10 Pathophysiology: Trauma-Induced Coagulopathy

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Learning Objectives

- Define the current understanding of physiologic coagulation
- Understand the pathophysiology of trauma induced coagulopathy by evaluating the components of coagulation, namely thrombin, platelets, the vascular endothelium, and fibrinogen

10.1 Introduction

Trauma-induced coagulopathy (TIC) refers to an alteration in the coagulation capacity that is attributable to injury, and manifests in a variety of phenotypes from hypocoagulability to hypercoagulability which are dynamic and time dependent. Considering this complexity, there is no standard definition of TIC, the diagnosis is generally a combination of laboratory testing and clinical symptoms. Clinical studies, based on conventional coagulation studies, suggest that TIC is evident in 25% of severely injured patients at the time of hospital arrival [1, 2], is associated with increased morbidity and mortality the coagulation status changes over time [3]. The hypocoagulable state, usually seen early after injury (<6 h), is characterized by inadequate hemostatic clots that can result in diffuse bleeding from sites uninvolved in the injured tissue, which is difficult to control with mechanical means such as compression, ligation, or embolization. On the other end of the TIC spectrum is a hypercoagulable phenotype that usually manifests with delayed (>24 h) post-injury micro and macrovascular thrombosis leading to a deep vein thrombosis, pulmonary embolism, acute respiratory distress syndrome (ARDS), and multisystem organ failure (MOF). Understandably the underlying pathophysiology of TIC is of intense interest to the medical community to tailor therapy to mitigate the associated complications. Though much remains to be elucidated, this chapter will attempt to consolidate the current understanding of TIC mechanisms.

10.2 Cell Mediated Hemostasis

The classical clotting cascade is taught as intrinsic and extrinsic systems of circulating plasma proteins that converge with the production of

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thrombin, factor IIa. Thrombin is then responsible for the cleavage of fibrinogen to fibrin and the formation of a hemostatic clot [4]. In the late 1990s, the cell-mediated hemostasis model was proposed by Hoffman et al. [5, 6]. After the introduction of this model, emphasis on circulating plasma proteins shifted to individual cells playing key roles in activating and regulating coagulation reactions surfaces [7]. In this model there are three defined phases of clot formation: initiation, amplification, and propagation. In the initiation step, vascular endothelium is disrupted exposing tissue factor which then binds to factor VIIa. This forms a Xase complex that promotes the formation of factors Xa and IXa leading to a low-level production of thrombin. Platelets then bind to the disrupted vascular endothelium and in combination with tissue factor and von Willebrand factor form an initial platelet plug. In the amplification phase, the low level of thrombin serves to activate platelets and factors XI, V, and VIII. These activated platelets release key procoagulant factors [8] such as adenosine diphosphate, thromboxane A2, and factor V. Through combination of proteolytic activation of clotting factors and procoagulant factors, factor Xa complexes with factor Va to form the prothrombinase complex that catalyzes the thrombin burst required to cleave fibrinogen and form a hemostatic fibrin clot over the disrupted endothelium.

There are several regulatory mechanisms that exist within this cell mediated hemostasis model that serve to prevent aberrant clot formation. The first is the vascular endothelium which must be breached by injury to allow for tissue factor exposure and clot initiation. The next regulators are protease inhibitors such as antithrombin (AT) and tissue factor pathway inhibitor (TFPI) that prevent the spread of coagulation beyond the site of injury where clot formation is needed. This coagulation spread is also prevented by the activated protein C system found in the endothelium that cleaves factor Va preventing thrombin generation in uninvolved endothelial cells. When these otherwise protective mechanisms are disrupted; i.e., lack of homeostasis, patients experience coagulopathy ranging from hypocoagulable to hypercoagulable states.

10.3 Diminished Thrombin Generation

Thrombin, a serine protease, is the final procoagulant enzyme of the clotting cascade that serves to cleave fibrinogen to fibrin allowing for clot formation [9]. Additionally thrombin stimulates platelet activation and aggregation via release of protease-activated receptors on their cell membrane and activates multiple other coagulation factors and inhibitors [10]. As normal coagulation subsides after injury, thrombin generation diminishes. This regulation is carried out by anticoagulants, such as antithrombin, thrombomodulin-protein C/S, and tissue factor pathway inhibitor (TAFI) [10].

Thrombin generation is influenced by a variety of factors that contribute to TIC including dilution of coagulation factors during resuscitation and post-injury consumption of coagulation factors. The correlation between coagulation factor levels and thrombin generation is inconsistent. Some studies have reported up to 20% of major trauma patients experience significantly low levels of clotting factors (<30%) [11]. In particular, severe trauma has been associated with low levels of FV, FVII, and FX. However, the majority of studies report coagulation factor levels >50% consistent with levels adequate for coagulation [12, 13]. Of note, when coagulation factor levels are found to be reduced, it does not necessarily correlate with diminished thrombin generation and may even be associated with elevated thrombin generation [12, 14]. This may reflect discrepancies between in-vitro coagulation assays and actual in-vivo activity as the assays may reflect coagulation factor consumption in-vivo that have resulted from enhanced thrombin generation. Indeed, trauma patients exhibit 2.5-fold higher average plasma thrombin generation compared to uninjured subjects with low thrombin generation present in 17%. Within these thrombin deficient patients a peak level of <250 nM was linked to a four-fold increased odds for a massive transfusion and three-fold greater odds of 30-day mortality [15]. Furthermore, there may be substantial differences between traditional plasma-based and

newer whole blood thrombin assays [16]. Recent data from whole blood assays indicate that patients who required a massive transfusion had thrombin generation levels below healthy controls [17]. With respect to late TIC, thrombin is at the cross-road of coagulation and inflammation, and excessive thrombin generation may have an important role in delayed hypercoagulability in injured patients [18].

Hypothermia and acidosis are also associated with diminished thrombin generation. In swine models of trauma, hypothermia resulted delayed thrombin generation initiation secondary to effects on the FVIIa/tissue factor pathway (193). In contrast, acidosis seems to affect the propagation phase of thrombin generation (193).

10.4 Platelet Dysfunction

Platelets have important hemostatic, endothelial [19], and immune-regulatory [20] functions that are critical to coagulation [21, 22] and thrombocytopenia and platelet dysfunction have important roles in TIC. The initial platelet plug is formed after vascular endothelial injury exposes tissue factor, collagen, and von-Willebrand Factor (vWF), resulting in platelet adhesion and aggregation. The resulting thrombin release and platelet glycoprotein VI-collagen binding cause platelet structural change to a spherical shape, calcium release, degranulation of procoagulant factors and glycoprotein IIb/IIIa conformation change to allow for fibrin crosslinking [7]. Additionally platelet degranulation causes the release of plasminogen activator inhibitor (PAI-1) and antiplasmin-2 which inhibit clot dissolution and promote clot formation [23, 24]. Degranulation also plays a role in recruiting immune cells and creating a local environment conducive to wound healing [25].

Qualitative platelet deficits due to dilution or consumption can cause major problems in trauma patients with studies reporting increased mortality in bleeding patients with platelet counts of less than 100,000/uL [26]. However, the majority of trauma patients have normal platelet counts and instead demonstrate impaired platelet function. Indeed a recent study reports up to 45% of trauma patients having platelet dysfunction measured by platelet aggregometry [27]. After severe traumatic hemorrhage, endothelial release of tissue factor, platelet activating factor, and vWF can result in platelet exhaustion and poor platelet aggregation [28, 29]. The lack of appropriate platelet degranulation results in increased tissue plasminogen activator (tPA) sensitivity and dysregulated fibrinolysis due to decreased PAI-1 release [30]. Platelet mediated inflammatory pathways involving toll-like receptor-4 (TLR-4) signaling, platelet-derived high mobility group box-1 (HMGB-1), and platelet-histone H4 interactions [31–33] may play significant roles in TIC hypercoagulability.

Despite improving understanding of these wide changes in platelet function after trauma, the question remains as to whether these alterations in platelet behavior are truly pathological or represent an adaptive response to an external insult [34]. Further research into platelet biology and platelet biochemical markers for targeted TIC therapy is sorely needed.

10.5 Endotheliopathy

The vascular endothelium allows for a barrier separating the hypocoagulable intravascular system, designed to prevent clot formation and enhance tissue profusion and prothrombotic extravascular system, which allows for hemostasis when the endothelium is breached. The endothelial architecture involves a glycocalyx of polysaccharides linked to membrane and transmembrane proteoglycans [35] and the intravascular hypocoagulable homeostasis is mediated by activation of endothelial protein C resulting in the inhibition of factors V and VIII promoting an anticoagulant environment where thrombin cannot be generated [36].

Endotheliopathy of trauma (EOT) is driven by hypoperfusion and is associated with endothelial barrier compromise, endothelial activation, altered leukocyte adhesion, a wide spectrum of coagulopathy, and ultimately end organ dysfunction [37]. The endothelial glycocalyx which

provides protection to endothelial cells and membrane integrity plays a role in maintaining the hypocoagulable intravascular state and when disrupted can result in thrombotic complications associated with TIC. Syndecan-1, a glycosaminoglycan component of the endothelial glycocalyx, has been implicated in TIC [35]. Cleavage of the heparan sulfate domain of syndecan-1 occurs during the hypoperfused state after hemorrhage [38] and results in an endogenous autoheparinization [39] contributing to TIC and resulting in prolonged PTT, increased inflammation, elevated fibrinolysis, and increased mortality [40]. Protein C may be an important systemic anticoagulant; when cleaved by the complex of thrombin and thrombomodulin, activated protein C (aPC) inactivates factors Va and may reduce PAI-1 [41, 42]. In critically injured trauma patients, early coagulopathy is associated with elevated levels of aPC and soluble thrombomodulin, and patients who demonstrate persistent protein C depletion are at higher risk of ventilator pneumonia, acute lung injury, multi-organ failure, and death [42, 43]. In addition to the anticoagulant properties of aPC, depletion of aPC leads to reduced endothelial protective signaling via the aPC receptors protease-activated receptor-1 (PAR-1) and endothelial protein C receptor (EPCP) resulting in endothelial dysfunction [43].

10.6 Hypofibrinogenemia

Fibrinogen is a large glycoprotein that is cleaved to fibrin by thrombin and plays a central role in hemostasis. Fibrinogen depletion is an important component in TIC and is the first coagulation factor to be depleted early after life-threatening hemorrhage [44]. Hypofibrinogenemia has been reported to occur in 14% of severely injured trauma patients, is associated with higher injury severity and higher levels of shock, and is reported as an independent predictor of mortality [45–47]. Fibrinogen supplementation during trauma resuscitation is thought to improve outcomes by increasing clot strength [48] and decreasing life-threatening hemorrhage [49]. Higher fibrinogen to RBC ratios during resuscitation have been associated with improved survival [50]. Current guidelines recommend fibrinogen supplementation at levels below 1.5 g/L [51].

Hypofibrinogenemia may occur secondary to blood loss, hemodilution during resuscitation, consumption during coagulation, hypothermia, and acidosis [52]. In swine models of trauma, hypothermia has been shown to decrease fibrinogen synthesis but has no effects of fibrinogen degradation [53]. Acidosis after trauma in swine models has been shown to result in an 1.8-fold increase in fibrinogen breakdown [54]. This profound effect of acidosis on fibrinogen plasma concentrations was supported in a human study of 675 patients that showed 81% of trauma patients who presented with a base excess of < -6 mmol/L manifested a fibrinogen level of <2 g/dL and 63% of patients had a fibrinogen level of <1.5 g/L. With a worsening base deficit of <-10 mmol/L, the percentages increased to 89% and 78%, respectively [55].

10.7 Fibrinolysis Dysregulation

The body maintains homeostatic microvascular patency through the fibrinolytic system. This physiologic level of fibrinolysis allows for normal clot dissolution and end organ perfusion. Dysregulation of this system is a key component of TIC. Fibrinolysis after traumatic injury manifests in three distinct phenotypes: physiologic fibrinolysis, hyperfibrinolysis, and fibrinolysis shutdown with the latter two phenotypes representing pathologic states that occur in approximately 80% of severely injured trauma patients [56].

Hyperfibrinolysis thought to be driven by overwhelming endothelial tissue plasminogen activator (tPA) release, and a decrease in circulating plasminogen activator inhibitor-1 (PAI-1) in the setting of hemorrhagic shock [57, 58]. This hyperfibrinolytic state is associated with increased clot dissolution, and uncontrolled, diffuse hemorrhage often from areas uninvolved in the traumatic injury [59–62]. Trauma patients with hyperfibrinolysis experience mortality rates upwards of 40% [56, 59, 63]. Rapid hemorrhagic

shock associated with elevated tPA levels and subsequent hyperfibrinolysis is exacerbated by crystalloid administration in both animal [64] and human studies [59]. This shock induced hyperfibrinolytic state is attenuated by plasma resuscitation and hypothesized to be related to improved platelet function with plasma resuscitation allowing for degranulation of antifibrinolytic factors released in platelet degranulation [65]. TPA is thought to be stored in Weibel–Palade bodies in the vascular endothelium and after co-localization with von-Willebrand Factor (vWf) is released into the circulation [66]. The leading hypothesis the stimuli for release involves trauma induced sympathetic activation and catecholamine surge [67].

In addition to tPA release, the loss of antifibrinolytic factors, including PAI-1 and alpha 2-antiplasmin exacerbates hyperfibrinolysis. Additionally, C-1 esterase inhibitor [68], alpha-1 antitrypsin, and vitronectin [69] all act to decrease PAI-1 activity and enhance fibrinolysis. Thrombin activated fibrinolysis inhibitor (TAFI) plays a role in clot degradation and factor XIII is vital to clot stability by cross-linking fibrin and alpha-2 antiplasmin which helps protect a newly formed clot from plasmin cleavage. Both of these factors are depleted in hyperfibrinolytic patients [69], but the exact mechanism by which TAFI and factor XIII are altered in TIC remains under investigation.

On the other end of the spectrum, fibrinolytic shutdown is the most common hypercoagulable phenotype in severely injured patients [70] and is associated with delayed morbidity and mortality secondary to venous thromboembolism and microvascular occlusion causing end organ dysfunction [71]. Patients in fibrinolytic shutdown have elevated D-Dimer and plasmin-antiplasmin complexes evidencing prior activation of the fibrinolysis system in conjunction with low tPA activity and diminished systemic fibrinolysis [69]. The mechanism behind fibrinolysis shutdown remains under investigation but is hypothesized to be regulated via PAI-1 [72, 73]. Emerging evidence also implicates S100-A10 pathway in tPA inhibition and subsequent fibrinolysis shutdown [74, 75]. Tissue injury is currently implicated as the driving force through the release of damage associated molecular patterns (DAMPs) which promote platelet release of alpha granules that contain a number of antifibrinolytic products [76–78]. The release of cellular breakdown products after tissue injury such as actin [79] and α-globin (manuscript submitted) has also been implicated in plasmin inhibition and enhanced clot propagation and fibrinolytic shutdown in vitro.

10.8 Conclusion

The definitive mechanisms behind trauma induced coagulopathy remain difficult to quantify though it is clear that alterations in thrombin generation, platelet dysfunction, endotheliopathy, hypofibrinogenemia, and pathologic fibrinolysis all play a significant role. The current literature describes aberrations in each of these areas, but it is still unclear whether these aberrations are all harmful or adaptive responses that serve a protective purpose in the injured trauma patient. Questions remaining include the appropriate level of thrombin generation after trauma, the critical level of hypofibrinogenemia that requires replacement, the role of whole blood in trauma resuscitation, and the appropriate time to treat hyperfibrinolysis with anti-fibrinolytics. The answers to these questions require further investigation with improved, real-time assessment of the behavior of these coagulation systems. The effects of injury mechanism on TIC and the temporal changes in coagulation after trauma are also an evolving field, with shock and tissue hypoperfusion appearing to be the inciting factors early in TIC, but tissue injury also playing a role in the dysregulation of fibrinolysis, particularly fibrinolysis shutdown. Ultimately, with improved understanding of TIC mechanisms, trauma surgeons can better provide personalized and precise care for their patients. We have seen this trend towards personalized medicine with the introduction of goal-directed resuscitation using viscoelastic assays of whole blood coagulation [80]. With advances in fields such as omics and microfluidics, we believe that the treatment of

trauma induced coagulopathy can be successfully tailored to the individual patient at a specific point in time.

Key Concepts

- Trauma-induced coagulopathy (TIC) is an alteration in the body's coagulation capacity that is attributable to injury and manifests in a spectrum of dynamic and time-dependent phenotypes ranging from hypocoagulable to hypercoagulable states.
- The pathophysiology behind TIC is complex and involves an intricate interplay between diminished thrombin generation, platelet dysfunction, vascular endothelial cell dysfunction, fibrinogen depletion, and dysregulated fibrinolysis.
- Improved understanding of the pathophysiology of trauma induced coagulopathy will allow for more personalized and precise care for patients (Fig. 10.1)

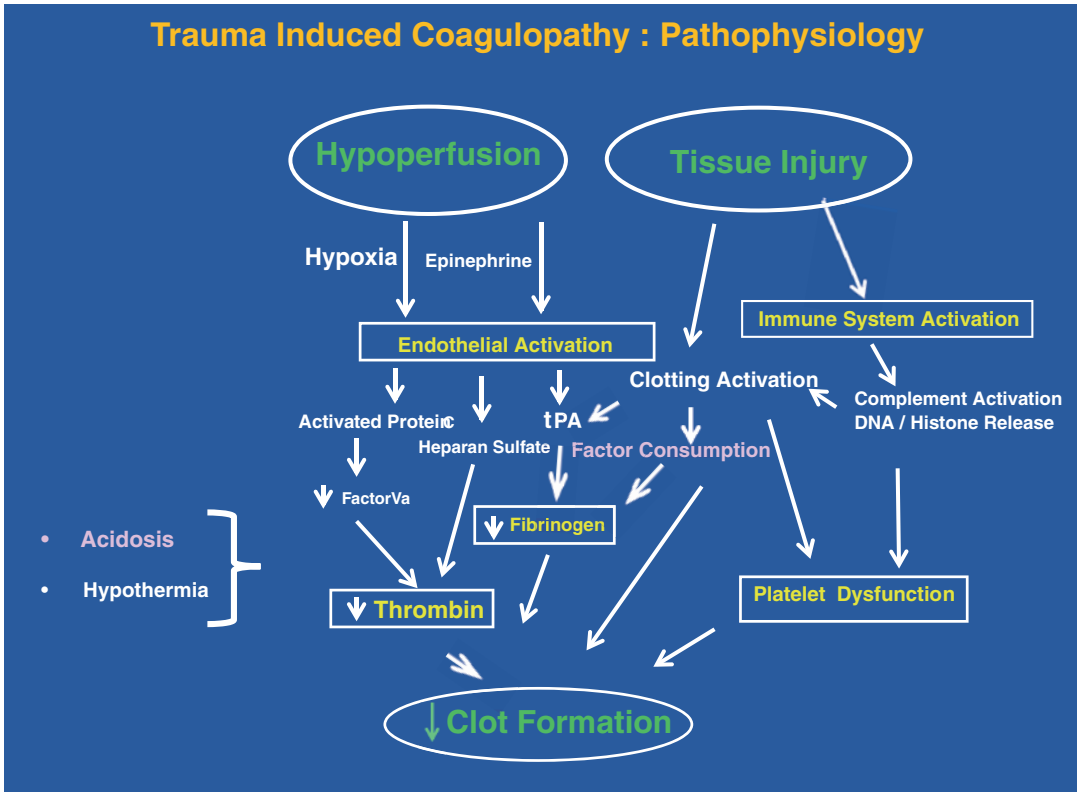

Fig. 10.1 The pathophysiology of trauma induced coagulopathy: a complex interplay between numerous factors such as diminished thrombin production, platelet dysfunction, endotheliopathy, hypofibrinogenemia, and dysregulated fibrinolysis, resulting in alterations in clot formation and stability

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