic battlefield descriptions of this date back to the eighteenth century. During the Korean and Vietnam Wars, patients in hemorrhagic shock were identified to have prolonged prothrombin and partial thromboplastin times early after injury and prior to interventions, hemodilution, or hypothermia, ultimately requiring more blood and having higher mortality(8). What followed was evolution of purported mechanisms of this coagulopathy including an initial focus on consumptive states and dilutional effects of resuscitation with fluids and bloods products.

These observations of coagulopathy during major wars stimulated significant military and civilian trauma research, and further critical concepts emerged including the recognition of the clear transition from a clinically hypocoagulable to hypercoagulable state and the central role that hypoperfusion due to shock played. Multiple groups simultaneously identified that hemorrhage and resuscitation induced depletion of coagulation factors and dilutional coagulopathy led to an irreversible physiologic collapse(9). These concepts were formally coalesced into the 'Bloody Vicious Cycle' by Kashuk and colleagues in the early 1980s(10). Following this, it was increasingly recognized that post-injury hemorrhage exacerbated by the 'lethal triad' of hypothermia, acidosis, and coagulopathy was a vicious cycle that led to more coagulopathy and ultimately high mortality rates(11). This increasing recognition led to changes in clinical practice in the 1980s with formalization of damage control surgical and resuscitative techniques to halt the cycle of acidosis, hypothermia, and coagulopathy(12). In the early 2000s, Brohi, Cohen, and colleagues formally described the entity of acute traumatic coagulopathy in human and animal models, that reflected an endogenous biology independent of resuscitation, required combined tissue injury and shock, and had significant associations with poor outcomes and mortality(6, 13–16). Although modern study of trauma patients has identified no significant difference in the presentation core temperature or amount of prehospital crystalloid given to patients that developed TIC requiring transfusion(17), there remains evidence that resuscitation and hypothermia continue to contribute to TIC(18), but are not necessary prerequisites. However, patients who develop TIC are profoundly more acidemic, supporting the pivotal importance of a shock state in the setting of tissue injury (17).

Finally, critical in the evolution of our understanding of TIC beyond consumption of coagulation factors, was the progress made in defining coagulation outside of the classic enzymatic coagulation cascade. In 2001, Hoffman and Monroe proposed the 'cell-based model of hemostasis' based on overlapping events of initiation (extrinsic pathway on tissue factor bearing cells), amplification (positive feedback of thrombin on platelets), and propagation of clotting (intrinsic pathway on activated platelets) that were regulated by cell surfaces rather than enzymatic protein and protease reactions alone(19). This model of hemostasis magnified research focused on multiple pathways contributing to TIC, rather than solely on a dilutional failure of the enzymatic processes of clot formation, and a large body of investigation has contributed to the current multi-dimensional understanding of the biologic contributors of TIC, to be addressed specifically below and summarized in Table 1.

However, despite years of basic and translational investigations of TIC, in 2013, Gando and the Standardization Committee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis reported that what was termed TIC was similar to consumptive states like DIC(20). However, best evidence at this time suggests that although TIC encompasses the criteria of DIC, it remains distinct from and not sufficiently characterized by the broad less-precise major (low platelet count, prolonged prothrombin time, increased soluble fibrin or fibrin-degradation products) and specific (low antithrombin, low protein C, and increased thrombin-antithrombin complexes) DIC criteria outlined by the Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis (21) (Table 2). The definition of TIC has been in evolution for decades, shifting from the perception of a resuscitation induced dilutional coagulopathy, to a

multifactorial and multi-mechanistic event. TIC is distinct and more complex than the DIC (Table 2), covering a wide range of impaired clot formation and lysis, in combination with failure of vascular homeostasis and immunoactivation resulting in multiple clinical phenotypic states that can cause pathologic bleeding, clotting, organ failure, and death.

Mechanisms and Mediators

Table 1 depicts the estimated average quantitative values (mean or median) for each listed coagulation parameter in trauma patients with TIC in the early and later periods after injury and without TIC, supported by existing literature, as cited (16, 17, 21–31).

Tissue Injury and Shock

Impaired coagulation after injury was long thought to be solely due to iatrogenic causes(9). For decades, trauma resuscitation practices guided by the luminaries of shock research were based on restoring flow and oxygen carrying capacity with large volumes of packed red blood cells (oxygen) and crystalloid (flow). The creep of resuscitation toward larger and larger volumes of cold anemic resuscitation resulted in an iatrogenic coagulopathy characterized by impaired thrombin production and platelet function due to hypothermia, acidosis, and dilutional coagulopathy(9–11). Although these iatrogenic effects are still contributors to coagulopathy and can coexistent with TIC, they are termed iatrogenic coagulopathy (IC), are separate in biology from TIC, and are fortunately more infrequent with modern hemostatic and goal-directed resuscitation techniques. An enlarging body of work has now demonstrated that to induce the mechanistic and clinical phenotypes of TIC, tissue injury (thought to activate the clotting cascade, produce thrombin, and stimulate resultant anticoagulant pathways) must be combined with tissue hypoperfusion (thought to release damage-associated molecular patterns [DAMPS], activate the contact pathway, induce thrombomodulin and endothelial protein C receptor [EPCR] expression at the endothelial surface to activate protein C). It has become clear that shock is essential to development of the phenotypes of TIC via multiple mediators described below.

Activation and Depletion of Protein C

One of the primary and first described mechanisms of TIC is activation of protein C system(13, 14, 16, 32, 33). Protein C is a serine protease with dual anticoagulant functions: induction of proteolytic cleavage of factors Va and VIIIa as well as a derepression of fibrinolysis through inhibition of plasminogen activator inhibitor-1 (PAI-1) (resulting in increased tissue plasminogen activator [t-PA] activity)(13, 14, 32). Since the initial description that severe injury combined with shock resulted in increased levels of activated protein C (aPC), concomitant reductions in coagulation factor V (FV) and factor VIII (FVIII), and increased fibrinolysis, a series of human studies and mechanistic animal and in-vitro cell culture models have confirmed these findings(13–16, 32). The activation of this pathway starts with tissue injury driven thrombin production that combines with thrombomodulin, the EPCR. The non-activated zymogen form of protein C on the endothelial surface is then activated and results in cleavage of FVa and FVIIIa and derepression of fibrinolysis. Multiple studies have corroborated that approximately 25–33%

of severely injured patients have elevated aPC, which is associated with increased blood transfusion and mortality, and in patients who survive, higher rates of infection and single and multiple organ failure(13, 14, 16, 32).

Interestingly, aPC also has cytoprotective functions including stabilization of endothelial and epithelial junctions, anti-apoptosis, and cleavage of extracellular histones. The enhanced activation of the protein C system may therefore represent an evolutionary maladaptive response. As humans may not be evolved to survive the massive injury created by being shot, stabbed, and run over by automobiles, it is hypothesized that the human physiologic response to these events is likely activating a large amount of protein C in an attempt to activate inflammomodulatory pathways to survive after severe trauma. The unfortunate sequela of this 'too much of a good thing' response is a systemic and local anticoagulation resulting in increased bleeding with incumbent enhanced mortality and morbidity. For those who survive their initial injury there is a rapid transition to a state of protein C depletion, characterized by hypercoagulability and impaired cytoprotectivity. Based on study of circulating aPC levels in trauma patients (16), the cytoprotective level can be assumed to be somewhere in the range of 1.05–6.00 ng/mL, as these levels correspond with preservation of Factor Va, VIIIa, and t-PA, as well as lower D-dimer levels. Conversely, the maladaptive level can be assumed to be in the >6.00ng/mL range as this level was shown to be associated with markedly decreased Factor Va and VIIIa, as well as increased t-PA and D-dimer levels (16).

The transition from hypo to hypercoagulability occurs very rapidly. Somewhere between 6 and 24 hours after injury the majority of patients are undergoing this transition, with 90% or more being normal or hypercoagulable in global hemostatic measures by 24 hours after injury, regardless of TIC (34). In addition, the coagulation factor activity in patients with and without TIC begin to rebound for most factors by 12 hours with significantly higher than baseline activity by 72 hours (17). The depletion of the non-active zymogen form of protein C is associated with both a transition to a thrombotic phenotype, and importantly a loss of cytoprotective signaling and resultant organ failure and infectious complications(16). With newly engineered activated forms of protein C which have augmented cytoprotective function with little or no anticoagulant protease activity, as well as antibodies or aptamers against the anticoagulant function of protein C, one can imagine in the near future a resuscitation where we might inhibit the anticoagulant function and concurrently augment the cytoprotective function of protein C immediately after trauma. Further precision medicine modulation of the relative amount of inhibition and augmentation could be performed as the patient moves through their post-injury coagulation and inflammation phases.

Factor Depletion, Impaired Thrombin Generation, and Fibrinogen Deficiency

Factor depletion does indeed exist after trauma(17). In addition, studies have demonstrated that clotting factor deficiencies occur without significant fluid resuscitation, immediately after injury, and are associated with worse outcomes(35). While reproducible and in

correlation with severity of injury and degree of shock, the factor level nadirs do not often reach the historically reported 20–30% level where coagulation should be impaired(17). Of course, the critical values of factor depletion were derived from closed studies in non-activated (non-injury) blood(36). Whether the reductions in factor levels do cause tissue specific impaired coagulation at the site of injury that requires levels higher than 20–30% in the setting of injury, and what circulating levels are ideal after significant injury for both tissue specific hemostasis and survival remains an open experimental and clinical question.

Clot formation requires thrombin generation on injured tissues. There are some suggestions that the measurement of thrombin generation is an optimal real-time assessment of coagulation capacity in the setting of injury because thrombin generation does not cease with fibrin deposition. However, both hypocoagulable and hypercoagulable thrombin generation profiles have been associated with trauma with variable associations to bleeding and thromboembolic outcomes(37, 38). Studies do suggest that there is sufficient thrombin generation in TIC(22, 38), yet both trauma patients with and without TIC show evidence of increased thrombin-antithrombin, and prothrombin fragments(39), and the biochemical milieu of injury and shock may increase thrombin generation due to decreased antithrombin activity(40).

Fibrinogen is the terminal substrate for clot formation and low quantity or quality of fibrinogen in TIC is associated with bleeding and death(41, 42). Animal models of TIC confirm low levels of fibrinogen(43). Fibrinogen replacement in the form of cryoprecipitate or newer fibrinogen concentrates is used in many protocols for treatment of TIC (44), and often to maintain levels of fibrinogen well above standard triggers for fibrinogen replacement despite weak supporting evidence for this(45). Whether this technique improves outcomes continues to be a moving target as goal-directed treatment of hypofibrinogenemia remains without clear evidence-based treatment cutoffs, but with ever-broadening therapies beyond blood components.

Altered Post-Injury Platelet Biology

Although the pivotal importance of platelets in the overlapping stages of clot formation is highlighted in Hoffman and Monroe's 'cell-based model of hemostasis', understanding the effect of local versus diffuse injury and shock states on platelet biology remains unclear in TIC(41, 46–48). However, platelets contribute significantly to the strength of clot formation in systemic blood during the post-injury state. Kornblith and colleagues demonstrated that the platelet contribution to clot strength is higher than that of fibrinogen at all time points after injury, using functional assessment of whole blood in trauma patients(41). In addition, thrombocytopenia is a poor prognostic marker following injury and is independently associated with transfusion, progression of brain injury, and death after injury(47). However, even with normal platelet counts, nearly half of injured patients demonstrate impaired platelet aggregation in aggregometry assays immediately after injury(24, 46), which has been replicated in animal models of injury and hemorrhagic shock(49). Excessive platelet activation(24) with subsequent exhaustion is one of the proposed mechanisms. This injury induced alteration in platelet biology has been found to have independent associations to brain injury, severe injury, and shock, and all injury patterns consistent with significant

endothelial damage(24). Multiple studies have demonstrated increased morbidity and mortality in patients that have impairments in platelet aggregation after injury(24, 46).

Numerous unresolved aspects of post-injury platelet biology remain to be addressed. For one, due to the nature of ex-vivo aggregometry assays (lack of endothelium, lack of flow, exogenous agonist stimulation of platelets), it remains unclear where on the spectrum of adaptive to maladaptive responses to injury impaired post-injury platelet aggregation lies. It should not be ignored that the majority of investigations in this area have relied on point-of-care platelet function assays that were intended to assess the effects of anti-platelet medication on platelet inhibition, and of concern is that viscoelastic assays do not always correlate well with point-of-care assessment of platelet function in trauma patients (50). In fact, using multiple electrode aggregometry, unpublished work by the authors of this review has identified that platelets may be endogenously activated by injury, diminishing their aggregation response to exogenous agonists. This raises concern that the identification of impaired platelet aggregation after injury may detect multiple phenotypes of post-injury platelet biology including a physiologic response (platelets activated by injury and unable to respond further to platelet activating agonists) and a maladaptive impairment in platelet aggregation. Therefore, future investigations need to use additional methods to assess the health and function of the post-injury platelets by incorporating endothelium and flow (microfluidics), assessment of structure (microscopy), mitochondrial health (mitochondrial respiration), and improved biomarkers of platelet and endothelial function(48, 51–53).

Additionally, given platelet function extends beyond coagulation to bidirectional endothelial interaction and regulation(54), control of local fibrinolysis at injury sites(19, 55), and their role as core effector cells in local and systemic inflammation(56, 57), a focus on multiple areas of post-injury platelet biology should remain an active area of TIC science. Finally, an expanded understanding of post-injury platelet biology is critical to improving the care of post-injury hemorrhage. The standard-of-care in TIC is platelet transfusion as part of a balanced resuscitation ratio (regardless of platelet count)(7), but investigations have identified that not only does impaired post-injury platelet aggregation fail to predict the need for platelet transfusion(58), platelet transfusion does not reverse post-injury impairment in platelet aggregation(59) and does not improve outcomes for patients on anti-platelet medications who have brain injury(60). Multiple studies have demonstrated that platelet transfusions may increase morbidity and mortality after injury(59). The explanative mechanisms for this are unknown, but it is without a doubt that further studies of TIC related post-injury platelet biology, platelet transfusions, and alternative platelet therapies are required(61).

Dysregulated fibrinolysis

Local hypercoagulability promoting hemostasis at the site of injury is proposed to activate systemic fibrinolysis to “guard against thrombosis” in remote non-injured tissue(62). Elevated fibrinolysis measured by viscoelastic assays has repeatedly been demonstrated to be associated with a high mortality rate and massive transfusion in trauma, but found in less than 20% of the most severely injured trauma patients(32, 63). While excessive fibrinolysis has pathologic consequences, low fibrinolytic activity in animals has also been demonstrated

to cause microvascular occlusion to vital organs, irreversible recovery from hemorrhagic shock(64), and be reversible by administration of a profibrinolytic agent(65).

Moore and colleagues identified that low fibrinolytic activity measured by viscoelastic assays, termed fibrinolysis shutdown, has also been associated with increased mortality in severely injured patients(66). Low fibrinolytic activity (defined by a lysis at 30 minutes by thromboelastography [LY30] <0.9%) has been associated with increased mortality compared to moderate levels of fibrinolysis (LY30 0.9–2.9%) at multiple large volume trauma canters(66–68). Fibrinolysis shutdown early after injury may be protective in some patients(68). This coagulation change could counter balance platelet inhibition and prolonged prothrombin time that has been described in patients with evidence of prior fibrinolytic activation (67, 69). Historic and recent observations in trauma support that patients can present to the hospital with a spectrum of fibrinolytic activity in which patients at the pathologic extremes are at risk of increased mortality. This concept has argued for the selective use of antifibrinolytics, supported by a reduction in mortality by use in goal directed resuscitation(70). Specifically, concerns have risen that TXA may cause harm in certain trauma patients, in particular patients with moderate (physiologic) levels of fibrinolysis(71). Patients who receive TXA are also at risk of prolonged fibrinolysis inhibition. Fibrinolysis shutdown beyond 24 hours of injury is associated with increase in mortality and ventilator requirements(72, 73), and Myers, Neal and colleagues identified in a propensity matched retrospective review of a modern population of trauma patients that TXA may be an independent risk factor for the development of VTE after injury (74). In aggregate, evidence supports the need for improved understanding of complex biologic and clinical interactions and outcomes related to TXA administration in trauma patients.

Inflammation and Immune Dysfunction: Endotheliopathy, Damage-Associated Molecular Patterns (DAMPs), and Others

While the effects of trauma on the biochemistry of coagulation are the subject of much important work, concurrent progress has been made on elucidating the effects of injury and shock on inflammatory and immune dysfunction. Emerging literature describes a conglomeration of sterile inflammatory and immune responses that center around the endothelium, which are related but unique to biochemical coagulopathies of TIC (52, 75–78). The injury response establishes a cascade of inflammatory and immune dysfunction resulting in single and multiple organ failure (acute kidney injury, Acute Respiratory Distress Syndrome, hepatic dysfunction) and a higher susceptibility to infection(79, 80). Much has been done in septic models, but it is more recently that bridging work has been done between coagulation and inflammation in trauma.

Endotheliopathy

Dr. Kozar and others have identified degradation of the endothelial glycocalyx after trauma. Further work has suggested that catecholamine surge is associated with glycocalyx degradation and associated auto-heparinization that can be identified on viscoelastic assays(81, 82) In addition, clinical studies have identified increased levels of Syndecan-1, a degradation product of the endothelial glycocalyx, to be associated with inflammation,

coagulopathy, and mortality(27). Important to this, plasma has been identified to be restorative to the endothelial glycocalyx(79, 83), but clinical studies of early plasma administration have had mixed results in protection from morbidity and mortality(84, 85). Other pathways may also contribute to the endotheliopathy of trauma. Multiple investigators have reported aPC's cytoprotective functions including endothelial barrier protection, anti-apoptosis, and cleavage of extracellular histones. Kutcher and colleagues identified that release of extracellular histones in the setting of injury and shock are associated with organ failure and death, and the compensatory activation of protein C and subsequent clearance of histones was found to be protective(86). This remains an active area of investigations, and there are hypothesis generating investigations that endothelial leak primes neutrophil reactive oxygen species release through the alternative pathway of complement(87), which could be mediated by coagulation products. Given that cultured endothelial cells exposed to plasma from coagulopathic trauma patients have increased permeability consistent with endothelial barrier dysfunction, suggesting circulating mediators in trauma patients can directly impair the endothelium, significant further work to characterize, diagnose, and treat the endotheliopathy of trauma is needed.

DAMPs and Others

The spectrum of DAMPs following injury remains a confusing mix of individual and combined mediators of biologic interest including: cytokines, soluble receptor for advanced glycation end-products [s-RAGE], high mobility group protein B1 [HMGB1], tissue inhibitor metalloproteinases-3 [TIMP-3], and numerous others(26, 30, 88, 89). These DAMPs have been measured and implicated in the sterile inflammation of trauma and the crosstalk between coagulation and inflammation(26, 30, 88, 89). Beyond this, many mechanisms abound; myosin may be implicated as a link between coagulation and inflammation biology and effects on TIC and fibrinolysis(90); metabolites are likely underappreciated in their contribution to TIC and post-injury hemorrhage(91); the relative production of alpha and meizo-thrombin is being investigated as a switch between coagulation and sterile inflammation after trauma(92). Indeed, whether each of these mediators has true mechanistic effect or is just a correlative measure of injured patients remains an important question which will be answered only by a combination of both reductionist fundamental mechanistic biology and multivariate big data approaches to clinical data. As highlighted by Dr. Timothy Billiar in PLOS Medicine in 2017 (93) and at his 2019 Western Trauma Association Founders Basic Science Lecture, both DAMP and pathogen-associated molecular pattern (PAMP) signaling are the scientific frontier of TIC and an expanded focus on trauma-induced immune activation in response to both sterile signal and microbial signal should guide the future of this field.

The Future

Improved assays

The evolution of identification and measurement of TIC has followed the evolution in mechanistic understanding. Originally TIC was identified by focusing on single, static, ex-vivo assessments of enzymatic coagulation cascade by measuring prolonged conventional

coagulation assays(6, 94), however functional assessment of whole-blood clot formation and degradation in real time via viscoelastic assays for both the identification and the management of TIC has become standard-of-care (70, 95). With the knowledge gained of the cellular and biochemical milieu created by combined tissue injury and shock, concerns have emerged regarding the ability to use ex-vivo conventional coagulation and viscoelastic assays for TIC interpretation, identification of 'normal ranges' of assays, and guidance of therapy.

Furthermore, there exists little ability to characterize and dynamically track the multiple competing and overlapping phenotypes which comprise TIC. Emerging evidence has highlighted that there are both clinical and biologic phenotypes of TIC and single assays are therefore ineffective for the purpose of identification and treatment of TIC(96). In addition, the optimal combination of assays that completely and effectively measure the complex and integrated pathways of all aspects of TIC related failure in coagulation, inflammation, and vascular homeostasis are unknown and perhaps undeveloped. Current best evidence supports that TIC can be identified by abnormalities in either conventional coagulation or viscoelastic assays, but not always both(96). Given this, combining multiple assays for diagnosis and therapy in TIC is likely the optimal strategy at this time. Future development of improved methods including in vivo biosensors of the biochemical milieu targeting assessments of circulating cells in flow and shear environments with the contribution of hematocrit and endothelium(97) should be a focus in the evolution of TIC science.

In-Silico Modeling

Ultimately however, we envision that biologic assays will be rapidly replaced by multivariate modeling of the complex coagulation milieu after trauma. This will be augmented by computational models which can target reductionist precision medicine approaches to resuscitation(98), while also predict and characterize dynamic phenotypes. This may allow for targeted predication and optimal personalized treatment rules for clinicians to use on their individual patients(99, 100). It is clear that we still have much to accomplish in the open science of TIC toward reducing morbidity and mortality for trauma patients.

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Table 1.

Estimated Average Coagulation Parameters in Trauma Patients With Trauma-Induced Coagulopathy Early (0h) and Later (beyond 0h) After Injury vs. Without Trauma-Induced Coagulopathy

	TIC		No TIC
Procoagulants (16, 17)	Early	Late	Early
Fibrinogen	160ng/mL	499ng/mL	234ng/mL
Thrombin	67%	70%	81%
Factor V activity	42%	74%	70%
Factor VII activity	75%	76%	95%
Factor VIII activity	200%	180%	275%
Factor IX	104%	185%	129%
Factor X	67%	71%	86%
Plasminogen Activator Inhibitor-1	25ng/mL	19ng/mL	38ng/mL
Native Thrombin Generation (22)			
Lag	16min	und	15min
Peak	163nmol/L	und	202nmol/L
Area Under the Curve	3145nmol/l *min	und	3129nmol/l *min
Anticoagulants (16, 17, 23)			
Protein C Activity	81%	74%	95%
Activated Protein C	12ng/mL	1.2ng/mL	2ng/mL
Tissue Plasminogen Activator	28ng/mL	4.5ng/mL	15ng/mL
Thrombin-Antithrombin III Complex	190 ug/L	75ug/L	37ug/L
Prothrombin Fragment 1 + 2	25nM/L	15nM/L	5nM/L
Antithrombin III	78%	74%	89%
D-dimer	6.8ug/mL	3.6ug/mL	4.0ug/mL
Platelet Biology (24–26)			
Platelet count	224× 109/L	95× 109/L	227× 109/L
Soluble P-selectin (CD62P+)	13%	7%	2%
GPIIb-IIIa (PAC-1)	16%	8%	1%
Platelet ADP response	59AU	49AU	60AU
Platelet TRAP response	97AU	88AU	97AU
Platelet Collagen response	47AU	50AU	49AU
TEG-Platelet Mapping ADP inhibition	96%	44%	79%
TEG-Platelet Mapping AA inhibition	37%	8%	39%
HMGB1 on Platelet Surface (CD42b+HMGB1+)	13%	17%	7%
Endothelial Markers (27, 28)			
Soluble Thrombomodulin	6.7ng/mL	und	4.7ng/mL
Von Willebrand Factor Activity	200%	und	175%
Syndecan-1	108ng/mL	und	17ng/mL
Angiopoietin-2	3000pg/mL	und	2000pg/mL
Complement Activation (29, 30)			
C3a	55ng/mg	15ng/mg	20ng/mg

	TIC		No TIC
C5a	0.5ng/mg	0.25ng/mL	0.20ng/mg
sC5b-9	0.18ng/mg	0.025ug/mg	0.01ug/mg
sRAGE	300pg/mL	und	275pg/mL
Global Hemostatic Measures (16, 21, 31)			
Rapid TEG ACT	113sec	113sec	113sec
Rapid TEG LY30 (physiologic phenotype)	1.6%	1.6%	1.6%
Rapid TEG LY30 (hyperfibrinolytic phenotype)	4.3%	1.6%	n/a
Rapid TEG LY30 (fibrinolytic shutdown phenotype)	0.1%	0.1%	n/a
Rapid TEG K Time	1.4min	1.5min	1.2min
Rapid TEG Angle	73degrees	72degrees	75degrees
Rapid TEG MA	61mm	62mm	65mm
Prothrombin Time	17sec	15sec	14sec
Partial Thromboplastin Time	38sec	39sec	28sec

*Estimated average quantitative values (mean or median) for each listed coagulation parameter in trauma patients with trauma-induced coagulopathy (TIC) at early and later timepoints after injury vs. without TIC. Quantitative values are supported by existing literature, as cited. Abbreviations: trauma induced coagulopathy (TIC), adenosine diphosphate (ADP), thrombin receptor activating peptide-6 (TRAP), thromboelastography (TEG), activated coagulation time (ACT), percent lysis at 30 minutes (LY30), maximum amplitude (MA), high mobility group box 1 protein (HMGB-1), soluble (s), receptor for advanced glycation endproducts (RAGE), under-defined in previous studies (und).

Table 2.

Qualitative Changes in Coagulation Parameters in Trauma-Induced Coagulopathy Compared to Major and Specific Criteria for Disseminated Intravascular Coagulation from the Scientific Subcommittee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis (21)

Procoagulants (16, 17)	**TIC**	**DIC**
Fibrinogen	↓	↓
Thrombin	↓	n/i
Factor V activity	↓	n/i
Factor VII activity	↓	n/i
Factor VIII activity	↓	n/i
Factor IX	↓	n/i
Factor X	↓	n/i
Plasminogen Activator Inhibitor-1	↓	n/i
Native Thrombin Generation (22)		
Lag	↓	n/i
Peak	↑	n/i
Area Under the Curve	↑	n/i
Anticoagulants (16, 17, 23)		
Protein C Activity	↓	↓
Activated Protein C	↑	n/i
Tissue Plasminogen Activator	↑	n/i
Thrombin-Antithrombin III Complex	↑	↑
Prothrombin Fragment 1 + 2	↑	n/i
Antithrombin III	↓	↓
D-dimer	↑	↑
Platelet Biology (24–26)		
Platelet count	→	↓
Soluble P-selectin (CD62P+)	↑	n/i
GPIIb-IIIa (PAC-1)	↑	n/i
Platelet ADP response	↓	n/i
Platelet TRAP response	↓	n/i
Platelet Collagen response	↓	n/i
TEG-Platelet Mapping ADP inhibition	↑	n/i
TEG-Platelet Mapping AA inhibition	→	n/i
HMGB1 on Platelet Surface (CD42b+HMGB1+)	↑	n/i
Endothelial Markers (27, 28)		
Soluble Thrombomodulin	↑	n/i
Von Willebrand Factor Activity	↑	n/i
Syndecan-1	↑	n/i
Angiopoietin-2	↑	n/i
Complement Activation (29, 30)		
C3a	↑	n/i

Procoagulants (16, 17)	**TIC**	**DIC**
C5a	↑	n/i
sC5b-9	↑	n/i
sRAGE	↑	n/i
Global Hemostatic Measures (16, 21, 31)		
Rapid TEG ACT	↑	n/i
Rapid TEG LY30 (physiologic phenotype)	→	n/i
Rapid TEG LY30 (hyperfibrinolytic phenotype)	↑	n/i
Rapid TEG LY30 (fibrinolytic shutdown phenotype)	↓	n/i
Rapid TEG K Time	↑	n/i
Rapid TEG Angle	↓	n/i
Rapid TEG MA	↓	n/i
Prothrombin Time	↑	**↑**
Partial Thromboplastin Time	↑	n/i

*Qualitative changes for each listed coagulation parameter in trauma patients with TIC vs. major (**bolded**) and specific (grey) criteria for Disseminated Intravascular Coagulation (DIC) by the Scientific Subcommittee on DIC of the International Society on Thrombosis and Haemostasis. Abbreviations: trauma-induced coagulopathy (TIC), disseminated intravascular coagulation (DIC), adenosine diphosphate (ADP), thrombin receptor activating peptide-6 (TRAP), thromboelastography (TEG), activated coagulation time (ACT), percent lysis at 30 minutes (LY30), maximum amplitude (MA), high mobility group box 1 protein (HMGB-1), soluble (s), receptor for advanced glycation endproducts (RAGE), not included (n/i).