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Review article

Progresses in understanding trauma-induced coagulopathy and the underlying mechanism

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ABSTRACT

Trauma-induced coagulopathy (TIC) is a clinical syndrome caused by imbalance between clotting, anti-coagulation and fibrinolysis resulting from multiple pathological factors such as hemorrhage and tissue injury in the early stage of trauma, and is closely related to the outcome of trauma patients. It is proved in growing evidence that the endogenous coagulation disturbance in trauma itself is the activating factor of TIC, rather than dilution or other acquired coagulopathy. Therefore, a thorough understanding of the molecular mechanisms in the pathogenesis and progression is crucial for effective prevention and treatment in patients with TIC. This review focuses on transitions in the concept of TIC and mechanical progress.

Introduction

Trauma is the third leading cause of death in the United States,[1] and results in 10% of all deaths worldwide.[2] Specifically, brain injury and massive bleeding are the leading causes of death in trauma patients. Although there is an up-regulation of the protective procoagulation after trauma, nearly one-third of patients have presented TIC, which is an important preventable factor for progressive brain injury and uncontrollable massive bleeding, and closely related to the prognosis of trauma patients.[3–6] In the present article, we reviewed transitions in the concept of TIC and mechanical progress.

Changes in understanding of TIC

Recognition of TIC causes

TIC is a clinical syndrome featuring coagulopathy occurring in the early stage of trauma that is caused by activation of coagulation, fibrinolytic, and anti-coagulation pathways due to various factors, such as tissue injury and bleeding. In 1954, Scott et al[7] initially reported coagulopathy in trauma patients who were wounded during the Korean and Vietnam wars. The study suggested that loss of coagulation factors and platelets was the basis for coagulopathy, while considerable fluid infusion and blood transfusion induced hemodilution and further aggravated the coagulopathy. In 1982, the American Trauma Society[8] proposed the “bloody vicious cycle,” which includes acidosis, hypothermia, and coagulopathy, as an important cause of death in patients with coagulopathy in the early stage of trauma. This term was gradually replaced by other terms, such as “lethal triad” and “iatrogenic trauma coagulopathy,” and is also the theoretical basis for damage control resuscitation. A large number of studies have confirmed that TIC is not merely the result of systemic acquired coagulopathy (SAC) caused by acidosis and hypothermia following traumatic shock or hemodilution following resuscitation, because early coagulopathy is caused by trauma alone within 30 min after trauma before fluid resuscitation is initiated.[9–15] The current opinion is that coagulopathy in the early stage of trauma is an endogenous acute coagulopathy (EAC) existing independently, and is essentially different from coagulation disorders caused by acquired factors. With progression, SAC may aggravate coagulation disorders and take part in the mechanism underlying TIC together with that of SAC.[16] In 2006, international experts launched the “educational initiative on critical bleeding in trauma (EICBT),” which suggested that TIC is a new disease entity, and proposed concepts, such as “coagulopathy of trauma” and “acute coagulopathy of trauma shock.” Unfortunately, our understanding of post-traumatic TIC is still inadequate, and there is still a

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lack of international standards in the definition and diagnostic criteria for TIC.

TIC and disseminated intravascular coagulation (DIC)

For a long time, it has been controversial whether or not TIC in patients with severe trauma is equal to the hyperfibrinolysis predominance type of DIC.[17] In the 1980s, it was reported that the coagulation indicators had reached the diagnostic criteria of DIC in some early-stage trauma patients who presented with a prolonged prothrombin time (PT), low fibrinogen and anti-thrombin levels, and increased fibrinogen degradation products and D-dimer levels.[10] These changes often indicate uncontrolled thrombin formation and hyperfibrinolysis. In contrast, Brohi et al[18,19] considered that the above-described abnormalities of coagulation indicators are more closely related to trauma and hypoperfusion, and suggested that the severity of acute coagulopathy of trauma shock (ACoTS)-induced hypoperfusion determines coagulation abnormalities. They considered that local endothelial damage in the early stage of trauma causes activation of coagulation factors X, II, V, and VIII to produce thrombin. Since the clearance of thrombin slows in a state of shock, and it combines with thrombomodulin and neighboring endothelial cells, and thereby further activates activated protein C, thus resulting in inactivation of activated factors V and VIII and plasminogen inhibitor-1 to further decrease thrombin production and enhance anti-coagulation and fibrinolysis. Although changes in coagulation parameters may be similar, this process is quite different from that of classical DIC induced by other diseases, such as sepsis. In addition, there is no evidence of thrombus formation in the microcirculation of trauma patients with excessive bleeding,[18] and no consumption of clotting substances, such as platelets in some patients with coagulopathies. Therefore, it is believed that ACoTS should be regarded as a coagulation disorder quite different from DIC.[19,20] In 2014, Wada et al[21] proposed DIC classification criteria based on the degree of hyperfibrinolysis, which explained the features of fibrinolysis-dominant DIC in the early stage of trauma using the coagulation mechanism, and provided a theoretical basis for early clotting factor replacement and administration of anti-fibrinolytic medications. At the same time, the CRASH-II study[22] not only proved that early anti-fibrinolytic therapy with tranexamic acid might improve prognosis, but also confirmed the existence of the hyperfibrinolysis-predominant type of DIC in the early stage of trauma.

Progress in the mechanisms underlying TIC

TIC is a complicated pathophysiologic state, the exact mechanism of which has not been fully elucidated.[23] TIC is generally considered to be related to many factors, including tissue injury, shock and secondary acidosis, hypothermia, and the bloody vicious cycle caused by acquired factors, such as hemodilution, inflammation, and endothelial damage.[24] As the recognition of the cell-based coagulation model,[25] more and more studies have focused attention on the cellular activation mechanisms underlying TIC. Herein we reviewed the effects of endothelial damage on TIC and several new molecular mechanisms leading to endothelial injury during trauma.

Endothelial cell damage and coagulation imbalance

Endothelial cells are monolayer cells covering the surface of arteries, veins, and lymphatic vessels. The total weight of endothelial cells is approximately 1.5 kg and the total area may be 4000–7000 square meters.[26,27] The endothelial glycocalyx (EG), which is located on the surface of endothelial cells, is a 0.2–1 μm layer rich in negatively charged anti-adhesion and anticoagulant carbohydrates. Both substances form the “vascular portal” to take part in important physiologic functions, such as the balance between coagulation and fibrinolysis, and blood–tissue exchange. When tissues are injured, activation of the endothelial cells induces up-regulation of coagulation, which results in local hemostasis; while inflammation secondary to traumatic stress and shock will magnify the pro-coagulant activation of endothelium, resulting in systemic thrombin generation and endogenous consumptions of amounts of coagulation factors and platelets. Currently, it is considered that the microvascular thrombosis after trauma maybe dissolved quickly by enhanced fibrinolysis because of no clot found in TIC patients.[1]

Recent studies shows that EG is destroyed or degraded to release some components such as chondroitin sulfate and heparin sulfate into the blood in severe trauma patients, which results in self-heparinization,[28,29] and is an important mechanism for enhancing endogenous anti-coagulation during TIC. A prospective study conducted by Ostrowski et al[30] showed that the plasma level of heparin-like substances was relatively high in 4 of 77 (5.2%) acute trauma patients. Second, the activated protein C pathway is one of the main initiating factors for TIC. Activation of protein C in the circulation occurs after protein C binds to the protein C receptor in endothelial cells, which inhibits coagulation by affecting factors V and VIII, and promotes fibrinolysis by affecting plasminogen inhibitor-1 (PAI-1). A prospective study conducted by Cohen et al[31] showed that increased severity of injury and hypoperfusion is related to protein C level, coagulation parameters (PT and PTT), and hyperfibrinolysis. A decrease in the factor V and VIII levels was closely related to the severity of injury and the degree of hypoperfusion, which suggests that the activated protein C pathway plays an important role in TIC. Many papers have shown that the levels of coagulation factors are relatively low, while fibrinolysis is enhanced in TIC patients.[32,33] This may be related to the degradation of fibrinolysis inhibitors caused by protein C activation; however, some scholars prefer to believe that it is the result of the tissue-type plasminogen activator (tPA) secreted by the endothelial cells after being activated by stresses, such as injury. Chapman et al[34] reported that compared to patients without fibrinolysis, trauma patients with hyperfibrinolysis had significantly high tPA levels and significantly low free PAI-1 levels, but there was no significant difference between the two groups in total PAI-1 levels, including free PAI-1 and bound PAI-1, which suggests that hyperfibrinolysis in patients with TIC may be related to the release of tPA, but not related to inhibition of PAI-1. In conclusion, endothelial injury induced coagulation imbalance and in turn to TIC by activating coagulation and then enhanced anticoagulation and fibrinolysis.

Endothelial cells in various places may have different functions according to the requirements of surrounding tissues. In general, large arteries participate in the conduction of blood and materials, middle and small arteries are resistance vessels, and capillaries are responsible for material exchange. Therefore, it should be further determined whether or not coagulation changes in various blood vessels are the same, while the relationship between the features of coagulation changes in the microcirculation and endothelial cells should be investigated to find a more effective prevention and treatment strategy on the basis of the microcirculation and coagulopathy.

Endothelial cells and molecular mechanism underlying TIC

Damage-associated molecular patterns (DAMPs)

Recent studies have shown that the DAMPs in the early stage of trauma bind to the pattern recognition receptors on endothelial

cells and other immune cells, to activate the intracellular signaling pathway, initiate the innate immune system in the body, and result in inflammation and coagulation cascade. It has been reported that high mobility group box-1 protein (HMGB1), as an important medium of DAMPs, acts on Toll-like receptors 4 (TLR4) and then activates its downstream signals, which plays a critical role in the pathogenesis of traumatic coagulopathy,[35] and is closely related to bleeding, shock, and hypoperfusion. The level of TLR4 reflects not only the degree of severity in trauma, but also the intension of secondary innate immune response caused by hypotension or shock.[36]

PARs and the inflammation-coagulation pathway

Protease activated receptors (PARs) are G protein-coupled receptors widely distributed in endothelial cells. The family of PARs includes four members (PAR1, PAR2, PAR3, and PAR4). As the main thrombin receptor, PAR1 is closely related to inflammation and coagulation. Thrombin binds to the endothelial cell receptor, PAR1, to further activate platelets, while the platelet is an important activator among the cell-based coagulation model, and is the prerequisite for amplification and spread of the coagulation cascade. In addition, activated PAR1 may lead to activation of transcription factors to up-regulate the expression of tissue factor (TF) and Von-Willebrand factor (vWF),[37,38] while the latter two factors are involved in the coagulation process, including the initiation of coagulation cascade and platelet aggregation, respectively. Activation of PAR1 can also make endothelial cells produce mediators related to cell adhesion and trans-endothelial cell migration, including cytokines (IL-1 and IL-8), growth factors, cell adhesion molecules (such as E-selectin and P-selectin), intercellular adhesion molecules, and vascular cell adhesion molecules. Moreover, activation of endothelial cell PAR1 may lead to up-regulation of the pro-apoptotic gene expression,[39] which induces apoptosis of endothelial cells to change the secretion of coagulation and fibrinolysis factors. It is reported that thrombin and its PARs participated in the molecular mechanism of cerebral injury caused by ischemia, hemorrhage and brain trauma. It is closely associated with the degree of cerebral hemorrhage, encephaledema and cerebral angiospasm.[40] Although recent researches on the molecular pathogenesis of TIC are limited, it is reasonable to speculate that the interaction between thrombin and its endothelial receptor PAR1 could play an important role in the mechanism, and inhibition of PAR1 expression should be an effective target in the early treatment of TIC.

Inflammasome and endothelial cell inflammation and pyroptosis

Nlrp3 is an intracellular Nod-like receptor that acts as a danger signal receptor, is activated by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) stimulation, induce the recruitment of the apoptosis speck-like protein containing a caspase-recruitment domain (ASC) to inform the inflammasome. It is a multiprotein complex and necessary for caspase-1 and IL-1β activation.[41,42] IL-1β is a key mediator, plays a synergistic role with TNF-α, amplifies inflammatory signals, and generates the "inflammation cascade".[43,44] Caspase-1 is a key regulator of tissue damage-induced inflammation, not only takes part in the amplification of inflammation, but also enhances cell pyroptosis.[45] Using a mouse model of hemorrhagic shock, Jie et al[46] showed that IL-1β release induced by the activation of Nlrp3 inflammasome in pulmonary endothelial cells is an important mechanism by which pulmonary inflammation is amplified into pulmonary injury. Multi-factors like oxidative stress, hypoxia and hemorrhagic shock can activate inflammasome.[47] Besides, high expression of plasma IL-1β dependent on the activation of Nlrp3 inflammasome was closely related to the pathogenesis and the severity of DIC in the early stage of trauma, which is associated with the fact that inflammatory cytokines induced further activation of endothelium and complement system and facilitated in the biological changes of fibrinolysis.[12,48]

Conclusion

TIC is an endogenous coagulopathy caused by inflammation and shock after trauma. Hypothermia, acidosis, and hemodilution may aggravate TIC. Even though it is controversial whether or not TIC belongs to DIC, most scholars believe that fibrinolysis-type DIC is the characteristic manifestation of TIC in the early stage of trauma. The current review does not clarify the mechanism underlying TIC entirely; however, it points out that the endothelial cell-centered inflammation-coagulation pathway participated in coagulation, anti-coagulation, and fibrinolysis in patients with TIC. Recent studies have verified that the TLR4, PAR1, and Nlrp3 inflammasomes may serve as the major molecular mechanism underlying endothelial cell activation and subsequent TIC occurrence. More studies should be carried out to further explore the molecular mechanism underlying TIC and provide an effective strategy for the early treatment of TIC.

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