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Review Article

AN UPDATE ON THE COAGULOPATHY OF TRAUMA

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ABSTRACT—Trauma remains the leading cause of death with bleeding as the primary cause of preventable mortality during the first 24 h following trauma. When death occurs, it happens quickly, typically within the first 6 h after injury. One of four patients to arrive in the emergency department after trauma is already in the state of acute traumatic coagulopathy and shock. The principal drivers of acute traumatic coagulopathy have been characterized by tissue hypoperfusion, inflammation, and the acute activation of the neurohumoral system. Hypoperfusion leads to an activation of protein C with cleavage of activated factors V and VIII and the inhibition of plasminogen activator inhibitor 1 with subsequent hyperfibrinolysis. Endothelial damage and activation result in Weibel-Palade body degradation and glycocalyx shedding associated with autoheparinization. In contrast, there is an iatrogenic coagulopathy that occurs secondary to uncritical volume therapy leading to acidosis, hypothermia, and hemodilution. This coagulopathy then may be an integral part of the "vicious cycle" when combined with acidosis and hypothermia. The present article summarizes an update on the principal mechanisms and triggers of the coagulopathy of trauma including traumatic brain injury.

KEYWORDS—Trauma, hemorrhage, coagulopathy, mechanisms

INTRODUCTION

Trauma is the leading cause of death worldwide in persons younger than 40 years (1) and accounts for approximately 10% of all deaths in general (2). Despite substantial improvements in acute trauma care, uncontrolled hemorrhage is still responsible for more than 50% of all trauma-related deaths in both civilian and military settings within the first 48 h after hospital admission (3). Uncontrolled hemorrhage and its downstream effects have also been determined to be the most common cause of preventable deaths (4–6). Several studies independent from each other have demonstrated that one of four severely injured patients presents to the emergency department (ED) with hemodynamic depletion and acute traumatic coagulopathy (ATC) (7–10). Acute traumatic coagulopathy is associated with higher transfusion requirement, greater incidence of organ failure, longer stays on the intensive care unit (ICU), and in-hospital and mortality (7–9). Vice versa, it has been shown that early recognition of ATC accompanied by adequate and aggressive management can correct coagulopathy, control bleeding, reduce blood product use, and improve outcome in severely injured patients (11, 12). In contrast to ATC, there is an iatrogenic coagulopathy (IC) that occurs secondary to uncritical volume therapy leading to acidosis, hypothermia, and dilution. This coagulopathy then may be an integral part of the "vicious cycle" when combined with acidosis and hypothermia. In the following, the principal mechanisms and drivers of the coagulopathy of trauma including traumatic brain injury (TBI) as discussed today are presented (Fig. 1).

Activation of the protein C pathway

Significant clinical and animal data suggest that activation of the protein C pathway is a principal component of ATC, which occurs when tissue injury is associated with tissue hypoperfusion (shock) (13–16). Protein C is a vitamin K–dependent glycoprotein circulating in plasma, which is activated on the surface of endothelial cells by thrombin bound to its own receptor, the endothelial protein C receptor (EPCR), and the transmembrane glycoprotein thrombomodulin (TM) forming the so-called thrombin-TM complex (13). While the mechanisms for this enhanced activation remain an open experimental question, some data suggest that tissue hypoperfusion (shock) leads to an increased expression of TM and EPCR on the endothelial surface. Endothelial cell protein C receptor binds protein C to the endothelial cell surface and enhances the rate of protein C activation by the thrombin-TM complex by 5- to 20-fold (17). Once activated, protein C has dual anticoagulant actions, thereby driving ATC: (i) it proteolytically cleaves peptide bonds in activated procoagulant factors V and VIII that act as cofactors in the activation of factors X and II, and (ii) it promotes fibrinolysis through the inhibition of plasminogen activator inhibitor 1 (PAI-1). In addition to its anticoagulant function, it is also a profound anti-inflammatory reducing inflammation via binding through PAR-1 and EPCR and decreasing leukocyte nuclear factor κB activation (18). Finally, activated protein C has been shown to cleave extracellular histones (19, 20). Cofactor protein

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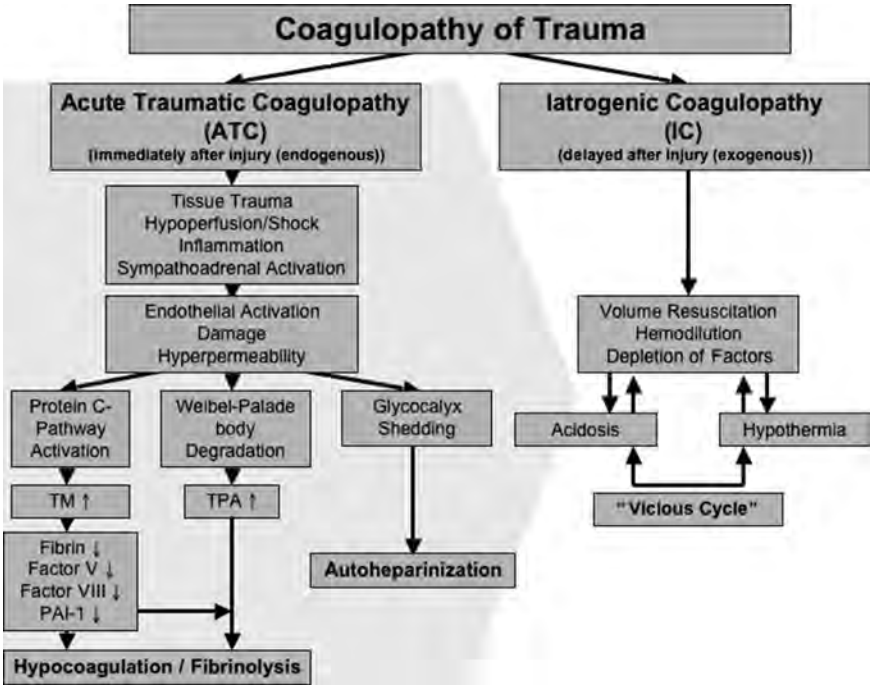

FIG. 1. **The principal drivers of ATC have been characterized by tissue trauma, hypoperfusion, inflammation, and the acute activation of the neurohumoral system.** Hypoperfusion leads to an activation of protein C with cleavage of activated factors V and VIII and inhibition of PAI-1 with subsequent hyperfibrinolysis. Endothelial damage and activation result in Weibel-Palade body degradation and glycocalyx shedding associated with autoheparinization. In contrast, there is an IC that occurs secondary to uncritical volume therapy leading to acidosis, hypothermia, and dilution. This coagulopathy may be an integral part of the vicious cycle when combined with acidosis and hypothermia.

S increases the activity of activated protein C. Protein S and factor V are required for the regulation of the tenase complex, which leads to an inactivation of factor VIII; protein S participates in the regulation of the prothrombinase complex, which leads to an inactivation of factor V.

Endothelial injury

Recent evidence suggests that ATC may also be linked to the disruption of the vascular endothelium and its glycocalyx. The endothelial glycocalyx covers the endothelium as a negatively charged antiadhesive and anticoagulant surface layer, thus protecting the endothelium and maintaining vascular barrier function (21). Tissue trauma, inflammation, hypoperfusion, and sympathoadrenal activation result in systemic endothelial activation and damage and subsequently leading to early coagulopathy and endothelial hyperpermeability. Injury and damage to the endothelium trigger the release of small molecules into the circuitry reflecting endothelial glycocalyx degradation (syndecan 1) (22), endothelial cell damage (soluble TM), vascular endothelial growth factor (VEGF) and Weibel-Palade body degranulation (tissue plasminogen activator, angiopoietin 2) (23).

The entire endothelial glycocalyx contains approximately 1 L of noncirculating plasma with significant amounts of heparin-like substances. When degraded, this ultimately leads to autoheparinization (24). Ostrowski et al (25) from Copenhagen reported evidence of high-degree autoheparinization among severely injured trauma patients as well as associations of increasing magnitude of injury in patients with high syndecan 1 levels with progressive protein C depletion, increasing soluble TM, hyperfibrinolysis, and prolonged activated partial thromboplastin times (22). These results may indicate the link between endothelial glycocalyx degradation and ATC.

Coagulation factor deficiency

Coagulation factor abnormalities occur quickly after trauma, with fibrinogen levels reaching critical levels first. As the major substrate, fibrinogen is essential for clotting. A prospective cohort study from the United Kingdom reported declining levels of fibrinogen below the critical levels of less than 1.5, 1.0, and 0.8 g/L in 14%, 5%, and 3% of trauma patients, respectively (26). In another study involving 45 trauma patients, more than half of these displayed coagulation abnormalities within 25 min after injury (27). In general, these coagulation abnormalities appear to occur more pronounced in patients with higher levels of injury including acidosis and higher transfusion requirement. Critical factor V levels, as also often seen in trauma patients, may be related to the activation of protein C and the cleavage of factor V as described above.

Hyperfibrinolysis

Under physiological conditions, the coagulation system modulates fibrinolysis in that blood clots are maintained stable for a given time to control bleeding and to promote adequate wound healing. High concentrations of thrombin inhibit plasmin activation via the activation of TAFI (thrombin-activated fibrinolysis inhibitor) and PAI-1. Vice versa, if the thrombin burst is weak, TAFI remains unactivated. Furthermore, if thrombin encounters TM on endothelial cells, protein C may be activated, which then inactivates PAI-1.

Hyperfibrinolysis has been identified as a major contributor of mortality in bleeding trauma patients (28, 29). Hyperfibrinolysis

diagnosed via thromboelastography is present in 7% to 20% of adult trauma patients and associated with increased mortality (30, 31). Raza and colleagues (32) have reported from their cohort of trauma patients that only 5% had severe fibrinolysis on thromboelastometry, but 57% had evidence of "moderate" fibrinolysis, with PAP complex levels elevated to more than twice the normal without lysis on thromboelastometry, indicating that fibrinolytic activation occurs in the majority of trauma patients. If present, hyperfibrinolysis occurs early (<1 h) and is associated with massive transfusion requirements, coagulopathy, and hemorrhage-related death (28). Schöchl and colleagues (28) have reported a mortality rate of approximately 88% in trauma patients with hyperfibrinolysis present upon ED admission as detected by viscoelastic testing. Even a small reduction of the maximum amplitude in thromboelastography (>15%) is likely to be associated with higher transfusion requirements including massive transfusion, coagulopathy, and hemorrhage-related death (29).

Platelet dysfunction

The question of early platelet dysfunction in ATC remains unclear but may be secondary to attenuation of platelet stimulation to adenosine diphosphate agonism. Wohlauer and colleagues (33) have prospectively assessed platelet function in assembly and stability of the thrombus within 30 min of injury using whole-blood samples from 51 trauma patients versus control subjects at the point of care using thromboelastography-based platelet functional analysis. There were significant differences in the platelet response between trauma patients and healthy volunteers, such that there was impaired aggregation to these agonists. In trauma patients, the median adenosine diphosphate inhibition of platelet function was 86.1% compared with 4.2% in healthy volunteers. After trauma, the impairment of platelet function in response to arachidonic acid was 44.9% compared with 0.5% in volunteers. This study indicated that platelet dysfunction is manifest after major trauma and before substantial fluid or blood administration. In another study, Kutcher and colleagues (34) prospectively collected blood from 101 patients with critical injury upon ED arrival and thereafter and functionally assessed the responsiveness to adenosine diphosphate, thrombin receptor-activating peptide, arachidonic acid, and collagen using multiple electrode impedance aggregometry. Of the 101 enrolled patients, 46 (45.5%) had below-normal platelet response to at least one agonist at admission ("platelet hypofunction"), and 92 patients (91.1%) had platelet hypofunction some time during their ICU stay. Admission platelet hypofunction was associated with low Glasgow Coma Scale scores and a nearly 10-fold higher early mortality.

The vicious cycle: hypothermia, acidosis, and hemodilution

The traditionally so-called "lethal triad" comprising coagulopathy, hypothermia, and acidosis may be extended to the "lethal quartet" if hemodilution is added, thus emphasizing the detrimental role of uncritical overuse of fluid resuscitation resulting in further dilution of coagulation factors.

Direct loss and the consumption of coagulation factors, dilution, hypothermia, acidosis, and fibrinolysis and the release of anticoagulation factors, e.g., activated protein C, all interfere with coagulation and diminish hemostasis. There seems to be an additive effect among the clinical drivers of the process as the probability of life-threatening coagulopathy increases with the number of drivers present. Cosgriff and colleagues (35), e.g., have shown that the conditional probability of developing coagulopathy after trauma was 1% in moderate injury without the presence of additional triggers but increased to 39% in severe injury (injury severity score >25) combined with hypotension, to 58% when injury occurred with acidosis (pH <7.1), and to 98% in cases of injury severity score of greater than 25 together with hypotension (systolic blood pressure <70 mmHg), hypothermia (<34°C), and acidosis (pH <7.1).

Hypothermia and acidosis

Meng and colleagues (36, 37) have frequently demonstrated the effects of temperature and pH on coagulation factor and complex activity. Both temperature and acidosis contribute to coagulopathy by reducing the pace of plasma coagulation factor biochemical reactions. This activity is slowed down by approximately 5% with each 1°C drop in temperature. The von Willebrand factor–glycoprotein Ib interaction, which activates platelets, is absent in 75% of individuals at 30°C (38, 39). Similarly, drops in pH to values of 7.2 have been shown to reduce coagulation factor complex activities by half and down to 20% of normal activity at pH 6.8 (38). Hypothermia primarily inhibits the initiation of thrombin generation and fibrinogen synthesis, with no effect on fibrinogen degradation (40). Acidosis disrupts the interplay of coagulation factors with the negatively charged phospholipids on the surface of activated platelets (41).

Hemodilution

Dilution may occur both physiologically and iatrogenically. In trauma-associated physiologic hemodilution, the unopposed osmotic activity of plasma in states of hypotension is prompted by a water shift into the intravascular space, thus diluting plasma proteins until equilibrium is reestablished. In this scenario, each protein is diluted to the same amount, and their interactions, e.g., the intrinsic "tenase complex" comprising combined factors IXa, VIIIa, and X, are reduced proportionally to their individual factor concentrate changes. In this model, Monroe (42) calculated a 37% reduction in single factor concentration to result in a 75% reduction in overall complex activity.

Iatrogenic dilution is caused by unguided and often overadministration of fluids in the acute phase of trauma care. In patients from the TR-DGU database (Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie/German Trauma Society), coagulopathy upon ED admission was observed in more than 40% of patients with more than 2,000 mL, in more than 50% with more than 3,000 mL, and in more than 70% with more than 4,000 mL of fluids administered during the prehospital phase of care (9). More recently, a prehospital intravenous colloid-to-crystalloid ratio of 1:2 or greater and the amount of prehospital intravenous fluids of 3,000 mL or greater have been identified as independent contributors to hemostatic abnormalities after trauma (43). This dilution is accompanied by consumption and inactivation not only of coagulation factor

substrates but also coagulation enzymes with magnitudes matching the degree of individual injury (44).

Coagulopathy of TBI

Traumatic brain injury is often associated with hemocoagulative disorders, but incidence rates vary considerably. A recent meta-analysis of 34 studies has indicated that one of three patients suffering from TBI displays signs of coagulopathy (45). Whereas hemocoagulative disorders may occur in more than 60% of patients with severe TBI (46), in mild head injury coagulopathy is uncommon (<1%) (47). Stepwise logistic regression analysis has identified the following independent risk factors for the development of coagulopathy after blunt TBI: (i) severity of head trauma as reflected by AIS_{head} (Abbreviated Injury Scale for the head), (ii) Glasgow Coma Scale score at scene of 8 or less, (iii) hypotension of 90 mmHg or less at scene or upon emergency room (ED) arrival, (iv) prehospital intravenous fluid administration of 2,000 mL or greater, and (v) age 75 years or older (48). It has been observed that the number of patients with isolated TBI and coagulopathy may double within the first 24 h after trauma and that hemostatic abnormalities reflected by impaired global coagulation parameters may continue until the third day after injury or even longer (49). The time interval to the onset of coagulopathy decreases substantially with increasing magnitude of injury.

Meanwhile, coagulopathy upon ED arrival in TBI has been identified as a powerful predictor related to outcome and prognosis (45, 48, 49). The risk of dying in patients with coagulopathy after TBI is about 10 times higher than in patients without coagulopathy, and the risk of unfavorable outcome in surviving patients is even more than 30 times higher if coagulopathy is present upon ED arrival (45).

The complex pathophysiological mechanisms of the coagulopathy of TBI are still undefined, and the nature of these abnormalities seems to differ from non-TBI patients with multiple somatic injuries. The current hypothesis for the development of coagulopathy of TBI includes a combination of both hypocoagulable and hypercoagulable states promoted by the magnitude and the extent of the traumatized brain tissue resulting in secondary injury via subsequent ischemic or hemorrhagic lesioning (45). The proposed underlying mechanisms of the coagulopathy of TBI may overlap, in part, with those listed above for the coagulopathy of somatic injuries and may comprise hyperfibrinolysis, shock, and hypoperfusion, thus triggering the protein C pathway, disseminated intravascular coagulation, platelet dysfunction, and also the substantial release of tissue factor (50).

CONCLUSIONS

The pivotal drivers of initial ATC are tissue trauma, hypoperfusion, inflammation, and sympathoadrenal activation leading to hemostatic abnormalities including hypocoagulability, fibrinolysis, and endothelial hyperpermeability. Endothelial damage and activation results in Weibel-Palade body degradation and glycocalyx shedding associated with autoheparinization. This ATC combined with worsening acidosis and hypothermia due to uncritical volume loading during resuscitation (fluids and blood products) forming also the so-called vicious cycle may lead to further exacerbation and may be considered as the precursor state for later IC. One of four patients arriving to the ED after severe injury already displays signs of disturbed hemostasis. Acute traumatic coagulopathy has frequently been shown to be associated with higher transfusion requirement, morbidity and mortality, and length of stay in ICU and overall in-hospital stay. The nature of hemostatic abnormalities in the context of TBI seems to differ from non-TBI patients with multiple somatic injuries.

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