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Trauma-Induced Coagulopathy

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Abstract

Trauma-induced coagulopathy (TIC) is a heterogeneous entity that contributes to a significant morbidity and mortality following trauma. The activated protein C system, endotheliopathy and platelet dysfunction have been implicated in the pathogenesis of TIC, although there are still controversies on the exact pathogenesis. TIC can be modified by hypoperfusion, acidosis, hypothermia, haemodilution, underlying disease conditions, pre-injury medications as well as genetic predispositions. Current definition of this syndrome is based on laboratory abnormalities that do not easily allow a distinction between adaptive and maladaptive changes of the haemostatic system. The management of the coagulopathy in the early phase of trauma focuses on the treatment of bleeding. The improving quality in the early damage control following trauma has led to a marked reduction in morbidity and mortality. In the later phase, hypercoagulopathy and inflammation contribute to organ dysfunction, venous thromboembolism and poor outcome. Despite considerable advances in trauma management, TIC remains a diagnostic and therapeutic challenge both in the early and late phases of trauma. This review mainly focuses on the pathogenesis of TIC, with a very short discussion on diagnostic and therapeutic principles.

Keywords
- trauma
- coagulopathy
- trauma-induced coagulopathy
- bleeding

Zusammenfassung

Trauma-induzierte Koagulopathie ist eine heterogene Entität, die zu einer signifikanten Morbidität und Mortalität nach Trauma beiträgt. Das aktivierte Protein C System, Endotheliopathie und Plättchendysfunktion wurden in der Pathogenese der Trauma-induzierten Koagulopathie diskutiert. Dennoch gibt es weiterhin Kontroversen über die Pathogenese. Trauma-induzierte Koagulopathie kann durch Hypoperfusion, Azidose, Hypothermie, bereits vorliegende Erkrankungen, Vormedikation und genetische Prädisposition weiter modifiziert werden. Die aktuelle Definition dieses Syndroms basiert auf abnorme Laborparameter, die eine Unterscheidung zwischen adaptiven und maldaptiven hemostatischen Veränderungen nicht ohne weiteres erlauben. Die Behandlung der Koagulopathie in der Frühphase fokussiert auf die Therapie der Blutung. Die Qualitätssteigerungen in der Frühbehandlung nach Trauma haben zur erheblichen Senkung der Morbidität und Mortalität beigetragen. In der Spätphase tragen Hyperkoagulopathie und Inflammation in der Entstehung der Organdysfunktion und der venösen Thromboembolie und zu einer schlechten Prognose bei. Trotz den erheblichen Fortschritten im Trauma-Management stellt die Trauma-induzierte Koagulopathie nach wie vor sowohl in der Früh- als auch Spätphase eine diagnostische und therapeutische Herausforderung dar. Diese Übersicht fokussiert hauptsächlich auf die Pathogenese der Trauma-induzierten Koagulopathie, mit einer sehr kurzen Diskussion über diagnostische und therapeutische Prinzipien.

Schlüsselwörter
- Trauma
- Koagulopathie
- trauma-induzierte Koagulopathie
- Blutung

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Introduction

Trauma is one of the major global public health challenges. For the year 2013, it was estimated that 973 million people suffered injuries that warranted some type of medical service and 4.8 million people died. Injuries accounted for 10.1% of the global disease burden in 2013, mainly affecting the younger age group.[1] Although advances in trauma and intensive care as well as the widespread implementation of damage control principles resulted in a decline in death rates,[2] the death toll due to trauma is still high. According to a recent retrospective analysis of a large cohort, the prevalence of trauma death has declined since 1983, but the majority of deaths (56%) still occur within the first 24 hours after injury.[3]

Uncontrolled post-traumatic bleeding, which is a major concern in the early phase of trauma resuscitation, is the leading cause of potentially preventable death.[4–6] There are two mechanisms of bleeding following an injury: anatomical bleeding as a result of blood vessel damage and bleeding due to coagulopathy. Anatomical bleeding can be frequently managed through damage control strategies, which resulted in a decline in the mortality rate attributed to haemorrhage.[7] However, the coagulopathy following the injury may lead to a haemostatic dysfunction that can significantly contribute to further bleeding, organ dysfunction and poor clinical outcome.

During further course of trauma management, particularly in patients with severe injuries, hypercoagulopathy can ensue, which is associated with thromboembolic events and multiple organ dysfunction. Trauma induces local and systemic inflammation, similar to that described in sepsis. Inflammation, in turn, leads to initiation and propagation of the coagulation cascade, while coagulation also influences inflammation. Although their incidence has declined as a result of improved trauma management, multiple organ dysfunction and sepsis are frequent causes of late death following trauma.[8]

Depending on the criteria applied and the severity of injury, coagulopathy can be detected in up to 56% of trauma patients in the early phase of trauma (►Table 1).[9–17] However, defining a coagulopathy based on laboratory abnormalities alone does not necessarily translate into a clinically relevant coagulopathy.[18]

Mechanisms of Trauma-Induced Coagulopathy

Haemostasis is a complex process at the centre of the body's defence and wound healing system. Physiologic haemostasis is a balance between pro- and anti-coagulation as well as fibrinolysis and anti-fibrinolysis. This process takes place on the surface of endothelial cells and platelets.[19] The intact endothelium is anti-thrombotic, this property being maintained by several mediators, including tissue factor pathway inhibitor, endothelial protein C receptors, endothelial glycocalyx layer (EGL), thrombomodulin, nitric oxide, and tissue plasminogen activator. The EGL is a matrix of macromolecules, which is not only anti-coagulant but also important to maintain microvascular integrity. The most prominent among these molecules are heparan sulfates, accounting for 50 to 90% of the total pool, the rest being mainly chondroitin sulfates and hyaluronic acid.[20] The EGL is a sort of endothelial gatekeeper.[21]

An injury to a vessel wall exposes the subendothelial collagen that provides an adhesion platform for circulating platelets as well as for the interplay between the cellular and humoral components of the haemostatic system. This pro-coagulant activity is controlled by counter-regulatory anti-coagulant cascades. The net effect of these two opposing systems may be generation of pro-coagulation at the site of endothelial injury, while preventing uncontrolled microvascular thrombosis and tissue hypoperfusion by means of endogenous anti-coagulation and fibrinolysis. Thrombin plays a central role in this process by activating both coagulation and anti-coagulation as well as contributing to the crosstalk with the inflammatory response.[22]

The activated protein C (APC) system has been considered as a major player in the development of trauma-induced coagulopathy (TIC). APC is a physiologic anti-coagulant that irreversibly inactivates the pro-coagulant factors Va and VIIIa. It is also profibrinolytic by inhibiting plasminogen activator inhibitor-1 (PAI-1). APC is also cytoprotective through anti-inflammatory and anti-apoptotic mechanisms. Results from a mouse model indicated the role of APC in the endogenous coagulopathy following trauma.[23] In a single-centre study in 203 patients

Table 1 Prevalence of trauma-induced coagulopathy (TIC)

Ref.	*N*	TIC criteria	Prevalence (%)
Brohi et al[9]	1,088	PT or aPTT or TT	24.4
MacLeod et al[10]	10,790	PT	28.0
Maegele et al[11]	8,724	PT or platelet count	34.2
Hess et al[12]	15,728	INR, aPTT, platelet count, or fibrinogen concentration	5.5 up to 43.1, depending on injury severity
Floccard et al[13]	45	ISTH DIC score	56.0
Cohen et al[14]	1,198	INR	41.6
MacLeod et al[15]	701	PT	16.3
Hagemo et al[16]	808	INR	11.0
Fröhlich et al[17]	61,212	PT and/or platelet count	24.5

Abbreviations: aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; PT, prothrombin time; TT, thrombin time.

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with major trauma (mean injury severity score [ISS]: 25.2), a marked increase in APC was observed in those with an ISS >15 and a base deficit >6. The same study showed a correlation between protein C depletion in the first 12 hours and increased risk of ventilator-associated pneumonia.[24] A subsequent publication using data from the Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study supported the assumption that APC may have an important role in the development of TIC. In the PROMMTT study, which included 1,245 severely injured patients (mean ISS: 26.2), acute traumatic coagulopathy identified on arrival to the emergency department was associated with a depletion of the pro-coagulant factors I, II, V, VII, VIII, IX and X on the one hand and activation of the protein C system on the other.[14] A recent study by Davenport et al also showed that elevated APC concentration was associated with excess mortality and morbidity following TIC. In the second part of the same study using a murine model, mortality rate following trauma haemorrhage in transgenic mice with 1,000-fold reduced capacity to activate protein C was almost half that of wild-type mice, suggesting a central role of the protein C pathway in early TIC.[25] However, the data on APC in trauma are inconsistent. A recent study comparing 25 trauma patients with hyperfibrinolysis identified using thromboelastography with 14 healthy controls showed a significant early increase in tissue plasminogen activator but not PAI-1 following a severe injury.[26] This finding thus challenges the apparent role of APC-mediated hyperfibrinolysis. A recent systematic literature review concluded that there may not be a direct cause–effect relationship between APC and increased fibrinolysis.[27] This contradiction is not surprising, taking into consideration the complexity of the haemostatic system and the crosstalk with the myriad of mediators released following a trauma.[14]

Trauma activates the neurohumoral system that results in a catecholamine surge. This increase in catecholamine levels leads to an endothelial damage and glycocalyx degradation, generally known as endotheliopathy. A prospective study using blood samples from adult trauma patients directly admitted to a trauma centre showed that adrenaline level was increased in non-survivors, and this was independently associated with an increase in syndecan-1, which is a marker of glycocalyx degradation. The increase in adrenalin also correlated with biomarkers of endothelial damage and hyperfibrinolysis.[28] A recent study confirmed that high adrenaline levels and glycocalyx damage are associated with hypocoagulopathy and hyperfibrinolysis.[29] A high level of syndecan-1 in trauma patients was also associated with increased inflammation and endothelial damage.[30] Shedding of EGL components may also contribute to autoheparinization, which was observed in approximately 5% of trauma patients, and this was associated with a high ISS.[31] Endotheliopathy may also contribute to a capillary leak following trauma.[32] A secondary analysis of the data from 512 patients included in the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial showed that, after adjusting for ISS and transfusion requirements, elevated serum syndecan-1 levels were independently associated with the development of sepsis during hospitalization.[33] In a recent prospective observational study in 424 trauma patients, Johansson et al showed that both adrenaline and syndecan-1 were independent predictors of <24 hours, 7-day and 28-day mortality.[34] An animal study using male Sprague-Dawley rats showed that sympathetic denervation was anti-inflammatory, anti-fibrinolytic and endothelial protective in rats with acute traumatic coagulopathy, confirming the role of catecholamines in TIC.[35]

Hypofibrinogenemia as a consequence of TIC is frequently observed in the early phase of trauma. In a multicentre observational study from the United States,[36] including 1,133 trauma patients who arrived in a hospital within 180 minutes post-injury, a fibrinogen concentration <2 g/L measured by the Clauss method was identified in 19.2% of the patients. In another observational study on major trauma patients from Australia, 12.9% of the patients had fibrinogen levels <1.9 g/L during the initial resuscitation.[37] Low fibrinogen level was in both studies associated with a poor outcome. The age-associated increase in fibrinogen level should be kept in mind when interpreting results.[38]

Platelets contain a plethora of proteins involved in coagulation and fibrinolysis. It is not yet clear how these contradictory platelet secretions are exactly affecting TIC. Data on platelet function testing in trauma patients are scant, because platelet sample handling and availability of specific assays are complicated. One older small prospective observational study using thromboelastography (TEG)-based platelet functional analysis in whole blood samples collected from trauma patients at risk of TIC immediately after injury and before blood or substantial fluid administration showed a significantly impaired platelet aggregation in response to adenosine diphosphate (ADP) and arachidonic acid, whereby the ADP inhibition was more pronounced.[39] Another study on 101 trauma patients using multiple-electrode impedance aggregometry also showed platelet dysfunction in response to ADP, arachidonic acid, collagen and thrombin receptor activating peptide (TRAP), with response to the first three agonists markedly reduced within the first 24 hours.[40] In that study, platelet dysfunction was observed in 45.5% of trauma patients on admission and 91.1% at some time during their intensive care unit (ICU) stay. In another small more recent study on 40 trauma patients, a significantly decreased ADP- and TRAP-mediated platelet aggregation was observed, suggesting that thrombin receptor pathway plays an important role in trauma-induced platelet dysfunction.[41] Platelet dysfunction seems to be ubiquitous even in minor trauma. In a recent study, platelet dysfunction identified with TEG-platelet mapping was reported on 459 patients with minor trauma (median ISS: 5).[42] However, the mechanisms and the implication of this finding are not clear. Anaemia, be it due to haemorrhage or dilutional, can also affect platelet adhesion. In vitro experiments have shown the dependence of platelet adhesion on haematocrit.[43] Considering the available evidence, endotheliopathy and anaemia may be the triggers for platelet dysfunction in trauma.

While hyperfibrinolysis has been discussed as a major event in early TIC, a trauma-induced fibrinolytic shutdown is also demonstrated.[44] A study by Moore et al showed that there is a U-shaped distribution of mortality related to

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fibrinolysis in response to a major trauma, warning that inadvertent exogenous inhibition of fibrinolysis may have an adverse effect on survival.[45] Fibrinolysis shutdown may even be an adaptive physiologic response to trauma.[46]

Shock is an independent risk factor for trauma coagulopathy.[14,47,48] The true incidence of shock in trauma is not clear, since systolic blood pressure was frequently used in several studies as a determinant of hypoperfusion. Traumatic brain injury further hampers the use of blood pressure measurements as a sign of hypoperfusion.[49]

Hypothermia, acidosis and haemodilution are also associated with the development of TIC. Hypothermia can ensue following a trauma as a result of heat loss, reduced heat production and administration of fluids. Clinically significant reduction in platelet function and coagulation factor activity ensues at a core body temperature below 33°C.[50–52]

Metabolic acidosis, mostly associated with shock, leads to a reduction in the activity of coagulation factors.[50,53] In a swine model, acidosis, but not hypothermia, resulted in a decrease in plasma fibrinogen concentration by 18%.[54] Acidosis accelerated fibrinogen consumption, while it did not affect fibrinogen production.[55] The administration of bicarbonate to correct acidosis is not associated with a reversal of the coagulopathy.[56] Finally, pre-clinical fluid administration also contributes to the development of a dilutional coagulopathy,[11,14,57] with the incidence of coagulopathy rising with increasing amount of fluid administered.[11]

In summary, the pathogenesis of early coagulopathy is multifactorial, with the balance between pro- and anti-coagulation influenced by injury severity, hypoperfusion, acidosis, hypothermia, underlying disease conditions, medication history and genetic predispositions as well as emergency treatment (►Fig. 1).

Late Coagulopathy

The haemostatic reaction following trauma returns to baseline during recovery in patients without complications, while patients with severe injury may suffer from the sequelae of massive coagulopathy. Recovery of the coagulopathy after severe trauma may be delayed in such patients.[58] There is a massive reorganization of the human genome following trauma, which leads to a multitude of changes in innate immunity and inflammation.[59,60] Trauma also results in an uncontrolled local and systemic release of damage-associated molecular patterns (DAMPs) that trigger an inflammatory response.[61]

Similar to the haemostatic response, it remains difficult to distinguish between adaptive and maladaptive systemic inflammatory responses to injury. From clinical viewpoint, the feasible means to identify maladaptive systemic inflammation is at present the identification of organ dysfunction, in analogy to the current definition of sepsis.[62] Almost 30% of severely injured patients develop a multiple organ dysfunction syndrome (MODS) and this is associated with a high risk for nosocomial infections.[60,63] Similar to TIC, inflammation and infection result in a chain of coagulopathies that may culminate into a disseminated intravascular coagulopathy (DIC),[64] which is associated with a significantly high mortality rate.[65] The late hypercoagulopathy following trauma also contributes to an increased risk of venous thromboembolism (►Fig. 2).[66–70]

Diagnosis of Trauma-Induced Coagulopathy

The diagnosis of TIC is still based on laboratory abnormalities that may not necessarily correspond to a distinct clinical phenotype. Despite significant advances in coagulation research, there is no adequately valid test to predict and identify a clinically relevant acquired coagulopathy. Published reports on TIC have been mostly based on the evidence of abnormal laboratory findings of prothrombin time, activated partial thromboplastin time, plasma fibrinogen concentration, platelet count, either alone or in combination. However, an important caveat in this regard is comparing data from patients with those of the healthy population without due consideration of the physiological adaptive changes of the haemostatic system in trauma.

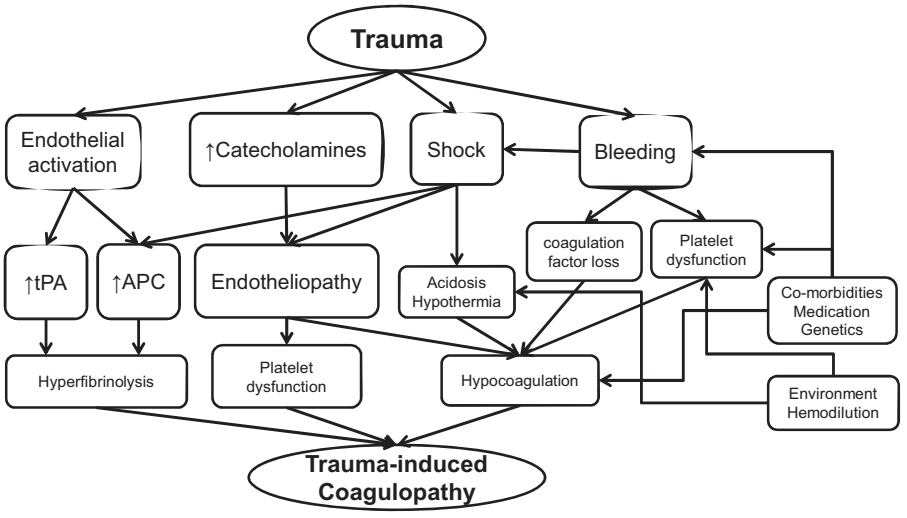

Fig. 1 Mechanisms of early trauma-induced coagulopathy (TIC). Patient factors (medication, comorbidities, genetic polymorphism) as well as environmental factors (heat loss) or iatrogenic injury (e.g. haemodilution) modify TIC.

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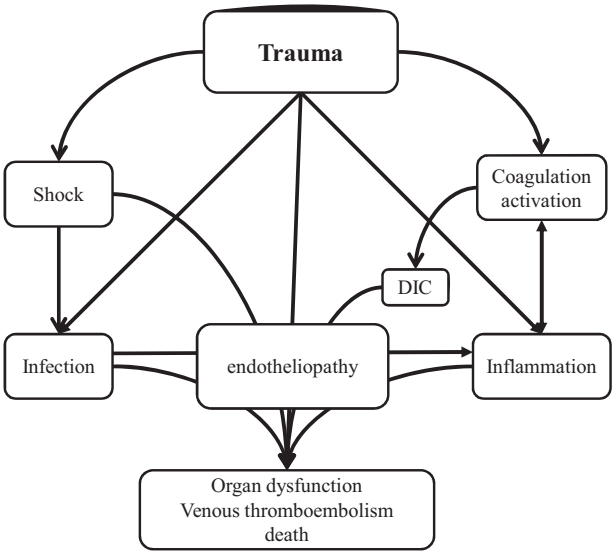

Fig. 2 Consequences of late coagulopathy in trauma. Damage to the endothelium plays a crucial role in inflammation and infection.

Viscoelastic point-of-care tests are increasingly used to diagnosis and manage TIC-associated bleeding. However, published data are mostly retrospective and/or observational.[71–74] Despite these drawbacks, viscoelastic point-of-care tests can help trauma caregivers to establish algorithms for rapid diagnosis of relevant bleeding diathesis and appropriate use of haemostatic drugs. Nevertheless, the extra-haemostatic effects of coagulation, such as its role in inflammation and immune modulation, are still difficult to characterize, let alone identify with routine laboratory assays.

Treatment of Trauma-Induced Coagulopathy

Changes in the haemostatic system following a trauma should be viewed in two ways. First, the urgent need in the early phase of trauma is to treat and avoid bleeding. The second issue, which is even more difficult to diagnose as well as manage, is the role and the dynamics of haemostasis in the development of organ dysfunction following trauma. There are limitations regarding conclusions derived from available evidence, because data from published studies show considerable heterogeneity in study design, study population and outcome measures.[75] Evidence for clinically meaningful modification of the haemostatic system in relation to inflammation and organ dysfunction is still lacking.

Early appropriate damage control contributes to the reduction of the incidence of TIC. Beyond the mechanical management of bleeding, hyperfibrinolysis during the early phase of TIC has been the subject of research and treatment strategies. The CRASH-2 trial has shown that early administration of tranexamic acid in adult trauma patients with, or at risk of, significant bleeding was associated with a reduced risk of death.[76] Guidelines for transfusion of red blood cells and platelets as well as administration of pro-coagulant factors in the management of bleeding have been developed based on available evidence.[77] Although such algorithms may help standardize the use of blood products, there are still several controversial issues to be considered. First, the use of fresh frozen plasma (FFP) in TIC is declining. While FFP may be a better volume replacement than a crystalloid solution during trauma management, it is not efficient in correcting a coagulopathy. Second, platelet count does not necessarily correlate with platelet function. There is still a lack of appropriate routine laboratory assays to test for platelet function during trauma, so that treatment recommendations are still mainly empirical. Third, current management strategies do not address the role of the coagulation system in inflammation due to lack of appropriate diagnostic tools. For instance, a very important lesson from the CRASH-2 trial is that administration of tranexamic acid later than 3 hours after trauma was associated with a poor outcome.[76] This underscores the dynamics of the coagulation system and the role of every coagulation step in the inflammation and wound healing process. Both hyperfibrinolysis and fibrinolysis shutdown are part of this adaptive system, so that inadvertent exogenous manipulation of these steps may be harmful.

Conclusion

TIC is a complex heterogeneous syndrome with a multitude of pathogenetic factors, which include both adaptive and maladaptive changes in the haemostatic system. Comparing differences in laboratory parameters between trauma patients and healthy controls is not an ideal design to differentiate between adaptive and maladaptive changes following trauma. Based on available data, it is difficult to discern between simple association and cause–effect relationships. More high-quality research is still required to better define TIC both in the early and late phases and establish optimal treatment targets.

Conflict of Interest

The author received research grant from CSL Behring and Bayer Vital as well as honoraria and/or travel reimbursements over the last three years for lectures on topics of coagulation, but not related to trauma, from CSL Behring and Boehringer Ingelheim.

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